Health Technology Assessment 2008; Vol. 12: No. 11

Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation

Y-F Chen, P Jobanputra, P Barton, S Bryan, A Fry-Smith, G Harris and RS Taylor

April 2008

Health Technology Assessment
NHS R&D HTA Programme
www.hta.ac.uk

How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation

Y-F Chen,[1*] P Jobanputra,[2] P Barton,[3] S Bryan,[3] A Fry-Smith,[1] G Harris[4] and RS Taylor[5]

[1] Department of Public Health and Epidemiology, University of Birmingham, UK
[2] Department of Rheumatology, University Hospital Birmingham NHS Trust, Selly Oak Hospital, UK
[3] Health Economics Facility, University of Birmingham, UK
[4] Laurie Pike Health Centre, Birmingham, UK
[5] Peninsula Medical School, Universities of Exeter and Plymouth, Exeter, UK

* Corresponding author

Declared competing interests of authors: P Jobanputra has received funding from Pfizer for two research studies: 'quality of care in patients with musculoskeletal pain who use NSAIDs' and 'perception of risk in relation to NSAID use for patients with RA and OA'. He has also been entertained, paid to speak and provided with financial assistance for educational purposes by many manufacturers of non-steroidal anti-inflammatory drugs, new and old. RS Taylor has undertaken paid presentations for Pfizer (Canada) and Novartis (UK) not related to rheumatoid arthritis or osteoarthritis management.

Published April 2008

This report should be referenced as follows:

Chen Y-F, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, *et al*. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. *Health Technol Assess* 2008;**12**(11).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE and *Science Citation Index Expanded (SciSearch®)* and *Current Contents®*/Clinical Medicine.

NIHR Health Technology Assessment Programme

The Health Technology Assessment (HTA) Programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Secondly, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Thirdly, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer-reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned and funded by the HTA Programme on behalf of NICE as project number 03/34/01. The protocol was agreed in November 2001. The assessment report began editorial review in September 2006 and was accepted for publication in February 2007. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

T

Abstract

Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation

Y-F Chen,[1*] P Jobanputra,[2] P Barton,[3] S Bryan,[3] A Fry-Smith,[1] G Harris[4] and RS Taylor[5]

[1] Department of Public Health and Epidemiology, University of Birmingham, UK
[2] Department of Rheumatology, University Hospital Birmingham NHS Trust, Selly Oak Hospital, UK
[3] Health Economics Facility, University of Birmingham, UK
[4] Laurie Pike Health Centre, Birmingham, UK
[5] Peninsula Medical School, Universities of Exeter and Plymouth, Exeter, UK
* Corresponding author

Objectives: To review the clinical effectiveness and cost-effectiveness of cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drugs (NSAIDs) (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis (OA) and rheumatoid arthritis (RA).
Data sources: Electronic databases were searched up to November 2003. Industry submissions to the National Institute for Health and Clinical Excellence (NICE) in 2003 were also reviewed.
Review methods: Systematic reviews of randomised controlled trials (RCTs) and a model-based economic evaluation were undertaken. Meta-analyses were undertaken for each COX-2 selective NSAID compared with placebo and non-selective NSAIDs. The model was designed to run in two forms: the 'full Assessment Group Model (AGM)', which includes an initial drug switching cycle, and the 'simpler AGM', where there is no initial cycle and no opportunity for the patient to switch NSAID.
Results: Compared with non-selective NSAIDs, the COX-2 selective NSAIDs were found to be equally as efficacious as the non-selective NSAIDs (although meloxicam was found to be of inferior or equivalent efficacy) and also to be associated with significantly fewer clinical upper gastrointestinal (UGI) events (although relatively small numbers of clinical gastrointestinal (GI) and myocardial infarction (MI) events were reported across trials). Subgroup analyses of clinical and complicated UGI events and MI events in relation to aspirin use, steroid use, prior GI history and *Helicobacter pylori* status were based on relatively small numbers and were inconclusive. In the RCTs that included direct COX-2 comparisons, the drugs were equally tolerated and of equal efficacy. Trials were of insufficient size and duration to allow comparison of risk of clinical UGI events, complicated UGI events and MIs. One RCT compared COX-2 (celecoxib) with a non-selective NSAID combined with a gastroprotective agent (diclofenac combined with omeprazole); this included arthritis patients who had recently suffered a GI haemorrhage. Although no significant difference in clinical GI events was reported, the number of events was small and more such studies, where patients genuinely need NSAIDs, are required to confirm these data. A second trial showed that rofecoxib was associated with fewer diarrhoea events than a combination of diclofenac and misoprostol (Arthrotec). Previously published cost-effectiveness analyses indicated a wide of range of possible incremental cost per quality-adjusted life-year (QALY) gained estimates. Using the simpler AGM, with ibuprofen or diclofenac alone as the comparator, all of the COX-2 products are associated with higher costs (i.e. positive incremental costs) and small increases in effectiveness (i.e. positive incremental effectiveness), measured in terms of QALYs. The magnitude of the incremental costs and the incremental effects, and therefore the incremental cost-effectiveness ratios, vary considerably across all COX-2 selective NSAIDs. The base-case incremental cost per QALY results for COX-2 selective NSAIDs compared with diclofenac for the simpler

model are: celecoxib (low dose) £68,400; celecoxib (high dose) £151,000; etodolac (branded) £42,400; etodolac (generic) £17,700; etoricoxib £31,300; lumiracoxib £70,400; meloxicam (low dose) £10,300; meloxicam (high dose) £17,800; rofecoxib £97,400; and valdecoxib £35,500. When the simpler AGM was run using ibuprofen or diclofenac combined with proton pump inhibitor (PPI) as the comparator, the results change substantially, with the COX-2 selective NSAIDs looking generally unattractive from a cost-effectiveness point of view (COX-2 selective NSAIDs were dominated by ibuprofen or diclofenac combined with PPI in most cases). This applies both to 'standard' and 'high-risk' arthritis patients defined in terms of previous GI ulcers. The full AGM produced results broadly in line with the simpler model.

Conclusions: The COX-2 selective NSAIDs examined were found to be similar to non-selective NSAIDs for the symptomatic relief of RA and OA and to provide superior GI tolerability (the majority of evidence is in patients with OA). Although COX-2 selective NSAIDs offer protection against serious GI events, the amount of evidence for this protective effect varied considerably across individual drugs. The volume of trial evidence with regard to cardiovascular safety also varied substantially between COX-2 selective NSAIDs. Increased risk of MI compared to non-selective NSAIDs was observed among those drugs with greater volume of evidence in terms of exposure in patient-years. Economic modelling shows a wide range of possible costs per QALY gained in patients with OA and RA. Costs per QALY also varied if individual drugs were used in 'standard' or 'high'-risk patients, the choice of non-selective NSAID comparator and whether that NSAID was combined with a PPI.

With reduced costs of PPIs, future primary research needs to compare the effectiveness and cost-effectiveness of COX-2 selective NSAIDs relative to non-selective NSAIDs with a PPI. Direct comparisons of different COX-2 selective NSAIDs, using equivalent doses, that compare GI and MI risk are needed. Pragmatic studies that include a wider range of people, including the older age groups with a greater burden of arthritis, are also necessary to inform clinical practice.

Contents

List of abbreviations

ACCES	Arthritis Cost Consequences Evaluation System
ADVANTAGE	Assessment of Difference Between Vioxx and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness
AGM	Assessment Group Model
APTC	Antiplatelet Trialists' Collaboration
BNF	British National Formulary
CI	confidence interval
CLASS	Celecoxib Long-term Arthritis Safety Study
COX	cyclooxygenase
Coxib	refers to certain chemical classes of NSAID but does not necessarily reflect COX-2 selectivity
CV	cardiovascular
DMARD	disease-modifying antirheumatic drug
EMEA	European Medicines Agency
FDA	Food and Drug Administration
GI	gastrointestinal
GORD	gastro-oesophageal reflux disease
GPA	gastroprotective agent
GPD	gastroprotective drug
H2RA	histamine-2 receptor antagonist (such as cimetidine and ranitidine)
HAQ	Health Assessment Questionnaire
ICER	incremental cost-effectiveness ratio
ITT	intention-to-treat
MELISSA	Meloxicam Large-Scale International Study Safety Assessment
MI	myocardial infarction
MUCOSA	Misoprostol Ulcer Complications Outcome Safety Assessment
NICE	National Institute for Health and Clinical Excellence
NNT	number-needed-to-treat
NNH	number-needed-to-harm
NSAID	non-steroidal anti-inflammatory drug (excluding aspirin)
OA	osteoarthritis
OR	odds ratio
POB	perforation, obstruction or bleed: refers only to complicated UGI events (see below)
PPI	proton pump inhibitor (such as omeprazole and lansoprazole)
PUB	perforation, ulcer or bleed: refers to symptomatic ulcers (see below) and complicated UGI events (see below) combined
QALY	quality-adjusted life-year
RA	rheumatoid arthritis
RCT	randomised controlled trial
RR	relative risk
SA	sensitivity analysis

continued

List of abbreviations (*continued*)

SELECT	Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies
Syst Rev	systematic review
SR	(following a drug name) slow-release
SUCCESS	Successive Celecoxib Efficacy and Safety Studies
TARGET	Therapeutic Arthritis Research and Gastrointestinal Event Trial
UGI	upper gastrointestinal
VACT	Vioxx, Acetaminophen, Celecoxib Trial
VAS	visual analogue scale
VIGOR	Vioxx Gastrointestinal Outcomes Research
WOMAC	Western Ontario and McMaster Universities

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Definitions

COX-2 selective NSAIDs For the purposes of this review, the following NSAIDs are included in this category: celecoxib, etodolac, etoricoxib, lumiracoxib, meloxicam, rofecoxib, and valdecoxib. Diclofenac appears to have similar levels of COX-2 selectivity as some of these agents but is not included in this category.

Clinical upper GI events This includes symptomatic upper GI ulcers and complicated upper GI events (see below).

Complicated upper GI events This includes perforations, obstructions and bleeding of the stomach and/or duodenum.

Serious cardiovascular thrombotic events The definition by the Antiplatelet Trialists' Collaboration is adopted. These include cardiovascular, haemorrhagic and unknown death, non-fatal myocardial infarction and non-fatal stroke.

Symptomatic upper gastrointestinal (GI) ulcers Symptomatic upper GI ulcers are defined as ulcers seen on endoscopy or radiographs with associated symptoms, for example where patients have been investigated for upper GI symptoms of dyspepsia during a study (i.e. evaluated 'for cause').

Note

The contents of this monograph are based upon a technology assessment report that was compiled during a review of Technology Appraisal Guidance No. 27 for cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drugs (NSAIDs) for osteoarthritis (OA) and rheumatoid arthritis (RA) carried out by the National Institute for Clinical Excellence (NICE) in 2003–4. The publication of the monograph was substantially delayed due to the unusual circumstances surrounding this technology appraisal, which was subsequently suspended. Readers are referred to Chapter 10, 'Postscript', for an overview of the project history and are reminded that new evidence that has emerged since the initial completion of the technology assessment report should be considered alongside the evidence presented in this monograph.

Data that were commercial-in-confidence at the initial completion of this report in 2004 have been removed.

Executive summary

Objectives

The objectives were to review the clinical effectiveness and cost-effectiveness of cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drugs (NSAIDs) (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis (OA) and rheumatoid arthritis (RA).

Epidemiology and background

OA and RA are common conditions that cause pain, disability and reduced physical function. Treatment costs of arthritis to the NHS are substantial, and rising. NSAIDs are effective treatments for symptomatic relief of arthritis. COX-2 selective NSAIDs have the potential for maintaining symptomatic benefits but also may reduce the adverse gastrointestinal (GI) effects associated with non-selective NSAIDs.

Methods

Clinical effectiveness

Systematic reviews of randomised controlled trials (RCTs) were undertaken. Electronic databases were searched up to November 2003. Industry submissions to NICE in 2003 were also reviewed. Meta-analyses were undertaken for each COX-2 selective NSAID compared with placebo and non-selective NSAIDs.

Cost-effectiveness

A new modelling exercise was undertaken that used the Markov model developed originally by Maetzel and colleagues (2001) as a starting point. The model was designed to run in two different forms: the 'full Assessment Group Model (AGM)', which includes an initial drug switching cycle, and the 'simpler AGM', where there is no initial cycle and no opportunity for the patient to switch NSAID.

The main data sources for clinical parameters were the meta-analysis results from this systematic review. Where necessary, other sources have been used.

Results

Clinical effectiveness

Etodolac

Twenty-nine RCTs were included. Studies compared etodolac with either placebo or non-selective NSAIDs. Compared with non-selective NSAIDs (naproxen, piroxicam, diclofenac, indomethacin, tenoxicam, ibuprofen, nabumetone or nimesulide), etodolac (600–1000 mg/day) was equally efficacious and of equivalent or superior gastrointestinal (GI) tolerability. Pooled analysis did not show a difference in complicated upper gastrointestinal (UGI) events (POBs) [relative risk (RR) 0.39, 95% confidence interval (CI) 0.12 to 1.24]. Etodolac was associated with significantly fewer clinical UGI events (PUBs) (RR 0.32, 95% CI 0.15 to 0.71). No myocardial infarctions (MIs) were reported.

Meloxicam

Sixteen RCTs were included (plus 11 trials available only in abstract form that were included in sensitivity analysis). Studies compared meloxicam with either placebo or non-selective NSAIDs. Compared with non-selective NSAIDs (naproxen, diclofenac, nabumetone or piroxicam), meloxicam (7.5–22.5 mg/day) was of inferior or equivalent efficacy and superior GI tolerability. Pooled analysis did not show a difference in complicated UGI events (RR 0.56, 95% CI 0.27 to 1.15). Meloxicam was associated with significantly fewer clinical UGI events (RR: 0.53, 95% CI: 0.29 to 0.97). There were insufficient events to comment on MI risk. Inclusion of abstract-only data made no difference to these conclusions.

Celecoxib

Forty RCTs were included. Studies compared celecoxib with placebo, non-selective NSAIDs or other COX-2 selective NSAIDs. Compared with non-selective NSAIDs (naproxen, diclofenac, ibuprofen or loxoprofen), celecoxib (200–800 mg/day) was equally efficacious and of superior GI tolerability. Celecoxib was associated with significantly fewer clinical UGI events (RR 0.55, 95% CI 0.40 to 0.76) and complicated UGI

events (RR 0.57, 95% CI 0.35 to 0.95) and a significantly higher risk of MI (RR 1.77, 95% CI 1.00 to 3.11).

Rofecoxib

Twenty-seven RCTs were included. Studies compared rofecoxib with placebo, non-selective NSAIDs, Arthrotec or other COX-2 selective NSAIDs. Compared with non-selective NSAIDs (naproxen, ibuprofen, or nabumetone), rofecoxib (12.5–50 mg/day) was equally efficacious and had superior GI tolerability. Rofecoxib was associated with significantly fewer clinical UGI events (RR 0.43, 95% CI 0.32 to 0.57) and complicated UGI events (RR 0.40, 95% CI 0.23 to 0.70) and a significantly higher risk of MI (RR 2.92, 95% CI 1.36 to 6.28) compared with non-selective NSAIDs.

Etoricoxib

Seven RCTs were included. Studies compared etoricoxib with either placebo or non-selective NSAIDs. Compared with non-selective NSAIDs (naproxen, diclofenac and ibuprofen), etoricoxib (60–120 mg/day) was equally efficacious and of equivalent or superior GI tolerability. Pooled analysis did not show a significant difference in clinical UGI events (RR 0.23, 95% CI 0.05 to 1.08) and complicated UGI events (RR 0.46, 95% CI 0.07 to 3.10). MI events were reported in only one trial (RR 1.58, 95% CI 0.06 to 38.66).

Valdecoxib

Eleven RCTs were included. Studies compared valdecoxib with either placebo or non-selective NSAIDs. In comparison with non-selective NSAIDs (naproxen, diclofenac or ibuprofen), valdecoxib (10–80 mg/day) was equally efficacious and had equivalent or superior GI tolerability. Pooled analysis did not show a significant difference in clinical UGI events (RR 0.20, 95% CI 0.03 to 1.46). Valdecoxib was associated with significantly fewer complicated UGI events (RR 0.43, 95% CI 0.19 to 0.97) and lower risk of MI (RR 0.25, 95% CI 0.06 to 1.00). The latter estimate was based on a total of six MI events and needs to be interpreted with great caution.

Lumiracoxib

Fifteen RCTs were included. Studies compared lumiracoxib with either placebo, non-selective NSAIDs or other COX-2 selective NSAIDs. Compared with non-selective NSAIDs (diclofenac, ibuprofen or naproxen), lumiracoxib (100–1200 mg/day) appeared to be equally efficacious and of significantly superior GI tolerability. Lumiracoxib was associated with significantly fewer clinical UGI events (RR 0.47, 95% CI 0.37 to 0.61) and complicated UGI events (RR 0.34, 95% CI 0.23 to 0.52) and a statistically non-significant increase in clinically confirmed MI risk (RR 1.71, 95% CI 0.86 to 3.37), particularly compared with naproxen. Lumiracoxib at 400 mg/day was associated with significantly increased hepatotoxicity compared with naproxen and ibuprofen.

There is a need for caution in the interpretation of the above meta-analysis results as relatively small numbers of clinical GI and MI events were reported across trials.

Subgroup analyses

Celecoxib appears to reduce clinical GI events and significantly increase MI risk, relative to non-selective NSAIDs, in both aspirin users and non-users. Rofecoxib appears to reduce clinical GI events, relative to non-selective NSAIDs, in both patients with prior GI history and no prior GI history, steroid users and non-users and patients positive and negative for *Helicobacter pylori*. The GI protective effect of lumiracoxib appeared to be reduced in aspirin users. These subgroup analyses are based on small numbers and need confirmation. It is not possible to comment on the effect of the use of anticoagulants and age on clinical GI or MI risk of COX-2 selective NSAIDs.

Direct COX-2 comparisons

Fourteen RCTs were included. Studies compared rofecoxib (12.5–25 mg/day) with celecoxib (200 mg/day) or valdecoxib (10 mg/day) or lumiracoxib (200–400 mg/day) and celecoxib (200–400 mg/day) with lumiracoxib (200–800 mg/day). Compared drugs were equally tolerated and of equal efficacy. Trials were of insufficient size and duration to allow comparison of risk of clinical UGI events, complicated UGI events and MIs.

COX-2 versus non-selective NSAID combined with a gastroprotective agent

One RCT directly compared celecoxib with diclofenac combined with omeprazole. Arthritis patients who had recently suffered a GI haemorrhage were included. Although no significant difference in clinical GI events was reported, the number of events was small and more such studies, where patients genuinely need NSAIDs, are required to confirm these data. A second trial showed that rofecoxib was associated with fewer diarrhoea events than Arthrotec.

Cost and cost-effectiveness

A review of previous published cost-effectiveness analyses, principally comparing either celecoxib or rofecoxib with non-selective NSAIDs, indicated a wide range of possible incremental cost per quality-adjusted life-year (QALY) gained estimates.

Using the simpler AGM, with ibuprofen or diclofenac alone as the comparator, all of the COX-2 products are associated with higher costs (i.e. positive incremental costs) and small increases in effectiveness (i.e. positive incremental effectiveness), measured in terms of QALYs. The magnitude of the incremental costs and the incremental effects, and therefore the incremental cost-effectiveness ratios, vary considerably across all COX-2 selective NSAIDs.

The base-case incremental cost per QALY results for COX-2 selective NSAIDs compared with diclofenac for the simpler model are as follows: celecoxib (low dose) £68,400; celecoxib (high dose) £151,000; etodolac (branded) £42,400; etodolac (generic) £17,700; etoricoxib £31,300; lumiracoxib £70,400; meloxicam (low dose) £10,300; meloxicam (high dose) £17,800; rofecoxib £97,400; and valdecoxib £35,500.

When the simpler AGM was run using ibuprofen or diclofenac combined with proton pump inhibitor (PPI) as the comparator, the results change substantially, with the COX-2 selective NSAIDs looking generally unattractive from a cost-effectiveness point of view (COX-2 selective NSAIDs were dominated by ibuprofen or diclofenac combined with PPI in most cases). This applies both to 'standard' arthritis patients and to 'high-risk' arthritis patients defined in terms of previous GI ulcers.

The full AGM produced results broadly in line with the simpler model.

Limitations of the calculations

There are substantive differences in the incremental costs per QALY results in this report compared with industry submissions. These differences reflect, principally, variations in parameter values for clinical GI events and MI risk. There are also key differences in the choice of comparator non-selective NSAIDs and costs, and whether cardiovascular risks are included within the model.

Conclusions

The COX-2 selective NSAIDs examined in this report (i.e. etodolac, meloxicam, celecoxib, rofecoxib, valdecoxib, etoricoxib and lumiracoxib) were found to be similar to non-selective NSAIDs for the symptomatic relief of RA and OA and to provide superior GI tolerability (the majority of evidence is in patients with OA). Although COX-2 selective NSAIDs offer protection against serious GI events (i.e. PUBs and POBs), the amount of evidence for this protective effect varied considerably across individual drugs. The volume of trial evidence with regard to cardiovascular safety also varied substantially between COX-2 selective NSAIDs. Increased risk of MI compared to non-selective NSAIDs was observed among those drugs with greater volume of evidence in terms of exposure in patient-years.

Economic modelling shows a wide range of possible costs per QALY gained in patients with OA and RA. Costs per QALY also varied if individual drugs were used in 'standard' or 'high'-risk patients, and according to the choice of non-selective NSAID comparator and whether that NSAID was combined with a PPI.

Need for further research

With reduced costs of PPIs, future primary research needs to compare the effectiveness and cost-effectiveness of COX-2 selective NSAIDs relative to non-selective NSAIDs with a PPI. Direct comparisons of different COX-2 selective NSAIDs, using equivalent doses, that compare GI and MI risk are needed. Pragmatic studies that include a wider range of people, including the older age groups with a greater burden of arthritis, are also necessary to inform clinical practice.

Chapter 1

Aims of the review

The aims of this review are four-fold:

- To undertake a systematic review of the clinical effectiveness and cost-effectiveness of cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drugs (NSAIDs), including etodolac, meloxicam celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib, for osteoarthritis (OA) and rheumatoid arthritis (RA).
- To assess the cost-effectiveness of COX-2 selective NSAIDs from an NHS perspective.
- To explore the potential impact of concomitant gastroprotective agents, with either COX-2 selective NSAIDs, or other non-selective NSAIDs, on the incidence of symptomatic gastrointestinal (GI) ulcers and complications such as bleeding, perforation or gastric outlet obstruction.
- To explore the impact of low-dose aspirin ($\leqslant$325 mg/day) used in conjunction with COX-2 selective NSAIDs on the incidence of cardiovascular (CV) adverse events and symptomatic upper gastrointestinal (UGI) ulcers and their complications.

Chapter 2
Background

The National Institute for Health and Clinical Excellence (NICE) Technology Appraisal Guidance No. 27 issued in July 2001 is referred to as the 'current NICE guidance' in this report.[1] This guidance covers celecoxib, rofecoxib, meloxicam and etodolac. The guidance no longer applies to rofecoxib following the voluntary worldwide withdrawal of this drug by Merck Sharp & Dohme in September 2004.

Following the safety review by the European Medicines Agency (EMEA), which confirmed the increase in CV risk associated with the use of COX-2 selective NSAIDs, NICE issued a document detailing the interpretation of the original guidance in January 2006 in response to the changes in the summaries of product characteristics for both COX-2 selective and non-selective NSAIDs associated with the EMEA review.[2] Readers should take note of these changes.

NSAIDs are effective analgesics used commonly for musculoskeletal disorders such as OA, RA, soft-tissue disorders, spinal pain, headaches (including migraine), menstrual disorders and postoperative pain. Sales of ibuprofen, available over the counter and the most widely used NSAID, have increased as sales of aspirin and paracetamol have fallen.[3] The volume of prescribed NSAIDs has also increased and costs of prescription NSAIDs have increased by one-quarter due to the use of COX-2 selective NSAIDs. UGI toxicity, especially gastric ulcers with complications such as haemorrhage and perforation, is an important public health problem that may be reduced by wider use of COX-2 selective NSAIDs. Current NICE guidance[1] recommends that COX-2 selective inhibitors:

1. should **not** be used
   (a) routinely in patients with OA and RA
   (b) in preference to non-selective NSAIDs in those with CV disease or those taking low-dose aspirin
   (c) in combination with gastroprotective agents as a means of further reducing potential GI adverse events
2. should be used in preference to non-selective agents in high-risk patients such as
   (a) those aged 65 years or above
   (b) those with serious co-morbidity
   (c) those taking other medications known to increase the likelihood of UGI adverse events
   (d) those needing prolonged therapy with NSAIDs at maximal doses
   (e) those with a history of previous gastric or duodenal ulcers, upper gut bleeding or perforation.

About 6% of those over 65 years of age receive NSAIDs for at least three-quarters of a given year and up to 40% of this population at least one prescription for an NSAID.[4] The annual cost of prescribed NSAIDs is around £200 million in England.[5]

Description of health problem

Osteoarthritis

OA is the commonest cause of musculoskeletal disability and joint replacement surgery. It may be defined as **a condition of synovial joints characterised by cartilage loss and evidence of an accompanying periarticular bone response**.[6] Definitions such as this – which need radiographic confirmation – ignore the clinical experience of OA and have limited clinical utility, especially in primary care where most patients are treated. Radiographic changes of OA at sites such as the spine are universal with ageing – age is the strongest determinant of radiographic, and clinical, OA. However, the dissonance of symptoms and radiographic change, and the difficulties of defining OA, make it hard to estimate prevalence with confidence. For instance, 15% of women between the ages of 55 and 64 years have knee pain and 7% have radiographic knee OA (but not necessarily any pain).[7]

OA causes joint pain – often aggravated by physical activity; joint stiffness or gelling – often after periods of inactivity; and joint swelling, deformity or enlargement. Patients might also experience creaking or crepitus in affected joints. Symptoms may arise as a result of joint injury, endocrine or metabolic disturbances and developmental or heritable factors. The spine, certain finger and thumb joints, acromio-

clavicular, hip, and knee joints are commonly affected by OA. Physical impairments due to OA vary greatly and depend, to a limited extent, on radiographic change: individual factors such as occupation, psychological adjustment and degree of social support all have a bearing.[8]

The goals of treating OA are to relieve symptoms and improve functional limitations. At present no treatment seems to have a convincing, and clinically relevant, benefit in terms of delaying the structural progression of established OA or of preventing the development of OA in new joints.[9,10] Education about OA and advice on behaviour change, such as diets for weight reduction, may be successful for some and could even reduce the rate of deterioration. Others may need medication, including analgesics and NSAIDs,[11] topical rubefacients, nutritional supplements and, occasionally, joint injections.[12] Physical therapy for muscle strengthening, walking aids and advice on appropriate exercises have an important role in clinical practice. For more advanced disease, especially involving the knee and hip, surgery, including joint replacement, may be needed.

Rheumatoid arthritis

RA is a systemic inflammatory disorder of unknown cause that mainly affects synovial joints. It has an annual incidence of 31 per 100,000 women and 13 per 100,000 men and a prevalence of 1.2% in women and 0.4% in men.[13] Disease incidence peaks in the sixth decade and RA is more common in women than men by a ratio of 2.5:1.[14]

RA is diagnosed from a constellation of clinical, laboratory and radiographic abnormalities. The disease can cause pain, swelling and stiffness in a variety of joints, including the hands, wrists, neck and large joints. Symptoms may begin within days or evolve over many weeks and are often worse in the morning. Other organ systems, such as the lungs, the pericardium, blood vessels and eyes, may be also be affected with a potential for severe disability, systemic ill-health and life-threatening complications, in some cases. The severity of disease is variable: for instance, in a community cohort 18% of patients were in remission, and on no treatment, after 3 years of follow-up. By contrast, nearly half had moderate disability at 3 years[15] and one-quarter had a joint replaced after around 20 years.[16]

The goals of treating RA are also to relieve symptoms and improve functional limitations. Additional goals, attainable for RA with drug therapy, include reduction of structural joint damage.[17] Drugs used for RA include NSAIDs, analgesics, corticosteroids, disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and tumour necrosis α inhibitors, in varying combinations. Orthopaedic surgery, including joint replacement and soft tissue procedures, may be necessary and many professionals allied to medicine contribute to the care of patients with RA.[18]

Outcome measures for rheumatoid arthritis and osteoarthritis

Assessing outcomes in RA and OA is best done by relying on patient reports,[9,19] although some outcome scales have key elements that encompass physician judgements about disease status. In both OA and RA, radiographic assessment of joint damage is also an important research tool: radiographic outcomes are better validated and accepted as relevant end-points in RA.

At least two self-completed questionnaires are used widely to assess pain, function and stiffness of knee and hip OA: the Lequesne and the Western Ontario and McMaster Universities (WOMAC) OA index; both combine responses in these three symptoms to yield a single measure. Many studies of OA also report pain alone or **patient global assessments**, using either a Likert scale or a 10-cm visual analogue scale (VAS). Global assessments may refer to overall disease status or response to a particular therapy. The latter allows patients and physicians to make an overall judgement about efficacy, taking into account adverse effects. Global outcome scores are also well validated, and are accepted by regulatory agencies.[9]

In RA joint pain, swelling, assessments of physical function, blood acute phase response and patient and physician global assessments have been combined, in various ways, to give composite measures of disease activity. Most widely used are the American College for Rheumatology percentage criteria – ACR20 referring to a 20% improvement in several disease measures – and the disease activity score (DAS) – which relies on a formula using several disease measures.[17]

Non-steroidal anti-inflammatory drugs

NSAIDs, by inhibiting the enzyme COX and reducing prostaglandin production, diminish inflammation and pain. Currently three forms of COX are known: COX-1, found in most normal

tissues including the GI tract, kidneys and platelets; COX-2, found particularly in the kidney, brain, bone and reproductive organs but increased substantially in any tissue with inflammation or injury; and COX-3, a newly identified COX found in highest concentrations in the brain and heart and possibly one of many isoenzymes of COX-1.[20]

At present only COX-1 and COX-2 are clinically relevant. COX-1 is regarded as a housekeeping enzyme responsible – through prostaglandins and thromboxane A2 – for physiological functions such as helping to protect gut mucosal integrity and vascular homeostasis by aiding vasoconstriction and platelet activation and clumping. COX-2 appears to be a more important mediator in inflammation and thus a key factor in arthritis pain. This is supported by clinical studies of COX-2 selective NSAIDs that reduced arthritis pain equally as well as non-selective NSAIDs, while reducing the risk of gut ulceration. However, concerns have been raised that suppression of COX-2 may inhibit beneficial inflammation and cause harm; for example, COX-2 expression found with *Helicobacter pylori* infection of the stomach, and gastric ulcers, may contribute to tissue repair.[21,22]

Classification of NSAIDs

Aspirin inhibits COX-1 irreversibly in platelets; these cells, lacking a nucleus, are unable to re-synthesise COX-1. In higher doses, aspirin is an effective analgesic but also inhibits COX-1 in the gut and increases the risk of UGI bleeding and ulcers greatly. The risk of GI haemorrhage with low-dose aspirin (<325 mg/day), used for preventing strokes and heart attacks, is 2.5% compared with 1.4% for placebo [odds ratio (OR) 1.7].[23]

NSAIDs differ in their ability to inhibit COX-2 and can be separated according to the ratio of COX-1 to COX-2 inhibition. Such distinctions relate, to some extent, to clinical GI toxicity seen in observational studies. However, higher doses used in practice – or a longer plasma half-life – may make laboratory assessments of COX-2 selectivity irrelevant, at least for older NSAIDs.[24] Older NSAIDs are, mostly, not selective for COX-2, although some, such as diclofenac, are similar to celecoxib and meloxicam in laboratory assays of COX-2 selectivity. Drugs, safer for the gut, tend to be given to people at higher risk of bleeding, and tend to have less favourable results in observational studies than might be expected.[25] As there is no consensus on the best way of defining COX-2 selectivity, an emphasis on overall clinical advantage for each drug seems sensible.[26,27]

COX-2 selective NSAIDs

Rofecoxib and valdecoxib have been withdrawn after the initial completion of this report (see the section 'Safety of COX-2 selective NSAIDs', p. 133). Lumiracoxib was launched in the UK in January 2006. The recommended dose for lumiracoxib for OA is 100 mg/day and for acute pain 400 mg/day (not exceeding 5 days) according to the Summary of Product Characteristics.

The licensed doses for OA and RA for each of the COX-2 selective NSAIDS considered in this report are summarised in *Table 1*.

TABLE 1 *Recommended and maximum daily doses for COX-2 selective NSAIDs*

Drug	OA (mg)		RA (mg)	
	Recommended	Maximum	Recommended	Maximum
Etodolac	600	600	600	600
Meloxicam	7.5	15	15	15
Celecoxib	200	400	200–400	400
Rofecoxib	12.5	25	25	25
Etoricoxib	60	60	90	90
Valdecoxib	10	20	10	20
Lumiracoxib[a]	100–200	200	Not licensed	Not licensed

[a] Company submission.
Source: BNF 46 (September 2003).

Toxicity of NSAIDs

Gastrointestinal disorders

Anorexia, heartburn, nausea, dyspepsia, diarrhoea and abdominal pain are common symptoms in the general population and often lead to consultation in primary care. Around 5–10% of the population seek advice from a GP for dyspepsia and 1% are referred to hospitals.[28,29] Use of NSAIDs increases the likelihood of dyspeptic symptoms and of using drugs for dyspepsia[30] – so, up to 26% of NSAID users take drugs for dyspepsia or to prevent peptic ulcers in community studies.[4]

Dyspeptic symptoms occur in 4.8% of NSAID-treated patients compared with 2.3% on placebo, in randomised trials (which are likely to include healthier subjects) and are the most common reason for cessation of therapy.[31] Dyspeptic symptoms are especially common with indomethacin and piroxicam and with higher doses of NSAIDs, but seem to be equally common with COX-2 selective and non-selective drugs, with prolonged use,[32] and are a poor predictor of peptic ulcers. Half of those investigated for dyspepsia have a normal endoscopy, 15% gastro-oesophageal reflux disease (GORD), 25% peptic ulcers and 2% malignancies. Endoscopic abnormalities are more likely in people over 45 years of age.[33,34]

Serious UGI events such as perforation or bleeding from gastric or duodenal ulcers occur in up to 2% of NSAID users, with an estimated 2000 deaths annually in the UK.[35] Bleeding and perforation are often not heralded by symptoms[36] and ulcers seen at endoscopy occur in over one-quarter of people taking ibuprofen and other non-selective NSAIDs, but less commonly with COX-2 selective NSAIDs.[37] Endoscopic lesions are a poor surrogate for upper gut bleeding or perforation: there are only limited data linking ulcers on endoscopy with these complications. This may be because the gut mucosa adapts to noxious insults such as NSAIDs.[38] There are also indications that NSAIDs may cause ulcers, bleeding, inflammation and scarring in the small intestine and colon although, in contrast to UGI bleeding, such events are much less common.[39]

Predictors of serious GI toxicity

In January 2006, NICE issued a document detailing the interpretation of the 2001 guidance following the EMEA safety review of COX-2 selective NSAIDs. A summary of key points of this document can be found in the section 'Current licensing status and NICE guidance', p. 134. Readers should take note of these changes.

NICE guidance No. 27, issued in 2001,[1] does not recommend routine use of COX-2 selective NSAIDs but gives situations in which they may be preferred to non-selective NSAIDs, and others in which COX-2 selective drug use would be inappropriate. A brief commentary on NICE 2001 guidance is given below.

- *People aged 65 years or above*
  Age is a continuous risk factor; thresholds for use at specific ages are, therefore, arbitrary and depend on appropriate judgements. Relative risks (RRs) for each decade, from 50 years, rise from 1.8 (compared with those under 50) in the 50s to 9.2 over the age of 80 years.[40]
- *For people with a past history of peptic ulcer*
  History of a peptic ulcer confers a higher risk of bleeding from the upper gut for NSAID users (COX-2 selective or otherwise) and non-users.[41] The RRs are rofecoxib 5.2 and naproxen 13.5.[42]
- *For people with other serious illnesses*
  The NICE 2001 guidance is rather imprecise and cites additional co-morbidity including CV disease, renal or hepatic impairments, diabetes and hypertension. Data on these factors are limited and potentially unreliable;[43] however, serious disability, for example from RA, is linked with a higher risk of UGI bleeding.[44]
- *For people also taking anticoagulants*
  Very high rates of GI haemorrhage have been reported for people using warfarin and NSAIDs; RRs exceed 6.0.[45,46]
- *For people also using corticosteroids*
  A consistently higher risk is noted for steroid users, but it is unclear whether this is because steroids tend to be used in sicker individuals, especially in RA. RRs vary between 2 and 6.[44,45]
- *For people using NSAIDs for prolonged periods*
  Since both OA and RA are incurable conditions, and assuming that an individual gains sustained benefit from an NSAID, use is likely to be prolonged. On this basis, many patients with RA and OA would qualify for COX-2 selective agents from the outset.[47] The risk at a particular time point appears similar, regardless of the duration of prior NSAID use,[41] but cumulative risk is likely to be greater with longer use. Some studies have indicated a higher risk of complications earlier during treatment[48] and the Celecoxib Long-term Arthritis Safety Study (CLASS) showed that GI events were rare with diclofenac after 3 months of treatment but continued to accrue with celecoxib.[49,50]
- *Not for use with GI protective agents in order to reduce adverse effects*
  A report from the Canadian Coordinating Office for Health Technology also does not recommend the routine use of COX-2 selective

inhibitors and gastroprotective agents, such as proton pump inhibitors (PPIs), as a way of reducing GI toxicity.[51] However, experience is that gastroprotective agents are often used with the goal of reducing dyspeptic symptoms – using pragmatic approaches, and allowing continued use of an NSAID, where there is worthwhile benefit – not necessarily to reduce UGI bleeds or ulcers.[51,52] UGI symptoms or use of gastroprotective agents does appear to be linked, modestly, to higher rates of GI complications (RR 1.8).[44]

- *Not for use with concomitant aspirin*
  Low-dose aspirin, alone or combined with COX-2 selective or with non-selective NSAIDs, increases the risk of endoscopic ulcers[53] and complications of ulcers,[54] perhaps to a greater extent with non-selective NSAIDs. However, large enough trials have not been done, so far, to determine whether COX-2 selective agents should be preferred to non-selective NSAIDs in aspirin users.

Preventing gastrointestinal toxicity due to NSAIDs

PPIs such as omeprazole and lansoprazole, misoprostol, a prostaglandin analogue, and double doses of histamine-2 receptor antagonists (H2RAs) (equivalent to ranitidine 300 mg twice daily) all reduce the risk of NSAID-induced gastric and duodenal ulcers (detected on endoscopy).[51] Standard doses of H2RAs (equivalent to ranitidine 150 mg twice daily) reduce the risk of duodenal ulcers but not gastric ulcers: the latter are a more important problem with NSAIDs; so, standard doses of H2RAs should not be used for preventing ulcers. Lansoprazole reduces the risk of ulcer complications in people who had developed ulcer complications, and who had *H. pylori* infection, while taking low-dose aspirin.[55] Only one study, the Misoprostol Ulcer Complications Outcome Safety Assessment (MUCOSA) trial, has investigated the role of prophylactic drug therapy (misoprostol 800 μg/day), used with NSAIDs, to prevent ulcer complications.[56] In MUCOSA the risk of ulcer complications was 0.57% with misoprostol and a variety of NSAIDs compared with 0.95% for placebo with NSAIDs, but 10% of patients on misoprostol had diarrhoea compared with 4% on placebo.

Direct comparisons of gastroprotective agents show that omeprazole and misoprostol are superior to standard dose ranitidine for preventing NSAID-induced gastric ulcers (omeprazole also prevents duodenal ulcers).[51] Again, more people given misoprostol withdrew because of abdominal pain and diarrhoea. Lansoprazole was equally effective at 15 or 30 mg[57] and omeprazole at 20 or 40 mg in these trials.[58]

A COX-2 selective NSAID (celecoxib) was compared against diclofenac and omeprazole (20 mg) in people with arthritis who had experienced a bleeding ulcer, in a recent randomised trial. The probability of further bleeding was similar with either approach – around 6% over 6 months. Many patients in this study had other illnesses: over 20% had abnormal renal function, at entry, and over 20% more than one previous episode of ulcer bleeding.[59] About 6% of patients developed renal failure (creatinine >200 μmol/litre). It is questionable whether some of these patients should have received any NSAID at all.

Helicobacter pylori and NSAIDs

The two most important factors related to peptic ulcer disease are *H. pylori* infection and NSAIDs, although the proportion of ulcers associated with neither of these is increasing,[60] and the proportion attributed to aspirin now exceeds that due to NSAIDs, in some studies.[61] It might be assumed that NSAIDs and *H. pylori*, together, magnify ulcer risk. This is unclear. Studies are inconsistent: some show that *H. pylori* infection reduces NSAID risk, perhaps because *H. pylori* increases prostaglandins;[61,62] others, that NSAIDs increase risk only in people with *H. pylori* infection who have not previously had NSAIDs.[60] *Post hoc* analysis of the Vioxx Gastrointestinal Outcomes Research (VIGOR) and CLASS studies, in which COX-2 selective NSAIDs were compared with other NSAIDs and evidence of *H. pylori* infection was sought, shows no clear relationship between signs of infection and ulcer complications.[44,63]

Cardiovascular and renal toxicity of NSAIDs

See the section 'Current status of COX-2 selective NSAIDs and emerging evidence' (p. 133) for updated information regarding the CV safety of NSAIDs.

Non-selective NSAIDs that inhibit COX-1 have anti-platelet effects similar to aspirin but, because inhibition is reversible, are unreliable at inhibiting vascular thromboses.[64] Increased COX-2 expression, seen in tissue inflammation, may help maintain patent blood vessels, by limiting the effects of platelet activation. This is suggested by studies showing that COX-2 inhibitors reduce the production of prostacyclin, an important vasodilator and inhibitor of platelet clumping.[21,65] These laboratory data and the occurrence of more CV events in RA patients treated with rofecoxib

compared with naproxen raised concerns about the CV safety of COX-2 selective NSAIDs.[66,67] Ibuprofen, but not diclofenac, antagonises the effect of aspirin and it has been suggested that it too may be hazardous in people at increased CV risk.[64] This has not, in general, been substantiated in observational studies of people with myocardial infarctions (MIs).[68,69]

Prostaglandins control renal blood flow, glomerular filtration rate and salt and water excretion by the kidney. NSAIDs may cause oedema, hypertension and renal failure and exacerbate heart failure in susceptible individuals. Both COX-1 and COX-2 are important in regulating renal blood flow and COX-2 selective NSAIDs do not have any advantages over non-selective agents in terms of renal toxicity or hypertension. Care is needed with NSAIDs, of all classes, in people on antihypertensives, the elderly and others at risk of renal diseases.[70]

Other adverse effects

Pfizer suspended the sale of valdecoxib in 2005 following Food and Drug Administration (FDA) and EMEA reviews that highlighted serious skin reactions associated with this drug (see the section 'Safety of COX-2 selective NSAIDs', p. 133).

A variety of other adverse effects such as skin rashes including photosensitivity, allergic reactions, mouth ulcers, headaches and tinnitus may occur with NSAIDs. Newer COX-2 selective NSAIDs (coxibs) belong to three distinct chemical classes: aryl methyl sulphones, including rofecoxib and etoricoxib, aryl sulphonamides, including celecoxib and valdecoxib, and carboxylic acids, including lumiracoxib. Sulphonamides commonly cause skin reactions – sometimes severe and life-threatening – which might account for more skin rashes seen with celecoxib and valdecoxib than with other NSAIDs.[50,71]

In about 10% of cases, asthma may be aggravated by NSAIDs and aspirin. Reports suggest that COX-2 selective NSAIDs may be safer than non-selective NSAIDs in aspirin-sensitive asthmatics.[72] NSAIDs, including COX-2 selective drugs, may also exacerbate inflammatory bowel diseases.[73]

Use of NSAIDs in osteoarthritis and rheumatoid arthritis

Guidelines for OA management recommend that analgesics, other than NSAIDs, are tried first, for pain.[74] However, as NSAIDs are more efficacious than paracetamol in OA trials, NSAIDs may be considered as initial therapy, if they were to be as safe[75] – and especially as most people are familiar with the effects of paracetamol. In practice, patients sometimes use NSAIDs only for brief periods, perhaps for short-lived exacerbations of pain, and many choose not to use any regular medication at all. Analyses of NSAID prescribing patterns in primary care indicate that patients frequently switch NSAIDs and often also use a gastroprotective agent.[76,77] This probably reflects the difficulties of pain management in some cases.

Experts do not recommend NSAIDs as sole therapy in RA since other drugs may reduce the risk of joint damage.[78] Patients with RA are twice as likely as patients with OA to experience complications of NSAIDs, perhaps because of greater levels of disability, co-morbidity or concomitant steroid use.[78] In practice, effective disease management with DMARDs may allow cessation or reduction in use of NSAIDs and steroids, but some patients remain dependent on full doses of NSAIDs for many years.

Current use of NSAIDs

The prescribing pattern of NSAIDs has inevitably been changed since the initial completion of this report, because of the withdrawal of rofecoxib and valdecoxib and the EMEA safety review of COX-2 selective NSAIDs.

Prescribing of NSAIDs in primary care in England has shown little change during 2000–4: the key change is an increase in use of COX-2 selective NSAIDs, such that nearly one-quarter of all NSAID prescriptions are for COX-2 selective NSAIDs and these drugs account for half of all NSAID costs.[5] Diclofenac, ibuprofen and naproxen, in that order, are the most widely prescribed non-selective NSAIDs; prescribing volumes for diclofenac have increased slightly in recent years whereas prescribing for ibuprofen has declined.

Data from the Prescription Pricing Authority in 2002 indicate that rofecoxib was the most frequently prescribed COX-2 selective agent.[5] The indications for the use of NSAIDs cannot be ascertained from these data but primary care surveys show, unsurprisingly, the use of NSAIDs for a wide variety of indications. Audits of routine practice indicate that adherence to NICE guidance is poor, particularly in terms of underutilisation of COX-2 selective agents in relevant circumstances but also use in patients not meeting guidance.[47,79] Overall, it appears that strict adherence to current NICE guidance could lead to a substantial increase in the use of COX-2 selective NSAIDs.[47]

Chapter 3

Review of previous systematic reviews on COX-2 selective NSAIDs

The searches for this review of systematic reviews were carried out in November 2003.

At the time of writing of this report in 2004, a number of published systematic reviews have reported on the efficacy and safety of COX-2 selective NSAIDs in patients with RA or OA. A review of these previous systematic reviews was therefore undertaken.

Several systematic reviews were identified from searches (see Appendix 1). Reviews were included if they fulfilled the following criteria:

- reported a search strategy
- addressed one or more of the COX-2 selective NSAIDs included in this report
- reported results numerically [either in the form of a qualitative or quantitative (e.g. meta-analysis) synthesis].

In addition to traditional systematic reviews, a number of 'pooled analyses' were identified, many of which appeared to use individual patient data from trials.[32,80–111] These pooled analyses tended to provide little or no detail of trial search methods and criteria for selection of included trials and often failed to identify individual trials clearly. Therefore, these pooled analyses were judged to be open to major bias and were therefore excluded from this review.

Twenty English language systematic reviews meeting our inclusion criteria were found.[53,112–130] Two foreign language systematic reviews were not included due to difficulties in obtaining the references within the project time frame.[131,132] Three aspects of these reviews were assessed in detail:

- characteristics, that is, drug(s) examined
- trials included, patient population and outcomes assessed
- quality of the review; results of the review for key efficacy and safety outcomes, where possible in the form of a pooled numerical mean estimate and 95% confidence interval (CI).

A detailed overview of the characteristics, quality and findings of the included systematic reviews is provided in Appendix 1.

In summary, the findings of this review of existing systematic reviews are as follows:

- Systematic reviews of the safety and efficacy of meloxicam, etodolac, celecoxib, rofecoxib and valdecoxib were identified. No published systematic reviews for etoricoxib or lumiracoxib were identified.
- The findings of these reviews are remarkably consistent despite differences in quality, methods and inclusion criteria.
- COX-2 selective NSAIDs were, in general, superior to placebo and had comparable efficacy to non-selective NSAIDs for RA and OA.
- COX-2 selective NSAIDs and placebo had similar rates of withdrawal due to adverse effects (including withdrawals due to GI symptoms).
- Compared with placebo, some reviews suggested that COX-2 selective NSAIDs had similar rates of ulcers on endoscopy and PUBs, although data are limited and there are concerns about the overall quality of reviews.
- Compared with non-selective NSAIDs, reviews showed that selective NSAIDs had a reduced incidence of withdrawal due to adverse effects including GI adverse effects, ulcers on endoscopy and PUBs.
- Reviews suggested an increased risk of CV events with COX-2 selective NSAIDs.
- More recent and better quality systematic reviews also suggest important differences in safety for COX-2 selective NSAIDs related to dose, treatment duration and comparator non-selective NSAID.

Chapter 4

Clinical effectiveness

Methods

Protocol

This systematic review was undertaken in accord with the protocol published on the NICE website in November 2003. The methods for the identification of previous systematic reviews and meta-analyses are discussed in Chapter 3 and Appendix 1.

Search strategy

The following sources were searched:

- Bibliographic databases: Cochrane Library (CENTRAL) 2003 Issue 4, MEDLINE (Ovid) 1966–October 2003, MEDLINE in Process and Other Non-Indexed Citations (Ovid) 4 and 11 November 2003 and EMBASE (Ovid) 1980–October 2003. Index and text words representing the drug names were combined with terms for osteoarthritis and rheumatoid arthritis. A filter to identify clinical trials was incorporated as appropriate (see Appendix 2, for full details).
- Internet sites of EMEA and the FDA.
- Citations of relevant studies.
- Contact with experts.
- Invited pharmaceutical company submissions to NICE (both 2004 and 2000).

Because of the broader inclusion criteria of this review relative to the previous assessment report undertaken by NICE, databases were searched from their inception date for all drugs. Searches were not restricted by language. Industry submissions were also searched for both published and unpublished studies.

Inclusion and exclusion criteria

Studies were included if they met the following criteria:

- Study design: randomised controlled trials (RCTs) with duration of treatment $\geq$2 weeks (no restriction on patient numbers).
- Population: patients with OA or RA; other forms of arthritis were excluded.
- Intervention: COX-2 selective NSAIDs (i.e. celecoxib, rofecoxib, meloxicam, etodolac, etoricoxib, valdecoxib and lumiracoxib) with or without concomitant medication. Trials including licensed and supra-licensed doses were considered.
- Comparator: placebo, non-selective NSAIDs or direct comparisons between COX-2 selective NSAIDs.

The following categories of studies were excluded: dose-finding studies of COX-2 selective NSAIDs without a comparator, trials published only as abstracts (pharmaceutical companies were contacted to seek unpublished data in full) and trials that included only sub-therapeutic doses of COX-2 selective NSAIDs.

Based on these inclusion criteria, study selection was carried out independently by two reviewers. Disagreements were resolved by discussion. A third reviewer (PJ) was consulted when disagreements persisted after discussion. Agreement on study selection between reviewers was judged to be 'good' (weighted Cohen's kappa 0.78, 95% CI 0.74 to 0.82). Reviewers were not blinded to any features of the report including authorship; however, inclusion and exclusion decisions were made prior to detailed scrutiny of results.

Data extraction strategy

Data from included trials were extracted by one reviewer using a standard data extraction form and independently checked by another reviewer. Results were extracted, where possible, for the intention-to-treat (ITT) population as raw numbers plus any summary measures with standard deviations, CIs and *p*-values. Discrepancies were resolved by discussion.

Full trial reports were given primacy over published trial reports and, where possible, the published trial report results were cross-checked.

Quality assessment strategy

The methodological quality of included studies was assessed on the basis of randomisation, adequate concealment of randomisation, level of blinding, use of ITT analysis, and description

of loss to follow up. An overall quality score (Jadad) was assigned to each study. Quality was assessed by a single reviewer and checked by a second. Disagreements were resolved by discussion, with reference to a third party where necessary.

Data reporting and synthesis

The population characteristics, interventions and methodological quality of all included studies, and for each COX-2 selective NSAID, were tabulated.

The following outcomes were selected for data synthesis:

- *Effectiveness*
  OA trials: patient's assessment of pain due to arthritis assessed on a VAS or WOMAC subscale for pain where the former was not available; patient global assessment of response to therapy or disease status where the former was not available; and withdrawals due to lack of efficacy.
  RA trials: patient's assessment of VAS pain due to arthritis (or WOMAC pain subscale where the former was not available); ACR-20; patient global assessment of response to therapy or disease status where the former was not available; and withdrawals due to lack of efficacy.

- *Tolerability outcomes*
  For OA and RA trials: total adverse events; GI-specific adverse events (including clinical and complicated upper GI events); withdrawals due to adverse events; withdrawals due to GI-specific adverse events; and all withdrawals (for any reason).

- *Safety outcomes*
  For OA and RA trials: endoscopically confirmed GI ulcers; complicated UGI events [perforation, obstruction or bleed (POB)]; symptomatic UGI ulcers and complicated UGI events combined [perforation, ulcer or bleed (PUB)]; MI; and serious cardiovascular thrombotic events.

We experienced substantial difficulties in event classification and ascertainment, particularly in relation to POBs and PUBs during initial data extraction and analysis. We have subsequently developed algorithms (shown in Appendix 3) and re-checked the data for POBs and PUBs to ensure that our approach is consistent across trials as much as possible.

Given the policy basis of this report, the reporting and discussion of evidence focus on the benefits and harms of COX-2 selective NSAIDs relative to non-selective NSAIDs. To reflect this, in the results tables, placebo trials results are shaded in the tables and not discussed in the text of the report. Since not all trials have reported all the outcomes, the tables and figures for each outcome include only the trials for which the results of the specific outcome were reported.

Standard meta-analytic methods were used to pool data. Binary outcomes were expressed as RRs and pooled using the Mantel–Haenszel method. For continuous outcomes, the mean difference between baseline and follow-up was compared between pairs of treatment groups. Mean differences were pooled as weighted mean differences, weighted for variance. Where statistically significant heterogeneity was indicated (i.e. $p < 0.10$), outcomes were pooled using the DerSimonian Laird random effects approach and heterogeneity explored using meta-regression.[133,134] Where trials reported only a mean variance at baseline and follow-up, the baseline–follow-up mean difference variance was imputed assuming an intercorrelation coefficient of 0.50.[135]

For the purposes of economic modelling, we sought an overall pooled estimate of effect of each COX-2 drug. Trials outcome data were therefore pooled across trials, drug doses, follow-up and arthritis indication. The reasons for this were, first, that the effect of COX-2 selective drugs appears to be equivalent across arthritis indications[125,130] and, second, pilot meta-regression analyses for celecoxib showed that the duration of trial follow-up, dose and arthritis indication were not independent predictors of the effect of drug efficacy and safety (see Appendix 4). However, where possible, pooled results stratified by drug dose and arthritis indication are presented. Pooled results stratified by comparator NSAIDs are also presented for PUBs, POBs and MI. Where trials randomised patients to more than one dose of COX-2 or NSAID, results from the eligible arms were combined into a single estimate for inclusion in the meta-analysis.

Summary statistics are presented with 95% CIs throughout. Statistically significant results ($p \leq 0.05$) are *italicised* in the results tables. All analyses were undertaken using Microsoft Excel and Stata versions 7 and 8.

TABLE 2 *COX-2 selective NSAIDs – summary of number of identified RCTs*

	Included RCTs	Additional RCTs identified	Comments
Etodolac	29	0	A complete list of company-sponsored trial was not available
Meloxicam	16	11	RCTs were available in abstract or synopsis form at the time of this review. Company provided data for 10 of the trials and these were included in a sensitivity analysis
Celecoxib	40	9	Company identified nine RCTs. Trial reports were not available at time of this review
Rofecoxib	27	5	Poster presentations or part trial reports of RCTs were available at time of this review
Etoricoxib	7	3	Poster presentations or part trial reports of RCTs were available at time of this review
Valdecoxib	11	0	
Lumiracoxib	15	0	
Total	131[a]	28[b]	

[a] There were 14 head-to-head trials in which two COX-2 selective NSAIDs were compared against each other. The number of trials for each individual drug totals 145 as the head-to-head trials would have been counted twice.
[b] Details of the trials are listed in Appendix 5.

Results

Quantity of research available

Sensitive rather than specific search strategies were used and therefore a large number of publications were identified. Many of these could be excluded on the basis of title or abstract and, after detailed review of full papers and identification of duplicate publication, a total of 131 relevant RCTs (but see the footnote to *Table 2*) were included: 29 for etodolac, 16 for meloxicam, 40 for celecoxib, 27 for rofecoxib, seven for etoricoxib, 11 for valdecoxib and 15 for lumiracoxib (see *Figure 1*). Within these trials there were 14 that compared two COX-2 selective drugs directly: six trials compared rofecoxib with celecoxib, five compared celecoxib with lumiracoxib, two compared rofecoxib with lumiracoxib and one compared rofecoxib with valdecoxib.

Some RCTs that met inclusion criteria were not included as they were not available either as full publications or as full reports from industry at the time of this systematic review (see *Table 2* and Appendix 5).

Etodolac

Description of included trials

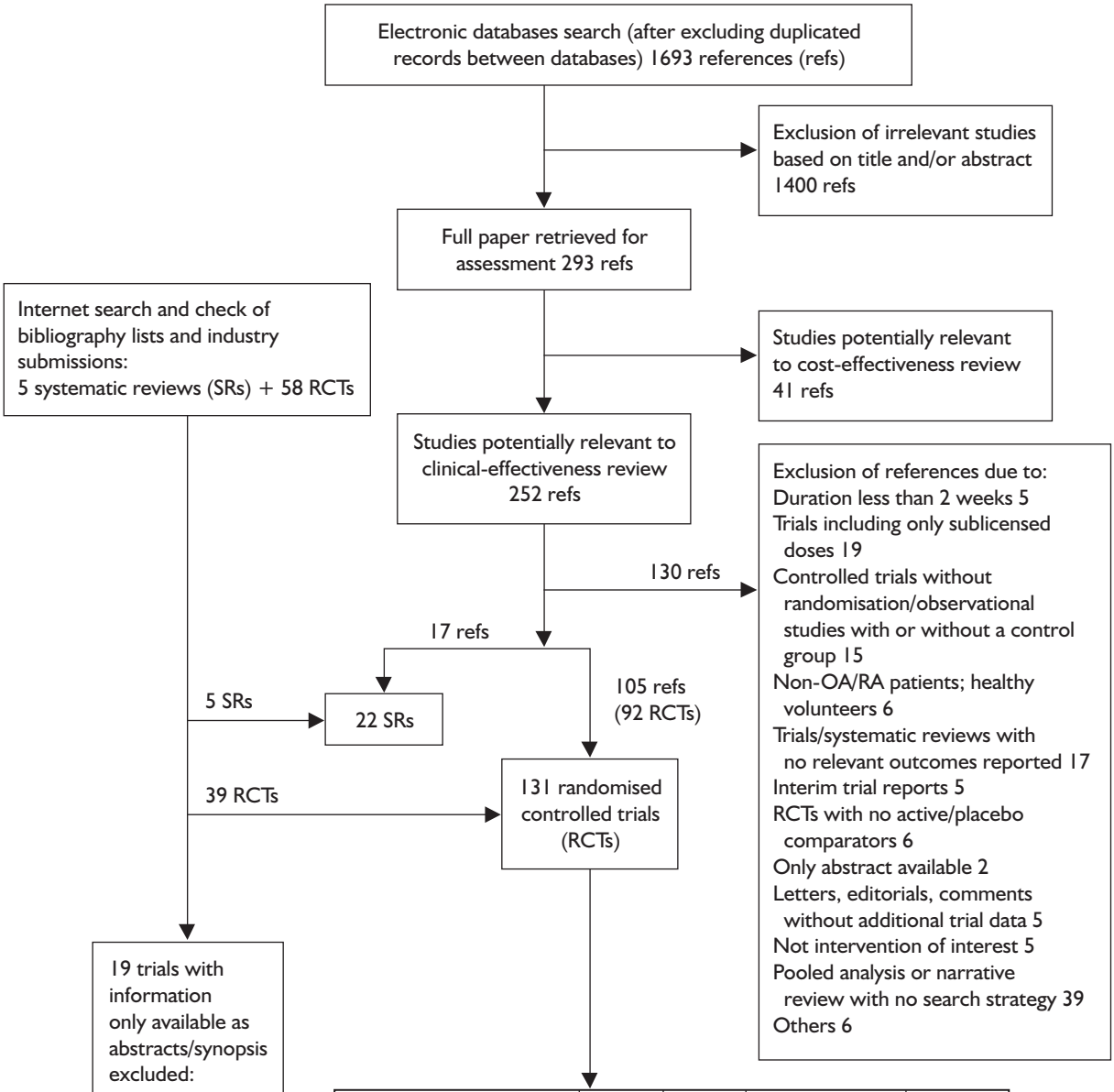
Twenty-nine trials of etodolac recruiting a total of 5775 participants met inclusion criteria. Only four trials had placebo controls; various non-selective NSAIDs were used as comparators (naproxen 10, piroxicam 7, diclofenac 4, indomethacin 2, tenoxicam 2, ibuprofen 1, nabumetone 1, nimesulide 1). Full details of the 29 trials are outlined in Appendix 6 and summarised in *Table 3*. Sample sizes of trials ranged from 20 to 1446 (median 120) patients. Nineteen of the trials had a sample of less than 200 patients. All but one trial had duration of treatment ≤3 months. The only long-term trial, which compared etodolac 300 or 1000 mg/day with ibuprofen 2400 mg/day in RA patients, lasted 3 years.

Patient characteristics

Twenty-four trials recruited exclusively OA patients and five trials RA patients. The mean age of patients was between 48 and 71 years. Many of the studies excluded patients with a history of peptic ulcers. The majority (22 out of 27) of the trials were published more than a decade ago (prior to 1995) and therefore information in relation to *H. pylori* and low-dose aspirin was scant.

Assessment of the quality of included trials

Only two trials were judged to be of good quality (Jadad score 5). Seven trials scored only 2 on the Jadad scale due to poor reporting of trial methodology. The quality of included trials is summarised in Appendix 7.



No. of included trials	OA	RA	OA and RA	Total
Etodolac	24	5	0	29
Meloxicam	12	4	0	16
Celecoxib	27[a]	6[b]	7	40[a,b]
Rofecoxib	23[c]	4	0	27[c]
Etoricoxib	4	2	1	7
Valdecoxib	6[d]	4	1	11[d]
Lumiracoxib	9[e]	6[f]	0	15[e,f]
Total	93	29	9	131

[a] Six of the trials had a rofecoxib arm and three of the trials had a lumiracoxib arm.
[b] Two of the trials had a lumiracoxib arm.
[c] Six of the trials had a celecoxib arm, two had a lumiracoxib arm and one had a valdecoxib arm.
[d] One trial had rofecoxib arm.
[e] Three of the trials had a celecoxib arm and two of the trials had a rofecoxib arm.
[f] Two of the trials had a celecoxib arm.

FIGURE 1 *Flow diagram for identified trials*

Assessment of etodolac efficacy

The efficacy results across trials are summarised in *Table 4*. It was not possible to carry out meta-analyses for several efficacy outcomes because of the variations in the assessment methods used and poor reporting of the variance of outcome measures.

Patient's assessment of arthritis pain

Etodolac was equivalent to non-selective NSAIDs for pain relief in OA patients. One RA trial observed no significant difference between etodolac 600 mg/day and indomethacin 100 mg/day.

Patient's assessment of global efficacy

Etodolac was equally efficacious compared with non-selective NSAIDs.

ACR-20 responder

No trial reported ACR-20 outcome.

Withdrawals due to lack of efficacy

Etodolac was associated with similar levels of withdrawals due to lack of efficacy compared with non-selective NSAIDs.

Etodolac tolerability

Adverse events

Compared with non-selective NSAIDs, etodolac was associated with a lower risk of all adverse events and GI adverse events (*Table 5*).

Withdrawals

There was no difference between etodolac and non-selective NSAIDs for withdrawals due to adverse events, GI adverse events and for all causes (*Table 6*).

Safety of etodolac

Endoscopic ulcers

One trial reported no difference in endoscopic ulcers between etodolac and non-selective NSAIDs (*Table 7*).

Clinical UGI events (PUBs) and complicated UGI events (POBs)

Compared with non-selective NSAIDs, etodolac appears to be associated with fewer PUBs (RR 0.32, 95% CI 0.15 to 0.71; number-needed-to-treat (NNT), RR 74, 95% CI 59 to 174). Given the small number of events reported, it was not possible to assess the impact of etodolac on POBs (*Table 7*, *Figures 2* and *3*).

Myocardial infarctions and serious cardiovascular thrombotic events

No trials reported the risk of MI. Only two trials reported a total of six serious CV thrombotic events (two events in the etodolac group versus four events in the NSAID groups).

A summary of serious CV thrombotic events for etodolac versus placebo or NSAIDs is given in *Table 8*.

Subgroup analyses

Few trials reported the results of subgroup analysis. Williams and colleagues[138] reported a slightly higher risk of adverse events in patients older than 65 years in both etodolac and placebo groups.

Impact of concomitant gastroprotective agents

No trials addressing this issue were identified.

Summary

Based on the systematic review and meta-analyses, it is concluded that:

- Twenty-nine RCTs were included. Studies compared etodolac (600–1000 mg/day) with either placebo or non-selective NSAIDs (naproxen, piroxicam, diclofenac, indomethacin, tenoxicam, ibuprofen, nabumetone or nimesulide). Twenty-four trials were exclusively in OA patients and five trials in RA patients.
- Only two trials were judged to be of good quality (Jadad score 5).
- Etodolac is of equivalent efficacy to non-selective NSAIDs.
- Etodolac was associated with a lower risk of all adverse events than non-selective NSAIDs.
- Withdrawals due to adverse events, GI adverse events and for all causes were equivalent between etodolac and non-selective NSAIDs.
- Compared with non-selective NSAIDs, etodolac appears to be associated with fewer PUBs. Given the small number of events reported, it is not possible to assess the impact of etodolac on POBs.
- There is no trial evidence to assess the effects of etodolac on MI.
- There is insufficient trial evidence to comment on the GI safety of etodolac in high-risk patients, those taking low-dose aspirin or anticoagulants or according to *H. pylori* status.
- There is no trial evidence comparing etodolac with non-selective NSAIDs with a GI-protective agent.

TABLE 3 *Characteristics and quality of included etodolac RCTs*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Etodolac	Placebo	NSAID	Efficacy[a]	Safety[a]		
Bacon, 1990a[136,137]	OA (knee)	600 mg/day (300 mg b.d.) (n = 70)	–	Naproxen 1000 mg/day (500 mg b.d.) (n = 73)	Pain, patient's global assessment	–	6	2
Bacon, 1990b[136,137]	OA (knee)	600 mg/day (300 mg b.d.) (n = 170)	–	Piroxicam 20 mg/day (20 mg o.d.) (n = 165)	Pain, patient's global assessment	–	12	2
Bacon, 1990c[136,137]	OA (knee)	600 mg/day (200 mg t.d.s.) (n = 98)	–	Diclofenac 150 mg/day (50 mg t.d.s.) (n = 106)	Pain, patient's global assessment	–	8	2
Williams, 1989[138]	OA (knee, hip)	Knee 600 mg/day (300 mg b.d.) (n = 50) Hip 600 mg/day (300 mg b.d.) (n = 54)	Knee n = 54 Hip n = 52	–	Patient's global assessment	Withdrawal due to AE, total withdrawal, dyspepsia, total AE, withdrawals due to GI AE	4	3
Freitas, 1990[139]	OA (knee)	600 mg/day (300 mg b.d.) (n = 33)	–	Piroxicam 20 mg/day (20 mg o.d.) (n = 32)	Patient's global assessment	Withdrawal due to AE, total withdrawal, total CV thrombotic, withdrawal due to GI AE	8	4
Astorga Paulsen, 1991[143]	OA (knee)	600 mg/day (300 mg b.d.) (n = 112)	–	Piroxicam 20 mg/day (20 mg o.d.) (n = 108)	Pain, patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, POBs, dyspepsia, total CV thrombotic	8	3
Brasseur, 1991[140]	OA (knee)	600 mg/day (300 mg b.d.) (n = 32)	–	Diclofenac SR 100 mg/day (100 mg o.d.) (n = 29)	Patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia, total AE, withdrawals due to GI AE	6	4
Karbowski, 1991[141]	OA (knee)	600 mg/day (300 mg b.d.) (n = 31)	–	Indomethacin 150 mg/day (50 mg t.d.s.) (n = 33)	Pain, patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, POBs, dyspepsia, total AE	6	3
Palferman, 1991[142]	OA (knee)	600 mg/day (300 mg b.d.) (n = 29)	–	Naproxen 1000 mg/day (500 mg b.d.) (n = 27)	Patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia, withdrawals due to GI AE	6	4

continued

TABLE 3 *Characteristics and quality of included etodolac RCTs (cont'd)*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Etodolac	Placebo	NSAID	Efficacy[a]	Safety[a]		
Pena, 1991[144]	OA (knee)	600 mg/day (300 mg b.d.) (n = 31)	–	Naproxen 1000 mg/day (500 mg b.d.) (n = 31)	Patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, total AE	8	3
Perpignano, 1991[145]	OA (knee, hip)	600 mg/day (600 mg o.d.) (n = 10)	–	Naproxen 750 mg/day (750 mg o.d.) (n = 10)	Patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, ulcer (endoscopic), PUBs, total AE, withdrawals due to GI AE	4	4
Dick, 1992[146]	OA (knee)	600 mg/day (300 mg b.d.) (n = 57)	–	Piroxicam 20 mg/day (20 mg o.d.) (n = 59)	Patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia, total AE, withdrawals due to GI AE	6	3
Grisanti, 1992[147]	OA (knee)	600 mg/day (200 mg t.d.s.) (n = 85)	–	Diclofenac 150 mg/day (50 mg t.d.s.) (n = 87)	Pain, patient's global assessment	Withdrawal due to AE, total withdrawal, total AE	8	3
Waterworth, 1992[148]	OA (knee)	600 mg/day (300 mg b.d.) (n = 28)	–	Piroxicam 20 mg/day (20 mg o.d.) (n = 29)	Pain, patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia, PUBs, POBs	6	3
Burssens, 1993[149]	OA (knee)	600 mg/day (600 mg slow-release o.d.) (n = 37)	–	Tenoxicam 20 mg/day (20 mg o.d.) (n = 36)	Patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, total AE	4	2
Eisenkolb, 1993[150]	OA (knee)	600 mg/day (200 mg t.d.s.) (n = 66)	–	Diclofenac 150 mg/day (50 mg t.d.s.) (n = 69)	Patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, total CV thrombotic, total AE, withdrawals due to GI AE	6	3
Chikanza, 1994[151]	OA (knee, hip)	600 mg/day (300 mg b.d.) (n = 39) for 4 weeks	–	Naproxen 1000 mg/day (500 mg b.d.) (n = 37) for 4 weeks	Pain, patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, total AE	4 × 2 (8 weeks)	4

continued

TABLE 3 *Characteristics and quality of included etodolac RCTs (cont'd)*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Etodolac	Placebo	NSAID	Efficacy[a]	Safety[a]		
Lucker, 1994[152]	OA (knee)	600 mg/day (300 mg b.d.) (n = 99)	–	Nimesulide 200 mg/day (100 mg b.d.) (n = 100)	Pain, patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, total AE	12	5
Perpignano, 1994[153]	OA (knee, hip)	600 mg/day (600 mg slow-release o.d.) (n = 60)	–	Tenoxicam 20 mg/day (20 mg o.d.) (n = 60)	Pain, patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, total AE	8	5
Dore, 1995[154]	OA (knee)	800 mg/day (400 mg b.d.) (n = 86)	n = 86	Naproxen 1000 mg/day (500 mg b.d.) (n = 82)	Patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, POBs, dyspepsia, total AE, withdrawals due to GI AE	4	4
Schnitzer, 1995[155]	OA (knee)	800 mg/day (400 mg b.d.) (n = 91)	n = 90	Nabumetone 1500 mg/day (1500 mg o.d.) (n = 89)	Patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia	4	4
Jennings, 1997[156]	OA (foot, ankle)	800 mg/day (400 mg b.d.) (n = 29)	–	Naproxen 1000 mg/day (500 mg b.d.) (n = 31)	–	Withdrawal due to AE, total AE	5	2
Rogind, 1997[157]	OA (knee, hip)	600 mg/day (300 mg b.d.) (n = 138)	–	Piroxicam 20 mg/day (20 mg o.d.) (n = 133)	Patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, POBs, total CV thrombotic, total AE	8	4
Schnitzer, 1997[158]	OA (knee)	800 mg/day (400 mg b.d.) (n = 106) 200 mg q.d.s. (n = 105)	n = 104	Naproxen 1000 mg/day (500 mg b.d.) (n = 109)	Patient's global assessment, withdrawal due to lack of efficacy	Total withdrawal, PUBs, total AE	4	4
Taha, 1989[159,160]	RA	600 mg/day (300 mg b.d.) (n = 15)	–	Naproxen 1000 mg/day (500 mg b.d.) (n = 15)	Pain, patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, ulcer (endoscopic)	4	2

continued

TABLE 3 *Characteristics and quality of included etodolac RCTs (cont'd)*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Etodolac	Placebo	NSAID	Efficacy[a]	Safety[a]		
Delcambre, 1990[339]	RA	600 mg/day (200 mg t.d.s.) (n = 50)	–	Indomethacin 100 mg/day (25 mg b.d. and 50 mg o.d.) (n = 52)	Spontaneous global pain (VAS, 100 mm), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, total AE	6	4
Taha, 1990[160,162]	RA	600 mg/day (300 mg b.d.) (n = 14)	–	Naproxen 1000 mg/day (500 mg b.d.) (n = 13)	Patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal	4	2
Lightfoot, 1997[163]	RA	400 mg/day (200 mg b.d.) (n = 140) 600 mg/day (300 mg b.d.) (n = 147)	–	Piroxicam 20 mg/day (20 mg o.d.) (n = 139)	Patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, POBs, dyspepsia	12	3
Neustadt, 1997[164]	RA	300 mg/day (150 mg b.d.) (n = 620) 1000 mg/day (500 mg b.d.) (n = 409)	–	Ibuprofen 2400 mg/day (600 mg q.d.s.) (n = 417)	Patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, dyspepsia	156 (3 years)	3

[a] Only the outcomes which were included in meta-analyses are listed.
AE, adverse events; b.d., twice daily; o.d., once daily; q.d.s., four times daily; t.d.s., three times daily.

TABLE 4 *Summary of efficacy results for etodolac versus placebo and NSAIDs*

	Placebo				NSAIDs			
	Pain difference: mean (95% CI)	**Global efficacy difference: mean (95% CI)**	**ACR-20: RR (95% CI)**	**Withdrawals due to lack of efficacy: RR (95% CI)**	**Pain difference: mean (95% CI)**	**Global efficacy difference: mean (95% CI)**	**ACR-20: RR (95% CI)**	**Withdrawals due to lack of efficacy: RR (95% CI)**
600 mg/day	[1][a]	[1][a]	No trials	No trials	2.06 (–2.09 to 6.22) [2]	–0.08 (–0.25 to 0.09) [3]	No trials	1.10 (0.76 to 1.61) [15]
>600 mg/day	[3][a]	[3][a]	No trials	*0.29 (0.18 to 0.45)* [3]	[4][a]	No difference or etodolac better [4][a]	No trials	0.97 (0.80 to 1.17) [4]
OA only	[4][a]	[4][a]	No trials	*0.29 (0.18 to 0.45)* [3]	2.06 (–2.09 to 6.22) [2]	–0.00 (–0.22 to 0.22) [2]	No trials	1.14 (0.72 to 1.78) [13]
RA only	No trials	No trials	No trials	No trials	[1][a]	–0.20 (–0.46 to 0.06) [1]	No trials	0.97 (0.81 to 1.17) [3]
All trials	[4][a]	[4][a]	No trials	***0.29 (0.18 to 0.45)*** **[3]**	**2.06 (–2.09 to 6.22) [2]**	**–0.08 (–0.25 to 0.09) [3]**	No trials	**1.00 (0.85 to 1.19) [16]**

[a] Insufficient data for meta-analysis; [ ] number of trials.

TABLE 5 *Summary of adverse events for etodolac versus placebo and NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	**NSAIDs: RR (95% CI) [*N* trials]**
All adverse events		
600 mg/day	1.47 (0.86 to 2.52) [1]	*0.76 (0.60 to 0.95)[a] [9]*
>600 mg/day	1.38 (0.95 to 2.00)[a] [2]	1.00 (0.86 to 1.17) [3]
OA only	*1.43 (1.19 to 1.73) [3]*	0.85 (0.71 to 1.01)[a] [11]
RA only	Not reported	0.62 (0.34 to 1.14) [1]
All trials	***1.43 (1.19 to 1.73) [3]***	***0.83 (0.70 to 0.99)[a] [12]***
GI adverse events		
600 mg/day	1.53 (0.78 to 3.01) [1]	*0.68 (0.53 to 0.87) [8]*
>600 mg/day	*1.93 (1.12 to 3.34) [1]*	1.38 (0.85 to 2.24) [1]
OA only	*1.75 (1.15 to 2.68) [2]*	0.77 (0.55 to 1.08)[a] [9]
RA only	Not reported	Not reported
All trials	***1.75 (1.15 to 2.68) [2]***	**0.77 (0.55 to 1.08)[a] [9]**

[a] Significant ($p < 0.10$) statistical heterogeneity – random effects meta-analysis.

TABLE 6 *Summary of withdrawals for etodolac versus placebo and NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
All adverse event withdrawals		
600 mg/day	1.22 (0.39 to 3.88) [1]	0.89 (0.69 to1.16) [17]
>600 mg/day	0.89 (0.54 to 1.48) [3]	0.96 (0.74 to 1.25) [5]
OA only	0.94 (0.59 to 1.49) [4]	0.94 (0.74 to 1.20) [19]
RA only	Not reported	0.90 (0.68 to 1.20) [3]
All trials	**0.94 (0.59 to 1.49) [4]**	**0.93 (0.77 to 1.12) [22]**
All GI withdrawals		
600 mg/day	1.02 (0.26 to 3.97) [1]	0.99 (0.56 to 1.75) [7]
>600 mg/day	0.33 (0.01 to 8.07) [1]	0.32 (0.01 to 7.70) [1]
OA only	0.83 (0.24 to 2.83) [2]	0.95 (0.54 to 1.65) [8]
RA only	Not reported	Not reported
All trials	**0.83 (0.24 to 2.83) [2]**	**0.95 (0.54 to 1.65) [8]**
All withdrawals		
600 mg/day	Not reported	0.96 (0.80 to 1.14) [17]
>600 mg/day	*0.50 (0.39 to 0.65) [3]*	0.98 (0.91 to 1.06) [4]
OA only	*0.50 (0.39 to 0.65) [3]*	1.01 (0.84 to 1.20) [18]
RA only	Not reported	0.96 (0.89 to 1.03) [3]
All trials	***0.50 (0.39 to 0.65) [3]***	**0.97 (0.90 to 1.05) [21]**

TABLE 7 *Summary of endoscopic GI ulcers and clinical and complicated UGI events (PUBs and POBs) for etodolac versus placebo or NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
Endoscopic GI ulcers	Not reported	
600 mg/day		0.50 (0.05 to 4.67) [1][a]
>600 mg/day		Not reported
OA only		0.50 (0.05 to 4.67) [1][a]
RA only		[a]
All trials		**0.50 (0.05 to 4.67) [1][a]**
PUBs		
600 mg/day	No trials	*0.33 (0.12 to 0.94) [6]*[141,143,145,148,157,163 a]
>600 mg/day	0.69 (0.08 to 5.67) [2][154,158]	0.32 (0.10 to 1.05) [3][154,158,164]
OA only	0.69 (0.08 to 5.67) [2][154,158]	0.45 (0.17 to 1.22) [7][141,143,145,148,154,157,158]
RA only	No trials	*0.20 (0.05 to 0.77) [2]*[163,164 a]
vs ibuprofen	–	0.23 (0.05 to 1.04) [1][164]
vs diclofenac	–	No trials
vs naproxen	–	0.60 (0.13 to 2.75) [3][145,154,158 a]
vs other NSAIDs	–	*0.30 (0.09 to 0.99) [5]*[141,143,148,157,163]
All trials	**0.69 (0.08 to 5.67) [2][154,158]**	***0.32 (0.15 to 0.71) [9]*[141,143,145,148,154,157,158,163,164 a]**
POBs		
600 mg/day	[a]	0.41 (0.12 to 1.40) [5][141,143,148,157,163 b]
>600 mg/day	0.33 (0.01 to 8.07) [1][154]	0.32 (0.01 to 7.70) [1][154]
OA only	0.33 (0.01 to 8.07) [1][154 a]	0.46 (0.13 to 1.63) [5][141,143,148,154,157 a]
RA only	No trials	0.19 (0.01 to 3.91) [1][163 a]
vs ibuprofen	–	No trials
vs diclofenac	–	No trials
vs naproxen	–	0.32 (0.01 to 7.70) [1][154 b]
vs other NSAIDs	–	0.41 (0.12 to 1.40) [5][141,143,148,157,163]
All trials	**0.33 (0.01 to 8.07) [1][154 a]**	**0.39 (0.12 to 1.24) [6][141,143,148,154,157,163 b]**

Additional trial(s) reporting zero events in both arms: [a] one trial; [b] two trials.

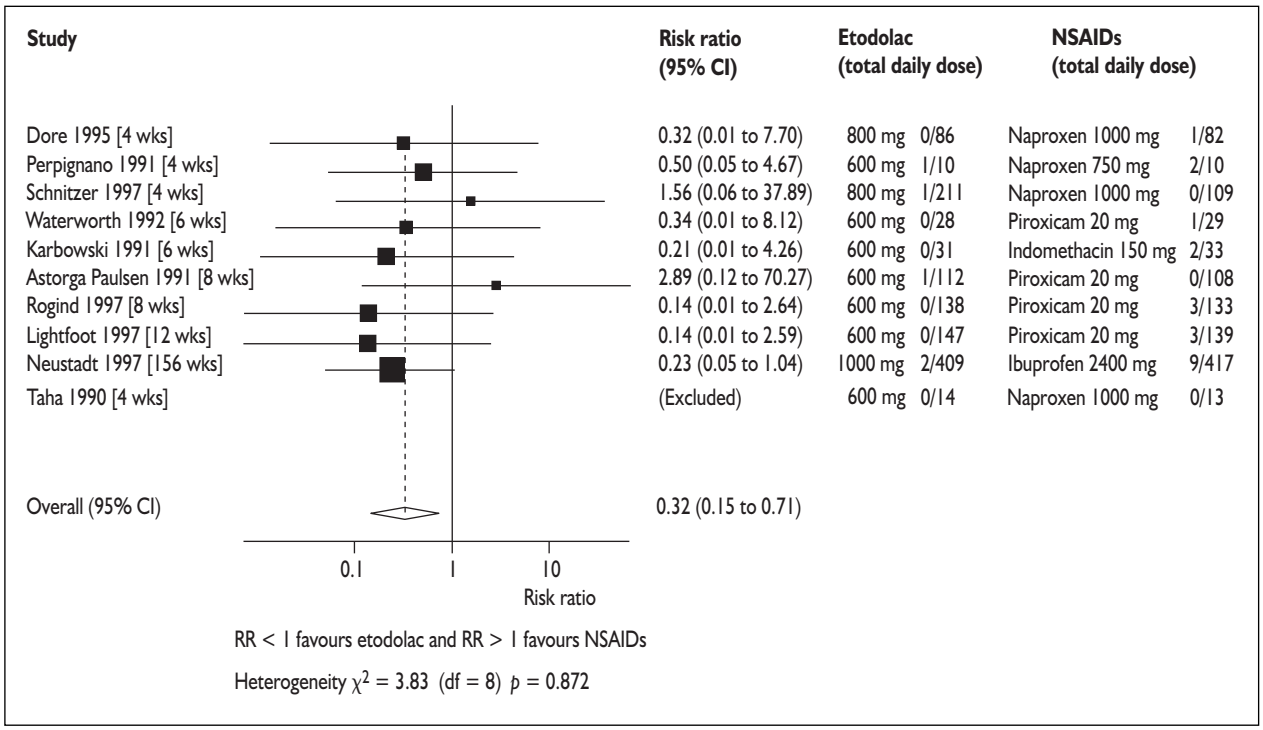


FIGURE 2 *Risk of PUBs with etodolac (all doses) versus NSAIDs (all drugs)*

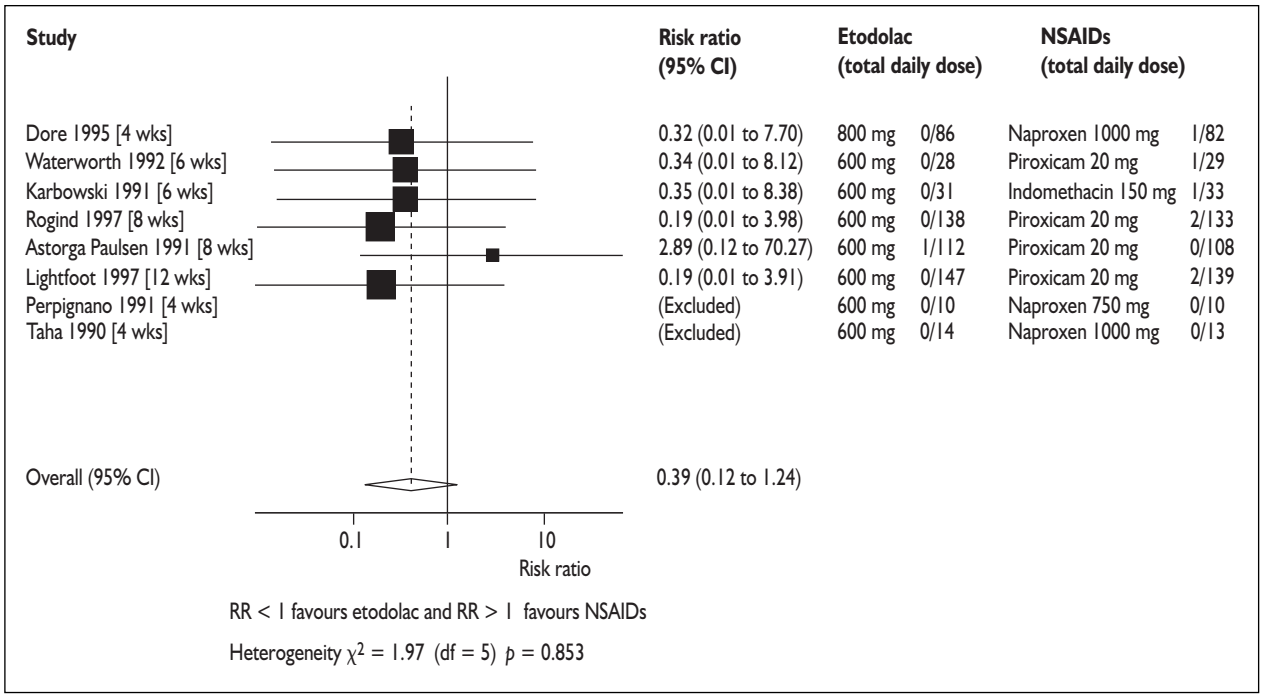


FIGURE 3 *Risk of POBs with etodolac (all doses) versus NSAIDs (all drugs)*

TABLE 8 *Summary of serious cardiovascular thrombotic events for etodolac versus placebo or NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
MI	Not reported	Not reported
Serious CV thrombotic events	Not reported	
600 mg/day		0.50 (0.09 to 2.66) [2]
>600 mg/day		Not reported
OA only		0.50 (0.09 to 2.66) [2]
RA only		Not reported
All trials		**0.50 (0.09 to 2.66) [2]**

Meloxicam

Description of included trials

Sixteen trials of meloxicam recruiting 22,886 patients met inclusion criteria. Full details of these trials are detailed in Appendix 6 and summarised in *Table 9*. We identified a further 11 trials with abstract-level information only. We were not able to assess the quality of these trials or to extract fully their outcome results. The key safety outcomes (POBs, PUBs and MI) reported by 10 of these abstracts were added to the main body of trial evidence meta-analyses. These additional data are therefore reported as sensitivity analyses in the section 'Summary' (p. 29).

Two major trials, Meloxicam Large-Scale International Study Safety Assessment (MELISSA) and Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies (SELECT), recruited over 8000 patients each. A majority (11/16) of trials were of short duration (<3 months) and ranged from 2 weeks to 6 months.

MELISSA

This large international multicentre double-blind RCT was designed to assess the tolerability and safety of meloxicam 7.5 mg/day (half the maximum licensed dose; $n = 4320$ patients) compared with slow-release diclofenac 100 mg/day (two-thirds of the usual full dose; $n = 4326$) in OA over 28 days. MELISSA was powered to detect a 1% difference in adverse events. Because of limited reporting, the quality of MELISSA was judged to be only 'moderate' (i.e. Jadad score 3).

SELECT

SELECT was similar in design to MELISSA, except that meloxicam 7.5 mg/day ($n = 4635$ patients) was compared with piroxicam 20 mg/day (two-thirds of the maximum licensed dose; $n = 4336$) in OA over 28 days. Again, because of limited reporting, the quality of MELISSA was judged to be only 'moderate' (i.e. Jadad score 3).

Patient characteristics

Most trials studied OA patients (12 trials) rather than RA patients (four trials) with a mean age in the range 54–72 years and females 54–90%. Patient characteristics were often poorly reported but, where reported, 5–12% had experienced a previous GI ulcer. Usage of low-dose aspirin and oral corticosteroids was not reported. It appeared that virtually all included patients were already taking NSAIDs at the time of recruitment.

Study interventions

Meloxicam at licensed doses (7.5 or 15 mg/day) was used in all trials and three trials also studied doses greater than 15 mg/day, but in two of these trials[165,166] data for 30 mg/day were not reported. One trial provided data on meloxicam 22.5 mg/day.[167] Four trials compared meloxicam with placebo, two of these trials being placebo-only trials. Fourteen trials compared meloxicam with NSAIDs: diclofenac (6/14), piroxicam (5/14), naproxen (1/14) and nabumetone (2/14).

Assessment of the quality of included trials

The median Jadad score across trials was 3, indicating that the trials were generally of 'moderate' quality (see *Table 9*). A detailed summary of the quality of trials is provided in Appendix 7.

Low quality scores were largely the result of poor reporting of methods. Very few trials provided details of randomisation (3/16) or concealment (0/16); most were double blind (14/16) and stated ITT analysis (15/16); and in four of six trials, where details were reported, there was a loss to follow-up of less than 5%. As with other COX-2 selective drugs, a potential source of the bias in these trials was the large proportion of withdrawals: withdrawal in the non-selective NSAIDs arm of trials exceeded that of meloxicam, although drug doses used are not directly comparable.

Assessment of meloxicam efficacy

Efficacy results across trials are summarised in *Table 10*.

TABLE 9 *Characteristics and quality of included meloxicam RCTs*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Meloxicam	Placebo	NSAID	Efficacy[a]	Safety[a]		
Carrabba, 1995[168,169]	OA (hip, knee)	15 mg/day (15 mg o.d.) (n = 216)	–	Piroxicam 20 mg/day (20 mg o.d.) (n = 109)	Patient's global assessment	Withdrawal due to AE, total withdrawal, total AE	3	1
Hosie, 1996,[170] BI Study 63	OA (hip, knee)	7.5 mg/day (7.5 mg o.d.) (n = 169)	–	Diclofenac SR 100 mg/day (100 mg o.d.) (n = 167)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, POBs, total AE	25 (6 months)	3
Linden, 1996,[165] BI Study 43	OA (hip)	15 mg/day (15 mg o.d.) (n = 129) 30 mg/day (30 mg o.d.) (n = ?)	–	Piroxicam 20 mg/day (20 mg o.d.) (n = 127)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, POBs, total AE	6	3
Goei The, 1997,[166] BI Study 44	OA (knee)	15 mg/day (15 mg o.d.) (n = 128) 30 mg/day (30 mg o.d.) (n = ?)	–	Diclofenac SR 100 mg/day (100 mg o.d.)	Patient's global assessment	Withdrawal due to AE, ulcer (clinical), PUBs, dyspepsia, total AE	6	2
Hosie, 1997,[171] BI Study 45	OA (hip, knee)	15 mg/day (15 mg o.d.) (n = 306)	–	Piroxicam 20 mg/day (20 mg o.d.) (n = 149)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, POBs, total AE, withdrawals due to GI AE	25 (6 months)	3
Dequeker, 1998,[172] SELECT, BI Study 154	OA (knee, spine, hip, hand)	7.5 mg/day (7.5 mg o.d.) (n = 4320)	–	Piroxicam 20 mg/day (20 mg o.d.) (n = 4336)	Pain 100 mm VAS (on active movement), pain 100 mm VAS (at rest), patient's global efficacy, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, POBs, MI, total CV thrombotic, total AE, withdrawals due to GI AE	4	3
Hawkey, 1998,[173] MELISSA, BI Study 153	OA (knee, spine, hip, hand)	7.5 mg/day (7.5 mg o.d.) (n = 4635)	–	Diclofenac SR 100 mg/day (100 mg o.d.) (n = 4688)	Pain 100 mm VAS – active movement, pain 100 mm VAS – at rest, patient's global efficacy, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, POBs, total AE, withdrawals due to GI AE	4	3

continued

TABLE 9 *Characteristics and quality of included meloxicam RCTs (cont'd)*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Meloxicam	Placebo	NSAID	Efficacy[a]	Safety[a]		
Lund, 1998,[174,175] BI Study 42	OA (knee)	7.5 mg/day (7.5 mg o.d.) (*n* = 140) 30 mg/day (30 mg o.d.) (*n* = 102)	*n* = 137	–	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, total AE	3	3
Yocum, 2000,[176–178] BI Study 181	OA (hip, knee)	3.75 mg/day (3.75 mg o.d.) (*n* = 154) 7.5 mg/day (7.5 mg o.d.) (*n* = 154) 15 mg/day (15 mg o.d.) (*n* = 156)	*n* = 157	Diclofenac 100 mg/day (50 mg b.d.) (*n* = 153)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia, total AE, withdrawals due to GI AE	12	3
Chang, 2001[179]	OA (knee)	7.5 mg/day (7.5 mg o.d.) (*n* = 36)	–	Piroxicam 20 mg/day (20 mg o.d.) (*n* = 36)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, ulcer (endoscopic, definition: ⩾3 mm), dyspepsia, total AE	4	4
Valat, 2001,[180] BI Study 94	OA (lumbar spine)	7.5 mg/day (7.5 mg o.d.) (*n* = 117)	–	Diclofenac 100 mg/day SR (100 mg o.d.) (*n* = 112)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, MI, total CV thrombotic, total AE	2	4
Xu, 2002a[181]	OA (knee)	7.5 mg/day (7.5 mg o.d.) (*n* = 31)	–	Nabumetone 1000 mg/day (1000 mg o.d.) (*n* = 29)	Pain during activity (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, total AE, withdrawals due to GI AE	4	5
Wojtulewski, 1996,[182,183] BI Study 61	RA	7.5 mg/day (7.5 mg o.d.) (*n* = 199)	–	Naproxen 750 mg/day (250 mg t.d.s.) (*n* = 180)	Pain (VAS), patient's global assessment efficacy, withdrawal due to lack of efficacy	Withdrawal due to AE, PUBs, total AE, withdrawals due to GI AE	25 (6 months)	4

continued

TABLE 9 *Characteristics and quality of included meloxicam RCTs (cont'd)*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Meloxicam	Placebo	NSAID	Efficacy[a]	Safety[a]		
Lemmel, 1997,[184,185] BI Study 35	RA	7.5 mg/day (7.5 mg o.d.) (*n* = 159) 15 mg/day (15 mg o.d.) (*n* = 162)	*n* = 147	–	Pain (VAS), patient's global assessment efficacy, withdrawal due to lack of efficacy	Withdrawal due to AE, total AE, withdrawals due to GI AE	3	3
Furst, 2002,[167,186] BI Study 183	RA	7.5 mg/day (7.5 mg o.d.) (*n* = 175) 15 mg/day (15 mg o.d.) (*n* = 184) 22.5 mg/day (22.5 mg o.d.) (*n* = 177)	*n* = 177	Diclofenac 150 mg/day (75 mg b.d.) (*n* = 181)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, POBs, dyspepsia, total AE, withdrawals due to GI AE	12	4
Xu, 2002b[187,188]	RA	15 mg/day (15 mg o.d.) (*n* = 59)	–	Nabumetone 1000 mg/day (1000 mg o.d.) (*n* = 61)	Patient's global assessment (disease status), withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, total AE, withdrawals due to GI AE	4	4

[a] Only the outcomes which were included in meta-analyses are listed.

TABLE 10 *Summary of efficacy results for meloxicam versus placebo and NSAIDs*

	Placebo				NSAID			
	VAS pain difference: mean (95% CI)	**Global efficacy difference: mean (95% CI)**	**ACR: RR (95% CI)**	**Withdrawals due to lack of efficacy: RR (95% CI)**	**VAS pain difference: mean (95% CI)**	**Global efficacy difference: mean (95% CI)**	**ACR: RR (95% CI)**	**Withdrawals due to lack of efficacy: RR (95% CI)**
7.5 mg/day	*–5.7 (–8.7 to –2.8) [1][a]*	–0.49 (–0.92 to 0.03) [2]	No trials	*0.59 (0.50 to 0.70) [4]*	*2.2 (1.2 to 3.1)* [7]	*–0.13 (–0.16 to –0.09)* [4]	No trials	*1.67 (1.36 to 2.04) [7]*
15 mg/day	*–7.4 (–10.3 to –4.4) [3]*	–0.85 (–1.31 to 0.39) [2]	No trials	*0.54 (0.43 to 0.68) [4]*	–1.2 (–4.0 to 1.6) [4]	0.02 (–0.37 to 0.40) [3]	No trials	*1.48 (1.08 to 2.04) [4]*
22.5 mg/day	*–9.9 (–15.7 to –4.1) [1]*	*–0.87 (–1.42 to –0.32) [1]*	No trials	*0.90 (0.53 to 0.89) [1]*	1.1 (–4.7 to 6.9) [1]	0.20 (–0.45 to 0.65) [1]	No trials	*1.65 (1.12 to 2.42) [1]*
OA only	*–5.3 (–10.5 to –0.1) [1]*	–0.50 (–1.20 to 0.20) [1]	No trials	*0.58 (0.44 to 0.77) [2]*	*1.7 (0.80 to 2.8)* [7]	–0.06 (–0.28 to 0.16) [3]	No trials	*1.40 (1.14 to 1.72) [8]*
RA only	*–7.2 (–10.2 to –4.3) [2]*	*–0.80 (–1.15 to –0.08) [1]*	No trials	*0.60 (0.48 to 0.74) [2]*	1.4 (–1.9 to 4.2) [3]	0.03 (–0.44 to 0.51) [2]	No trials	*1.61 (1.21 to 2.13) [3]*
All trials	***–6.8 (–9.3 to –4.2) [3]***	***–0.65 (–1.14 to –0.14) [2]***	**No trials**	***0.59 (0.49 to 0.70) [4]***	***1.7 (0.8 to 2.7)* [10]**	**–0.05 (–0.25 to 0.15) [5]**	**No trials**	***1.47 (1.24 to 1.73) [11]***

[a] [ ], No. of trials.

Patient's assessment of arthritis pain
Meloxicam was marginally inferior to non-selective NSAIDs for providing pain relief.

Patient's assessment of global efficacy
Meloxicam was no different to non-selective NSAIDs for global efficacy. These results were consistent across meloxicam doses and OA and RA patients.

ACR-20 responder
No included meloxicam trials reported ACR-20.

Withdrawals due to lack of efficacy
More people on meloxicam withdrew because of lack of efficacy compared with non-selective NSAIDs. Again, these results appeared to be consistent for OA and RA patients and across meloxicam doses.

Meloxicam tolerability
Adverse events
Significantly fewer people given meloxicam developed adverse events, overall and GI-specific events, compared with non-selective NSAIDs in OA and RA. There was evidence of substantial heterogeneity in the level of GI-specific adverse events across meloxicam trials (*Table 11*).

Withdrawals
Meloxicam significantly reduced the level of both overall and GI-specific withdrawals compared with non-selective NSAIDs (*Table 12*).

Safety of meloxicam
Few trials assessed the safety of meloxicam in terms of endoscopic GI ulcers, PUBs, POBs, MIs and serious CV thrombotic events (*Tables 13–15*, *Figures 4* and *5*).

Endoscopic GI ulcers
Meloxicam appeared to reduce the endoscopic ulcers compared to NSAIDs, although this difference failed to reach statistical significance.

Clinical UGI events (PUBs)
The pooled RR indicated that meloxicam was associated with significantly fewer PUBs compared with non-selective NSAIDs (RR = 0.53, 95% CI 0.29 to 0.97; NNT 707, 95% CI 468 to 11,083; *Figure 4*). This pooled estimate however was mainly driven by data from two short-term trials[172,173] (4 weeks) that used low-dose meloxicam (7.5 mg per day).

Complicated UGI events (POBs)
When meloxicam was compared with non-selective NSAIDs, no statistically significant differences in POBs were found.

Myocardial infarctions and serious cardiovascular thrombotic events
Only three events were reported across all included meloxicam trials providing insufficient data for meaningful comparisons.

Subgroup analyses
Low-dose aspirin
No relevant trial data were found.

H. pylori *status*
No relevant trial data were found.

TABLE 11 *Summary of adverse events for meloxicam versus placebo and NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
All adverse events		
7.5 mg/day	1.07 (0.94 to 1.22) [4]	*0.86 (0.84 to 0.89) [10]*
15 mg/day	1.12 (0.98 to 1.326) [4]	0.97 (0.87 to 1.09) [5]
22.5 mg/day	1.13 (0.95 to 1.35) [1]	1.00 (0.85 to 1.18) [1]
OA trials	1.11 (0.94 to 1.31) [2]	*0.88 (0.81 to 0.95)[a] [10]*
RA trials	1.10 (0.96 to 1.27) [2]	0.99 (0.87 to 1.13) [3]
All trials	**1.10 (0.99 to 1.23) [4]**	***0.91 (0.84 to 0.99)[a] [13]***
All GI adverse events		
7.5 mg/day	0.68 (0.41 to 1.10)[a] [4]	*0.29 (0.28 to 0.31)[a] [10]*
15 mg/day	0.86 (0.58 to 1.26)[a] [4]	*0.33 (0.21 to 0.51) [5]*
22.5 mg/day	*1.79 (1.42 to 2.27) [1]*	1.15 (0.99 to 1.94) [1]
OA only	0.68 (0.33 to 1.39)[a] [2]	*0.28 (0.22 to 0.37)[a] [10]*
RA only	0.91 (0.53 to 1.56)[a] [2]	*0.43 (0.31 to 0.61)[a] [3]*
All trials	**0.79 (0.55 to 1.12)[a] [4]**	***0.31 (0.24 to 0.39)[a] [13]***

[a] Significant statistical heterogeneity ($p < 0.10$) – random effects meta-analysis.

TABLE 12 *Summary of withdrawals for meloxicam versus placebo and NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
All adverse event withdrawals		
7.5 mg/day	1.21 (0.76 to 1.92) [2]	*0.60 (0.42 to 0.85)*[a] [8]
15 mg/day	1.32 (0.84 to 2.08) [3]	0.96 (0.66 to 1.35) [4]
22.5 mg/day	1.07 (0.53 to 2.15) [1]	0.77 (0.40 to 1.45) [1]
OA only	1.25 (0.72 to 2.20) [2]	0.97 (0.62 to 1.52) [3]
RA only	1.20 (0.68 to 2.11) [1]	0.86 (0.53 to 1.40) [1]
All trials	**1.23 (0.82 to 1.84) [3]**	**0.92 (0.66 to 1.28) [11]**
All GI withdrawals		
7.5 mg/day	1.40 (0.72 to 2.77) [4]	*0.60 (0.53 to 0.69)* [5]
15 mg/day	1.35 (0.69 to 2.65) [4]	0.76 (0.40 to 1.47) [3]
22.5 mg/day	1.18 (0.41 to 3.46) [1]	0.92 (0.38 to 2.11) [1]
OA only	2.01 (0.76 to 5.30) [2]	*0.60 (0.53 to 0.69)* [5]
RA only	1.04 (0.48 to 2.6) [2]	0.66 (0.41 to 1.06) [2]
All trials	**1.38 (0.76 to 2.51) [4]**	***0.61 (0.54 to 0.69)* [7]**
All withdrawals		
7.5 mg/day	0.83 (0.66 to 1.05) [2]	*0.85 (0.76 to 0.96)* [6]
15 mg/day	*0.73 (0.57 to 0.93)* [2]	1.14 (0.83 to 1.52) [3]
22.5 mg/day	*0.68 (0.53 to 0.89)* [1]	1.11 (0.87 to 1.49) [1]
OA only	0.82 (0.40 to 1.68) [1]	*0.80 (0.71 to 0.91)* [6]
RA only	*0.74 (0.61 to 0.90)* [1]	1.21 (0.94 to 1.55) [2]
All trials	***0.75 (0.62 to 0.90)* [2]**	***0.86 (0.77 to 0.96)* [8]**

[a] Significant statistical heterogeneity ($p < 0.10$) – random effects meta-analysis.

TABLE 13 *Summary of endoscopic GI ulcers for meloxicam versus placebo or NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
Endoscopic GI ulcers		
7.5 mg/day	No events [1]	0.50 (0.21 to 1.15) [5]
15 mg/day	No trials	No trials
22.5 mg/day	No trials	No trials
OA only	No events [1]	0.56 (0.23 to 1.36) [4]
RA only	No trials	0.18 (0.01 to 3.74) [1]
All trials	**No events [1]**	**0.50 (0.21 to 1.15) [5]**

Age

In SELECT, when subgroups of younger (≤65 years) and older (>65 years) male and female patients were analysed, in both the incidence of GI adverse events was found to be lower with meloxicam than piroxicam. Actual numbers of events were not reported in these two age groups. Furst and colleagues[167] reported the rate of all adverse events to be lower in meloxicam than diclofenac for both patients aged ≤65 years (24.1% versus 29.4%) and patients aged >65 years (36.4% versus 42.1%).

Prior GI disease (GI ulcer)

In SELECT, fewer people who had a history of an ulcer developed GI adverse events when given meloxicam (7.5 mg/day) than piroxicam (20 mg/day): 91/236 (38.6%) compared with 95/212 (44.8%), respectively. This, however, was not statistically significant ($p = 0.180$).

Impact of concomitant gastroprotective agents

No relevant trials were identified.

Summary

- Sixteen RCTs were included. Studies compared meloxicam (7.5–22.5 mg/day) with either placebo or non-selective NSAIDs (naproxen, diclofenac, nabumetone or piroxicam). Twelve trials were exclusively in OA patients and four trials in RA patients.

TABLE 14 *Summary of serious GI events for meloxicam versus placebo or NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
PUBs		
7.5 mg/day	5.06 (0.24 to 104.58) [1][167 b]	0.58 (0.31 to 1.09) [4][167,172,173,182 b]
15 mg/day	2.89 (0.12 to 70.39) [1][167 b]	0.59 (0.14 to 2.48) [3][165–167 b]
22.5 mg/day	3.00 (0.12 to 73.15) [1][167]	3.07 (0.13 to 74.80) [1][167]
OA only	[a]	*0.49 (0.26 to 0.95)* [4][165,166,172,173 c]
RA only	2.98 (0.16 to 55.14) [1][167 a]	0.82 (0.15 to 4.34) [2][167,182]
vs ibuprofen	–	No trial
vs diclofenac	–	0.85 (0.32 to 2.25) [3][166,167,173 a]
vs naproxen	–	0.18 (0.01 to 3.75) [1][182]
vs other NSAIDs	–	*0.42 (0.18 to 0.96)* [2][165,172 b]
All trials	**2.98 (0.16 to 55.14) [1][167 b]**	***0.53 (0.29 to 0.97)* [6][165–167,172,173,182 c]**
POBs		
7.5 mg/day	3.03 (0.12 to 73.98) [1][167 c]	0.56 (0.26 to 1.21) [4][167,170,172,173 e]
15 mg/day	2.89 (0.12 to 70.39) [1][167 c]	1.09 (0.24 to 5.00) [3][165,167,171 c]
22.5 mg/day	[a]	[a]
OA only	[b]	0.52 (0.25 to 1.10) [5][165,170–173 e]
RA only	1.66 (0.08 to 34.36) [1][167 a]	1.69 (0.08 to 35.13) [1][167 b]
vs ibuprofen	–	No trials
vs diclofenac	–	0.66 (0.21 to 2.12) [3][167,170,173 b]
vs naproxen	–	[a]
vs other NSAIDs	–	0.51 (0.21 to 1.27) [3][165,171,172 d]
All trials	**1.66 (0.08 to 34.36) [1][167 c]**	**0.56 (0.27 to 1.15) [6][165,167,170,172,173,182 f]**

Additional trial(s) reporting zero events in both arms: [a] one trial; [b] two trials; [c] three trials; [d] four trials; [e] five trials; [f] seven trials.

TABLE 15 *Summary of myocardial infarction and serious CV thrombotic events for meloxicam versus placebo or NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
MI		
7.5 mg/day	0.33 (0.01 to 7.94) [1][174 b]	0.33 (0.01 to 8.03) [1][170 d]
15 mg/day	0.34 (0.01 to 8.29) [1][174 b]	[b]
22.5 mg/day	No trials	No trials
OA only	0.17 (0.01 to 4.08) [1][174 a]	0.33 (0.01 to 8.03) [1][170 d]
RA only	[c]	[a]
vs ibuprofen	–	No trials
vs diclofenac	–	0.33 (0.01 to 8.03) [1][170 b]
vs naproxen	–	No trials
vs other NSAIDs	–	[c]
All trials	**0.17 (0.01 to 4.08) [1][174 b]**	**0.33 (0.01 to 8.03) [1][170 e]**
Serious CV thrombotic events		
7.5 mg/day	[f]	0.99 (0.05 to 15.7) [1]
15 mg/day	[f]	No trials
22.5 mg/day	[f]	No trials
OA only	[f]	0.99 (0.06 to 15.9) [1]
RA only	[f]	[f]
All trials	[f]	0.99 (0.06 to 15.9) [1]

Additional trial(s) reporting zero events in both arms: [a] one trial; [b] two trials; [c] three trials; [d] four trials; [e] five trials.
[f] Trials reported zero events.

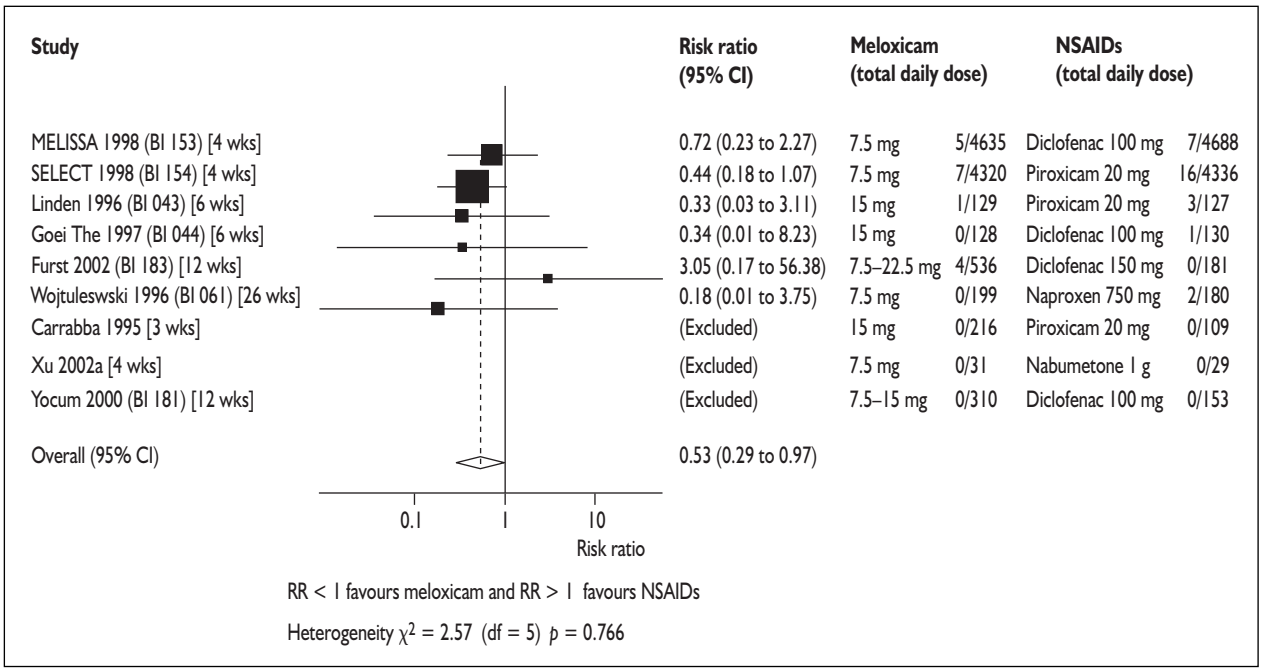


FIGURE 4 *Risk of PUBs with meloxicam (all doses) versus NSAIDs (all drugs). df, degree of freedom.*

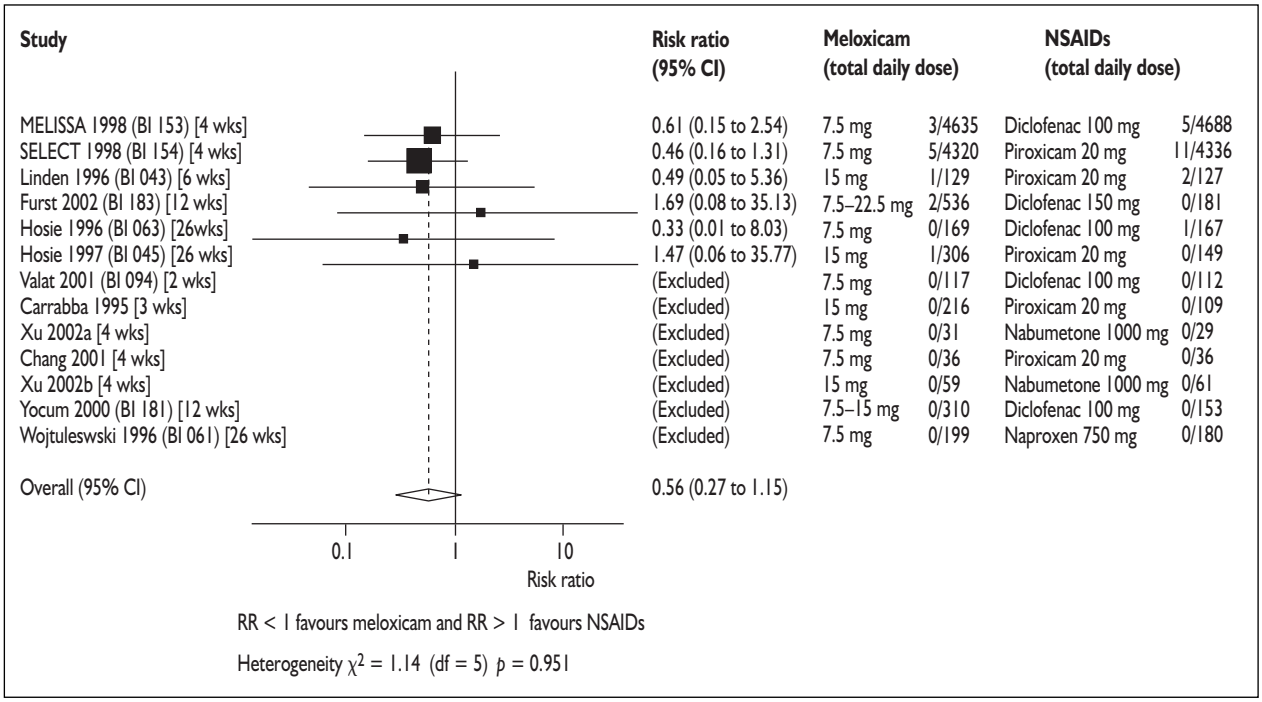


FIGURE 5 *Risk of POBs with meloxicam (all doses) versus NSAIDs (all drugs)*

- Meloxicam is of similar to or poorer efficacy than non-selective NSAIDs for the symptomatic treatment of OA and RA.
- Median Jadad score across trials was 3, indicating that the trials were generally of 'moderate' quality.
- Meloxicam is associated with significantly fewer GI-related adverse events and related withdrawals than non-selective NSAIDs.
- Meloxicam is associated with fewer endoscopic GI ulcers and clinical and complicated UGI events than non-selective NSAIDs, although only the difference in clinical UGI events (PUBs) reached statistical significance. The pooled estimate was mainly driven by data from short-term trials that used low-dose meloxicam (7.5 mg per day).

- There are insufficient trial events to assess the impact of meloxicam on the incidence of MI compared with non-selective NSAIDs.
- The GI-protective effects of meloxicam appear to be consistent across age (≤65 years versus >65 years) and prior history of GI events, but no trial evidence that examined the relative effect of meloxicam in patients taking concomitant low-dose aspirin, anticoagulants or *H. pylori* status was found.
- The inclusion of data from the 10 abstracts (for trials not available as full published reports or trial reports) slightly improved the pooled GI safety and MI estimates towards meloxicam relative to non-selective NSAIDs: RR for PUBs 0.42 (95% CI: 0.26 to 0.72); RR for POBs 0.44 (95% CI: 0.23 to 0.85); RR for MI 0.33 (95% CI: 0.01 to 8.02).
- No comparisons of meloxicam with non-selective NSAIDs with a gastroprotective agent were found.

Celecoxib

Description of included trials

Trials considered commercial-in-confidence in Table 16 *may have subsequently been published.*

Forty trials of celecoxib met the inclusion criteria. Six trials compared celecoxib with rofecoxib and five trials compared celecoxib with lumiracoxib. These direct comparisons are described in the section 'Direct comparison of COX-2 selective NSAIDs' (p. 78). This section describes 37 of the 40 trials in which celecoxib was compared with either placebo or non-selective NSAIDs. A detailed summary of the characteristics of the these trials is given in Appendix 6, and summarised in *Table 16*.

A large proportion of trials were of a relatively short duration (≤3 months), only two trials having a follow-up of 6 months or longer. The median sample size of trials was 655 patients. The two major trials were CLASS and Successive Celecoxib Efficacy and Safety Studies I (SUCCESS-I), each trial recruiting over 5000 patients.

CLASS

CLASS is a double-blind RCT that included patients with OA and RA with the aim of comparing the tolerability and safety of celecoxib at supra-licensed dose (400 mg twice daily, n = 3987) with diclofenac (75 mg twice daily, n = 1996) and ibuprofen (1.2 g twice daily, n = 1985).

This study has been highly controversial and the published findings, in 1999, were challenged because the published report described 26-week outcome data that claimed superiority of celecoxib (PUBs 32/3987) against pooled data for ibuprofen and diclofenac (PUBs 51/3981: RR 0.63, 95% CI 0.40 to 0.97).

This study comprised two study protocols designed prospectively to combine results into a single study that pooled celecoxib data.[189] The primary end-point for CLASS was to compare the incidence of clinically significant UGI events (which refers to UGI bleeding, perforation or obstruction). The sponsors justified publication of the 6-month data on the grounds that this was a clinically relevant time point and allowed comparison with the MUCOSA study, which studied misoprostol with NSAIDs for prevention of UGI toxicity. Pfizer also claimed that disproportionate withdrawal of patients treated with ibuprofen or diclofenac, due to the development of GI symptoms but not serious GI events, during the first 6 months contributed to fewer significant UGI events in these groups (described as 'informative censoring'.[189] These arguments were refuted by the FDA and the final study data were made available on their website. At 52 weeks, PUBs in the celecoxib group (46/3987) were not significantly different from those in the combined ibuprofen and diclofenac group (65/3981) (RR 0.71, 95% CI 0.49 to 1.03).

SUCCESS-I

This was a 12-week double-blind RCT of OA patients undertaken across 1142 centres in 37 countries. The primary objective was to compare the tolerability and safety of licensed doses of celecoxib (100 or 200 mg twice daily, n = 8840) with naproxen (500 mg twice daily, n = 914) or diclofenac (50 mg twice daily, n = 3510). Although efficacy was assessed in this trial, outcome means (and not measures of variance) were only available for individual countries or continents. It was therefore not possible to include efficacy data in a meta-analysis of all trials. However, the pattern of efficacy results indicated that both doses of celecoxib had similar efficacy to non-selective NSAIDs. The tolerability and safety results of this trial were included in our meta-analyses.

Patient characteristics

Most trials involved patients with OA (24 studies), usually hip or knee. Seven trials included both RA and OA patients and six trials only RA patients. The average age of patients across trials ranged from 50 to 74 years with 35–89% of patients being female.

Details of baseline risk characteristics were either not reported or not collected in many trials, for

TABLE 16 *Characteristic and quality of included celecoxib RCTs*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Celecoxib	Placebo	NSAID	Efficacy[a]	Safety[a]		
Simon, 1998a,[190] Pfizer Study 013	OA (knee)	80 mg/day (40 mg b.d.) (n = 71) 200 mg/day (100 mg b.d.) (n = 73) 400 mg/day (200 mg b.d.) (n = 76)	n = 73	–	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	–	2	3
Bensen, 1999,[191–193] Pfizer Study 020	OA	100 mg/day (50 mg b.d.) (n = 218) 200 mg/day (100 mg b.d.) (n = 217) 400 mg/day (200 mg b.d.) (n = 222)	n = 220	Naproxen 1000 mg/day (500 mg b.d.) (n = 216)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, ulcer (clinical or symptomatic), PUBs, POBs, dyspepsia, MI, total CV thrombotic, total AE, withdrawals due to GI AE	12	4
Williams, 2000,[194] Pfizer Study 060	OA (knee)	200 mg/day (100 mg b.d.) (n = 231) (200 mg o.d.) (n = 223)	n = 232	–	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia, MI, total CV thrombotic, total AE	6	1
Goldstein, 2001b,[195,224] SUCCESS-1, Pfizer Study 096 (Pfizer 2004 submission)	[**Confidential information removed**]							
Kivitz, 2001,[196] Pfizer Study 054	OA (hip)	100 mg/day (50 mg b.d.) (n = 216) 200 mg/day (100 mg b.d.) (n = 207) 400 mg/day (200 mg b.d.) (n = 213)	n = 218	Naproxen 1000 mg/day (500 mg b.d.) (n = 207)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, POBs, dyspepsia, MI, total AE severe, total AE, withdrawals due to GI AE	12	3
McKenna, 2001b,[197] Pfizer Study 152	OA (knee)	200 mg/day (200 mg o.d.) (n = 63)	n = 60	Rofecoxib[b]	Pain (VAS), withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia, MI, total CV thrombotic, total AE, withdrawals due to GI AE	6	5

continued

TABLE 16 *Characteristic and quality of included celecoxib RCTs (cont'd)*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Celecoxib	Placebo	NSAID	Efficacy[a]	Safety[a]		
McKenna, 2001a,[198] Pfizer Study 118	OA (knee)	200 mg/day (100 mg b.d.) (n = 199)	n = 201	Diclofenac 150 mg/day (50mg t.d.s.) (n = 200)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Total withdrawal, withdrawal due to AE, dyspepsia, total AE	6	3
Pfizer Study 021[221] (2000–1 submission)	[**Confidential information removed**]							
McKenna, 2002,[199] Pfizer Study 042	OA (hip, knee)	200 mg/day (100 mg b.d.) (n = 346)	–	Diclofenac 100 mg/day (50 mg b.d.) (n = 341)	Patient's global assessment, withdrawal due to lack of efficacy	Total withdrawal, dyspepsia, withdrawals due to GI AE	6	3
Pfizer Study 047[444] (2000–1 submission)	[**Confidential information removed**]							
Williams, 2001,[200] Pfizer Study 087	OA (knee)	200 mg/day (100 mg b.d.) (n = 243) (200 mg o.d.) (n = 231)	n = 244	–	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Total withdrawal, MI, total CV thrombotic, total AE, withdrawal due to AE, withdrawal due to GI AE	6	2
Suarez-Otero, 2002[201]	OA (knee, hand, hip)	200 mg/day (100 mg b.d.) (n = 40)	–	Diclofenac–cholestyramine 280 mg/day (140 mg b.d.) (n = 41)	Pain (VAS)	Withdrawal due to AE, dyspepsia	6	3
Gibofsky, 2003,[202] Pfizer Study 003	OA (knee)	200 mg/day (200 mg o.d.) (n = 189)	n = 96	Rofecoxib[b]	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia, total AE	6	5
Hawel, 2003[203]	OA (hip)	200 mg/day (100 mg b.d.) (n = 74)	–	Dexibuprofen 800 mg/day (400 mg b.d.) (n = 74)	Pain (VAS), patient's global assessment efficacy, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, total AE	2	4

continued

TABLE 16 *Characteristic and quality of included celecoxib RCTs (cont'd)*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Celecoxib	Placebo	NSAID	Efficacy[a]	Safety[a]		
Pincus, 2004a,[204,205] PACES-a, Pfizer Study 010	OA (hip, knee)	First 6 weeks: 200 mg/day (200 mg o.d.) (n = 181)	n = 172	– (Acetaminophen 4000 mg/day, n = 171)	MDHAQ[c] VAS pain	NR	6 × 2	1
Sowers, 2003,[206,249] CRESCENT, Pfizer Study 002 (2004 submission)	OA (hip, knee)	200 mg/day (200 mg o.d.) (n = 136)	–	Naproxen 1000 mg/day (500 mg b.d.) (n = 130) Rofecoxib[b]	[**Confidential information removed**]		12	5
Pincus, 2004b,[204] PACES-b, Pfizer Study 249	OA (hip, knee)	First 6 weeks: 200 mg/day (200 mg o.d.) (n = 189)	n = 182	– (Acetaminophen 4000 mg/day, n = 185)	MDHAQ[c] VAS pain	NR	6 × 2	1
Pfizer Study 209[439] (2004 submission)	[**Confidential information removed**]							
Pfizer Study 210[440] (2004 submission)	[**Confidential information removed**]							
Pfizer Study 211[225] (2004 submission)	[**Confidential information removed**]							
Pfizer Study 216[223] (2004 submission)	[**Confidential information removed**]							
Hawkey, 2004,[207,287] Novartis Study 0126	[**Confidential information removed**]							
Fleischmann, 2003,[208,209] Novartis Study 0109	OA (knee)	200 mg/day (200 mg o.d.) (n = 446)	n = 232	Lumiracoxib[b]	[**Confidential information removed**]		13	5
Tannenbaum, 2004,[210] Novartis Study 0112	OA (knee)	200 mg/day (200 mg o.d.) (n = 481)	n = 243	Lumiracoxib[b]	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, POBs, dyspepsia, total AE, withdrawal due to GI AE	13	5

continued

TABLE 16 *Characteristic and quality of included celecoxib RCTs (cont'd)*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Celecoxib	Placebo	NSAID	Efficacy[a]	Safety[a]		
Simon, 1998b,[190] Pfizer Study 012	RA	80 mg/day (40 mg b.d.) (n = 81) 400 mg/day (200 mg b.d.) (n = 82) 800 mg/day (400 mg b.d.) (n = 82)	n = 85	–	Patient's global assessment, withdrawal due to lack of efficacy	NR	4	3
Emery, 1999,[211] Pfizer Study 041	RA	400 mg/day (200 mg b.d.) (n = 326)	–	Diclofenac 150 mg/day (75 mg b.d.) (n = 329)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, ulcer (endoscopic, definition: ⩾7 mm), POBs, dyspepsia, MI, total CV thrombotic, total AE	24	5
Simon, 1999,[212,213] Pfizer Study 022	RA	200 mg/day (100 mg b.d.) (n = 240) 400 mg/day (200 mg b.d.) (n = 235) 800 mg/day (400 mg b.d.) (n = 218)	n = 231	Naproxen 1000 mg/day (500 mg b.d.) (n = 500)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, ulcer (endoscopic, definition: ⩾3 mm), dyspepsia, MI, total CV thrombotic, total AE, withdrawals due to GI AE	12	5
Pfizer Study 023[227] (2000–1 submission)	[**Confidential information removed**]							
Kivitz, 2004,[214] Novartis Study 0110	RA	400 mg/day (200 mg b.d.) (n = 223)	–	Ibuprofen 2400 mg/day (800 mg t.d.s.) (n = 216) Lumiracoxib[b]	Pain (Likert), patient's global assessment, withdrawal due to lack of efficacy	Total withdrawal, PUBs, dyspepsia, MI, total CV thrombotic, total AE	13	4
Novartis Study 0114[222] (2004 submission)	[**Confidential information removed**]							

continued

TABLE 16 *Characteristic and quality of included celecoxib RCTs (cont'd)*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Celecoxib	Placebo	NSAID	Efficacy[a]	Safety[a]		
Silverstein, 2000,[50,54,215–219] CLASS study, Pfizer Study 035/102	RA (27%) and OA (73%)	800 mg/day (400 mg b.d.) (n = 3987)	–	Diclofenac 150 mg/day (75 mg b.d.) (n = 1996), Ibuprofen 2400 mg/day (800 mg t.d.s.) (n = 1985)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, POBs, withdrawals due to GI AE	⩾26	5
Goldstein, 2001,[220,269] Pfizer Study 062	RA (28%) & OA (72%)	400 mg/day (200 mg b.d.) (n = 270)	–	Naproxen 1000 mg/day (500 mg b.d.) (n = 267)	Patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, ulcer (endoscopic, definition: ⩾3 mm), POBs, dyspepsia, MI, total CV thrombotic, total AE, withdrawals due to GI AE	12	5
Pfizer Study 071[226] (2000–1 submission)	[**Confidential information removed**]							
Chan, 2002[59]	OA (87%), & RA (2%) & other (11%)	400 mg/day (200 mg b.d.) (n = 144) + placebo	–	Diclofenac 150 mg/day (75 mg b.d.) + omeprazole 20 mg/day (20 mg o.d.) (n = 143)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total AE, withdrawals due to GI AE	25 (6 months)	5
Pfizer Study 105[445] (2004 submission)	[**Confidential information removed**]							
Pfizer Study 106[446] (2004 submission)	[**Confidential information removed**]							
Pfizer Study 107[447] (2004 submission)	[**Confidential information removed**]							

NR, not reported.
[a] Only the outcomes which were included in meta-analyses are listed.
[b] See the section 'Direct comparison of COX-2 selective NSAIDs' (p. 78).
[c] Multidimensional Health Assessment Questionnaire.

example current steroid use, *H. pylori* status or previous peptic ulcers. Where such information was reported, included patients were of functional class I to III, 3–100% had experienced a previous GI ulcer, 7–21% were taking low-dose aspirin and over 75% of patients were chronic NSAIDs users.

Study interventions

Most trials assessed licensed celecoxib doses (200 mg/day, $n = 26$, and 400 mg/day, $n = 18$); six trials also included supra-licensed doses of celecoxib (>400 mg/day). Twenty-two studies compared celecoxib with placebo and 22 compared celecoxib with non-selective NSAIDs: naproxen 500 mg twice daily ($n = 11$), diclofenac 100–150 mg daily ($n = 9$), diclofenac–cholestyramine 280 mg/day ($n = 1$), diclofenac 150 mg plus omeprazole 20 mg/day ($n = 1$) and ibuprofen 800 mg three times daily ($n = 4$).

Assessment of the quality of included trials

A median Jadad score across trials of 5 indicated that trials were generally of 'very good' quality (*Table 16*). A detailed summary of the quality of included trials is provided in Appendix 7).

It was possible, because of access to full trial reports for most celecoxib trials, to assess methodological aspects of their trial design in detail. The majority of trials were properly randomised, double blind, stated ITT analysis and reported small losses to follow-up (<5%). A small number of trials reported concealment details.

Although trial quality was good, a large proportion of patients withdrew (20–50%) due to adverse events, lack of efficacy or other reasons. Withdrawal often differed between drugs and, in general, was lower for celecoxib than for non-selective NSAIDs. This meant that the duration of drug exposure was unequal across randomised groups, leading to a potential bias against celecoxib, although appropriate expression of data, for example as events per 100 patient years of exposure in CLASS, allowed meaningful comparisons.

Assessment of celecoxib efficacy

Efficacy results are summarised in *Table 17*.

Patient's assessment of arthritis pain

There was no statistically significant improvement in pain over non-selective NSAIDs. These results held for OA and RA patients, different celecoxib doses and choice of NSAID comparator.

Patient's assessment of global efficacy

There was no significant difference in global efficacy to comparator NSAIDs. This result held for OA and RA patients, celecoxib doses and also the choice of NSAID comparator.

ACR-20 responder

ACR-20 response was reported in three trials of RA patients. Celecoxib was no better than comparator NSAIDs. These effects were consistent for different celecoxib doses and choice of NSAID comparator.

Withdrawals due to lack of efficacy

There was no difference in withdrawal rates on comparing celecoxib with non-selective NSAIDs. These results held for OA and RA patients, celecoxib dose and choice of NSAID comparator.

Celecoxib tolerability

Adverse events

Adverse events were considered at two levels: all adverse events and GI-related adverse events (*Table 18*).

There were no statistically significant differences in overall and GI-specific adverse events compared with NSAIDs. There was evidence of significant heterogeneity across trials.

Withdrawals

Withdrawals were considered at three levels: withdrawal from the trials for any reason (including loss to follow-up, lack of efficacy or adverse events), withdrawal due to adverse events and withdrawal due to GI-specific adverse events (*Table 19*).

The proportion of GI-specific withdrawals with celecoxib was lower than that with NSAIDs. However, the reduction in withdrawal due to any adverse events and withdrawal for any reason did not reach conventional levels of statistical significance. There was evidence of significant heterogeneity across trials for the latter two outcomes. Stratified analysis by celecoxib dose (*Table 19*) showed that the decrease in GI withdrawal with celecoxib was independent of celecoxib dose.

Safety of celecoxib

The safety of celecoxib was evaluated by considering the development of endoscopic GI ulcers, clinical UGI events (PUBs), complicated UGI events (POBs), MIs and serious CV thrombotic events (*Tables 20* and *21*).

TABLE 17 *Summary of efficacy results for celecoxib versus placebo and NSAIDs*

	Placebo				NSAIDs			
	VAS pain difference: mean (95% CI)	**Global efficacy difference: mean (95% CI)**	**ACR-20: RR (95% CI)**	**Withdrawals due to lack of efficacy: RR (95% CI)**	**VAS pain difference: mean (95% CI)**	**Global efficacy difference: mean (95% CI)**	**ACR-20: RR (95% CI)**	**Withdrawals due to lack of efficacy: RR (95% CI)**
200 mg/day	*–9.7 (–11.8 to –7.8)[a] [17]*	*–0.36 (–0.40 to –0.29) [11]*	*1.38 (1.13 to 1.69) [2]*	*0.39 (0.28 to 0.53)[a] [11]*	–1.4 (–4.1 to 1.9)[a] [12]	0.00 (–0.05 to 0.06) [10]	0.92 (0.62 to 1.33)[a] [2]	0.81 (0.57 to 1.15)[a] [13]
400 mg/day	*–9.4 (–10.9 to –7.8) [6]*	*–0.36 (–0.42 to –0.29) [7]*	*1.64 (1.38 to 1.95) [3]*	*0.44 (0.34 to 0.58)[a] [6]*	2.3 (–2.2 to 6.8) [5]	–0.01 (–0.06 to 0.05) [9]	1.07 (0.92 to 1.25) [3]	1.02 (0.89 to 1.16) [8]
>400 mg/day	*–11.6 (–16.6 to –6.6)[a] [3]*	*–0.39 (–0.48 to –0.29) [4]*	*1.53 (1.28 to 1.82) [3]*	*0.54 (0.47 to 0.62)[a] [4]*	–0.8 (–2.0 to 0.4) [2]	–0.01 (–0.07 to 0.05) [3]	0.97 (0.78 to 1.21) [2]	0.89 (0.74 to 1.07) [3]
OA only	*–10.4 (–12.4 to –8.3)[a] [15]*	*–0.37 (–0.51 to –0.21)[a] [8]*	No trials	*0.31 (0.21 to 0.47)[a] [8]*	1.73 (–1.24 to 4.70) [4]	0 (–0.05 to 0.07) [4]	No trials	0.72 (0.48 to 1.27)[a] [7]
RA only	*–9.9 (–13.7 to –6.1) [3]*	*–0.32 (–0.45 to –0.20) [4]*	*1.54 (1.32 to 1.79) [3]*	*0.53 (0.44 to 0.65)[a] [4]*	–0.1 (–3.6 to 3.4) [2]	–0.02 (–0.17 to 0.13)[a] [4]	1.01 (0.89 to 1.14) [3]	1.05 (0.50 to 2.22) [4]
All trials	***–10.6 (–12.1 to –8.5)[a] [18]***	***–0.35 (–0.45 to –0.25) [12]***	***1.54 (1.32 to 1.79) [3]***	***0.41 (0.33 to 0.52)[a] [12]***	**–0.42 (–2.4 to 1.6)[a] [14]**	**0 (–0.05 to 0.03) [15]**	**1.00 (0.89 to 1.14) [3]**	**0.94 (0.77 to 1.14)[a] [17]**

[a] Significant statistical heterogeneity ($p < 0.10$) – random effects meta-analysis; [ ], no. of trials.

TABLE 18 *Summary of adverse events for celecoxib versus placebo and NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
All adverse events		
200 mg/day	*1.07 (1.02 to 1.13) [13]*	*0.91 (0.89 to 0.95) [15]*
400 mg/day	*1.12 (1.06 to 1.11) [10]*	0.96 (0.93 to 1.00) [9]
800 mg/day	1.07 (0.38 to 1.16) [5]	1.00 (0.98 to 1.02) [4]
OA only	1.06 (1.00 to 1.12) [13]	*0.92 (0.89 to 0.96) [11]*
RA only	*1.13 (1.03 to 1.22) [4]*	1.00 (0.82 to 1.08) [4]
All trials	***1.03 (1.04 to 1.13) [17]***	**0.96 (0.91 to 1.01)[a] [21]**
All GI adverse events		
200 mg/day	1.13 (0.94 to 1.36) [9]	*0.80 (0.64 to 0.91)[a] [9]*
400 mg/day	1.40 (0.98 to 1.99) [8]	0.95 (0.81 to 1.11) [8]
800 mg/day	*1.44 (1.20 to 1.75) [5]*	0.85 (0.71 to 1.00) [3]
OA only	1.15 (0.89 to 1.50) [7]	*0.77 (0.65 to 0.91) [4]*
RA only	1.15 (0.89 to 1.50) [4]	1.04 (0.80 to 1.33)[a] [4]
All trials	***1.30 (1.05 to 1.61)[a] [11]***	**0.90 (0.78 to 1.04)[a] [13]**

[a] Significant statistical heterogeneity ($p < 0.10$) – random effects meta-analysis.

TABLE 19 *Summary of withdrawals for celecoxib versus placebo and NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
All adverse event withdrawals		
200 mg/day	1.20 (0.93 to 1.52) [14]	*0.74 (0.64 to 0.94) [15]*
400 mg/day	1.00 (0.51 to 1.97) [10]	1.00 (0.69 to 1.45)[a] [8]
800 mg/day	*1.61 (1.14 to 2.88) [5]*	*0.91 (0.84 to 0.98) [4]*
OA only	1.00 (0.64 to 1.58)[a] [13]	*0.75 (0.62 to 0.92)[a] [10]*
RA only	1.61 (0.87 to 2.98)[a] [4]	1.16 (0.68 to1.97)[a] [4]
All trials	**1.14 (0.76 to 1.69)[a] [17]**	**0.86 (0.73 to 1.00)[a] [21]**
All GI withdrawals		
200 mg/day	1.38 (0.74 to 2.58) [5]	*0.35 (0.24 to 0.52) [7]*
400 mg/day	1.54 (0.83 to 2.83) [4]	*0.48 (0.36 to 0.64) [7]*
800 mg/day	2.27 (1.00 to 5.17) [2]	0.62 (0.35 to 1.10) [2]
OA only	1.51 (0.85 to 2.66) [5]	*0.39 (0.26 to 0.57) [3]*
RA only	2.60 (0.60 to 11.20) [1]	*0.38 (0.25 to 0.58) [2]*
All trials	**1.65 (0.97 to 2.79) [6]**	***0.45 (0.35 to 0.56) [11]***
All withdrawals		
200 mg/day	*0.76 (0.61 to 0.95)[a] [12]*	1.03 (0.89 to 1.19)[a] [13]
400 mg/day	*0.65 (0.52 to 0.81)[a] [8]*	0.94 (0.75 to 1.19)[a] [7]
800 mg per day	*0.72 (0.61 to 0.84) [4]*	*0.94 (0.90 to 0.97) [3]*
OA only	*0.71 (0.59 to 0.86)[a] [13]*	1.05 (0.87 to 1.26)[a] [10]
RA only	0.60 (0.29 to 1.22) [2]	0.82 (0.68 to 1.00) [2]
All trials	***0.70 (0.39 to 0.83)[a] [15]***	**0.93 (0.84 to 1.05)[a] [18]**

[a] Significant statistical heterogeneity ($p < 0.10$) – random effects meta-analysis.

Endoscopic ulcers

There was a statistically (RR 0.32, 95% CI 0.23 to 0.47) significant decrease in endoscopically confirmed GI ulcers with celecoxib compared with non-selective NSAIDs. This decrease was consistent across celecoxib doses and type of arthritis. There was evidence of significant heterogeneity across trials.

Clinical UGI events (PUBs)

Significantly fewer patients experienced PUBs on celecoxib compared with non-selective NSAIDs (RR 0.55, 95% CI 0.40 to 0.76; NNT 225, 95% CI 168 to 421; *Figure 6*). There were too few trials to examine the effect of type of arthritis, follow-up time and choice of NSAID on the effect of celecoxib on PUBs relative to comparator NSAIDs.

TABLE 20 *Summary of endoscopic GI ulcers and serious GI events (PUBs and POBs) for celecoxib versus placebo or NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
Endoscopic GI ulcers		
200 mg/day	1.49 (0.66 to 3.34) [2]	*0.29 (0.10 to 0.54) [3]*
400 mg/day	1.78 (0.69 to 4.59) [2]	*0.31 (0.20 to 0.48)° [5]*
800 mg/day	1.52 (0.47 to 4.91) [1]	*0.23 (0.11 to 0.48) [1]*
OA only	2.07 (0.79 to 5.46) [1]	*0.28 (0.17 to 0.49) [1]*
RA only	1.25 (0.48 to 3.83) [1]	*0.22 (0.15 to 0.33) [2]*
All trials	**1.70 (0.83 to 3.45) [2]**	***0.32 (0.23 to 0.47)° [6]***
PUBs		
200 mg/day	2.19 (0.24 to 20.29) [2][210,221 *j*]	*0.31 (0.14 to 0.69) [4]*[191,196,223,224 *c*]
400 mg/day	3.01 (0.31 to 28.83) [2][212,222 *f*]	*0.45 (0.24 to 0.86) [4]*[191,196,214,224 *a*]
800 mg/day	–	0.69 (0.47 to1.02) [1][50 *a*]
OA only	1.54 (0.16 to 14.76) [2][221,210 *i*]	*0.42 (0.23 to 0.76) [4]*[196,191,223,224 *a*]
RA only	1.83 (0.21 to 16.16) [2][212,222 *b*]	*0.06 (0.01 to 0.98) [1]*[214 *a*]
vs ibuprofen	–	*0.51 (0.33 to 0.79)* [2][50,214]
vs diclofenac	–	0.79 (0.53 to 1.20) [2][50,224 *b*]
vs naproxen	–	*0.10 (0.04 to 0.22) [3]*[224,191,196 *a*]
vs other NSAIDs	–	[**Confidential information removed**][223]
All trials	**1.68 (0.35 to 8.05) [4][210,212,221,222 *j*]**	***0.55 (0.40 to 0.76) [6]*[50,191,196,214,223,224 *c*]**
POBs		
200 mg/day	0.17 (0.01 to 4.14) [1][202 *m*]	*0.17 (0.04 to 0.75) [4]*[191,196,224,225 *j*]
400 mg/day	[*g*]	0.45 (0.17 to 1.15) [6][191,196,211,220,224,226 *d*]
800 mg/day	[*d*]	0.81 (0.43 to 1.53) [1][50 *b*]
OA only	0.17 (0.01 to 4.14) [1][202 *l*]	*0.17 (0.05 to 0.55) [4]*[191,196,224,225 *h*]
RA only	[*d*]	0.34 (0.01 to 8.23) [1][211 *c*]
vs ibuprofen	–	0.84 (0.41 to 1.74) [2][226,50 *a*]
vs diclofenac	–	0.74 (0.38 to 1.43) [4][226,50,211,224 *e*]
vs naproxen	–	*0.12 (0.04 to 0.37) [5]*[191,196,220,224,225 *f*]
vs other NSAIDs	–	[*b*]
All trials	**0.17 (0.01 to 4.14) [1][202 *n*]**	***0.57 (0.35 to 0.95) [8]*[191,196,211,215,220,224–226 *k*]**

Additional trial(s) reporting zero events in both arms: [a] one trial; [b] two trials; [c] three trials; [d] four trials; [e] five trials; [f] six trials; [g] seven trials; [h] eight trials; [i] 11 trials; [j] 13 trials; [k] 14 trials; [l] 17 trials; [m] 19 trials; [n] 21 trials.
[o] Significant statistical heterogeneity ($p < 0.10$) – random effects meta-analysis.

Complicated UGI events (POBs)

Eight trials compared rates of POBs for celecoxib and NSAIDs (naproxen, ibuprofen or diclofenac). The pooled risk of POBs was reduced with celecoxib (RR 0.57, 95% CI 0.35 to 0.95; NNT 723, 95% CI 478 to 6215; *Figure 7*) and stratification by celecoxib dose indicated that POBs were independent of celecoxib dose.

Myocardial infarctions and serious cardiovascular thrombotic events

An almost two-fold increase in the RR of MI was seen with celecoxib compared with NSAIDs (RR 1.77, 95% CI 1.00 to 3.11; *Figure 8*). This increased risk appeared to be independent of celecoxib dose (*Table 21*).

Subgroup analyses

Subgroup analyses of endoscopic ulcers according to low-dose aspirin use, *H. pylori* status, age (≤65 years versus >65 years) and history of prior GI ulceration was done in six trials; two large trials (CLASS and SUCCESS-I) did subgroup analyses of PUBs and POBs by low-dose aspirin use. SUCCESS-I also presented MI rates in treatment groups stratified by low-dose aspirin use. No identified trials reported subgroup analysis based on the use of anticoagulants.

Endoscopic ulcers

Subgroup stratified pooled RRs for endoscopically detected ulcers with celecoxib compared with non-selective NSAIDs are summarised in *Table 22*.

Relatively small numbers of events in these subgroups counsel caution when interpreting these data. Celecoxib significantly reduced endoscopic events compared with non-selective NSAIDs in each subgroup pair.

TABLE 21 *Summary of myocardial infarction and serious CV thrombotic events for celecoxib versus placebo or NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
MI		
200 mg/day	0.85 (0.23 to 3.16) [4][194,196,212,227 *i*]	*5.45 (1.21 to 24.53) [3]*[196,224,227 *g*]
400 mg/day	2.98 (0.60 to 14.71) [3][191,196,212 *c*]	2.30 (0.80 to 6.58) [7][191,196,211,212,220,224,226 *b*]
800 mg/day	1.04 (0.15 to7.45) [2][212,227 *b*]	1.52 (0.76 to 3.01) [2][50,227 *a*]
OA only	1.32 (0.31 to 5.68) [3][191,194,196 *h*]	3.98 (0.92 to 17.27) [3][191,196,224 *e*]
RA only	0.78 (0.12 to 5.26) [2][212,227]	1.74 (0.30 to 10.23) [3][211,212,227]
vs ibuprofen	–	0.96 (0.45 to 2.07) [2][50,226]
vs diclofenac	–	*3.08 (1.18 to 8.00) [3]*[211,215,224 *d*]
vs naproxen	–	1.32 (0.45 to 3.87) [6][191,196,212,220,224,227 *c*]
vs other NSAIDs	–	*b*
All trials	**1.10 (0.35 to 3.49) [5][191,194,196,212,227 *j*]**	**1.77 (1.00 to 3.11) [9][191,196,211,212,215,220,224,226,227 *f*]**
Serious CV thrombotic events		
200 mg/day	1.20 (0.23 to 4.37) [3]	0.92 (0.42 to 2.01) [2]
400 mg/day	0.92 (0.31 to 2.74) [6]	1.07 (0.55 to 2.11) [6]
800 mg/day	1.00 (0.14 to 7.03) [2]	2.91 (0.12 to 7.11) [1]
OA only	0.89 (0.28 to 2.82) [5]	0.91 (0.47 to 1.76) [3]
RA only	0.35 (0.02 to 5.18) [1]	2.57 (0.33 to 20.03) [2]
All trials	**0.78 (0.27 to 2.22) [6]**	**0.99 (0.54 to 1.79) [6]**

Additional trial(s) reporting zero events in both arms: *a* one trial; *b* two trials; *c* five trials; *d* six trials; *e* nine trials; *f* 12 trials; *g* 14 trials; *h* 15 trials; *i* 16 trials; *j* 17 trials.

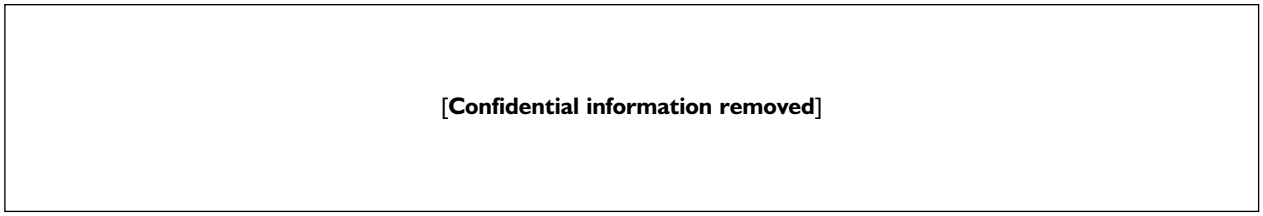


FIGURE 6 *Risk of PUBs with celecoxib (all doses) versus NSAIDs (all drugs) [figure confidential except pooled estimate]*

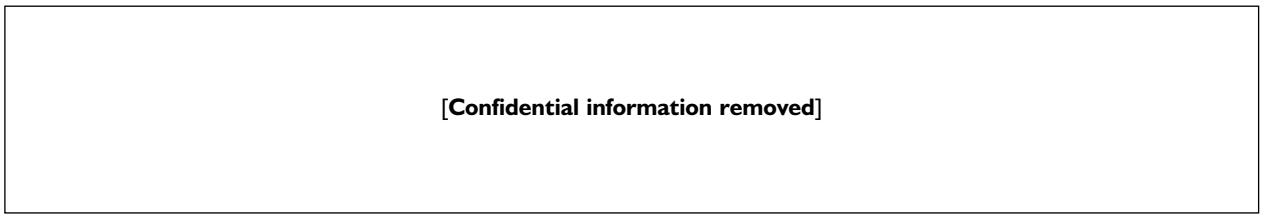


FIGURE 7 *Risk of POBs with celecoxib (all doses) versus NSAIDs (all drugs) [figure confidential except pooled estimate]*

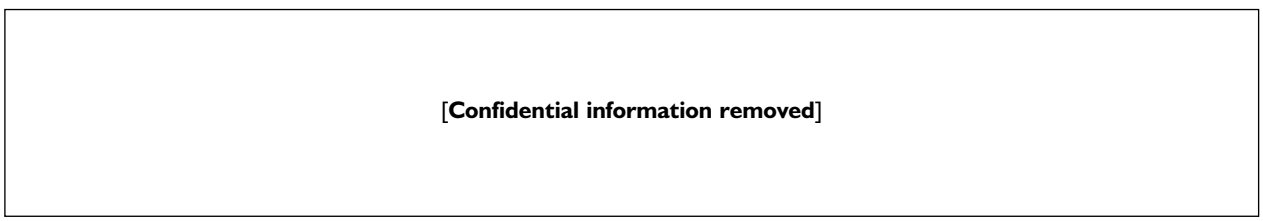


FIGURE 8 *Risk of MI with celecoxib (all doses) vs NSAIDs (all drugs)*

TABLE 22 *Endoscopic ulcer for celecoxib versus non-selective NSAIDs by subgroups*

Subgroup [*N* trials]	Pooled events: celecoxib vs NSAIDs	Pooled RR (95% CI)[a]	Comparative RR and *p*-value[b]
***H. pylori* status:**			
Positive [5]	31/326 vs 82/337	*0.39 (0.27 to 0.57)*	1.56
Negative [5]	44/884 vs 161/788	*0.25 (0.18 to 0.34)*	$p = 0.211$
Low-dose aspirin:			
User [5]	18/185 vs 44/164	*0.39 (0.23 to 0.66)*	1.18
Non-user [5]	78/1596 vs 233/1347	*0.33 (0.18 to 0.63)*[c]	$p = 0.678$
Age:			
≤65 years [5]	33/528 vs 104/430	*0.33 (0.19 to 0.59)*[c]	1.06
>65 years [5]	64/1452 vs 178/1178	*0.31 (0.21 to 0.44)*	$p = 0.756$
Prior GI ulcer:			
Present [5]	28/263 vs 68/208	*0.42 (0.29 to 0.62)*	1.68
Not present [5]	69/1737 vs 223/1334	*0.25 (0.15 to 0.42)*	$p = 0.171$
Steroids:			
User [4]	16/378 vs 44/238	*0.25 (0.10 to 0.63)*	0.69
Non-user [4]	58/877 vs 227/976	*0.36 (0.27 to 0.48)*	$p = 0.376$

[a] RR celecoxib vs non-selective NSAID.
[b] Significance of comparative RR ≠ 1.00.
[c] Significant heterogeneity – pooled by random effects.

TABLE 23 *POBs and PUBs for celecoxib versus non-selective NSAIDs by low-dose aspirin use*

Subgroup [*N* trials]	Pooled events: celecoxib vs NSAIDs	Pooled RR (95% CI)[a]	Comparative RR and *p*-value[b]
POBs			
User [2]	10/1134 vs 8/973	0.99 (0.39 to 2.50)	2.82
Non-user [2]	9/11283 vs 27/7860	*0.35 (0.17 to 0.72)*	$p = 0.138$
PUBs			
User [1]	[**Confidential information removed**]		*0.67*
Non-user [1]			*p = 0.04*

[a] RR celecoxib vs non-selective NSAID.
[b] Significance of comparative RR ≠ 1.00.

PUBs and POBs

The subgroup stratified pooled relative risks of PUBs and POBs for celecoxib compared with non-selective NSAIDs are summarised in *Table 23*.

Low-dose aspirin is suggestive of a reduction in celecoxib benefit on POBs and an increase in benefit on PUBs. However, given the very small number of events observed in the trials, these data need confirmation.

Myocardial infarction

Subgroup analyses for low-dose aspirin on MI rates from the the SUCCESS-I trial are summarised in *Table 24*.

The increase in risk of MI compared with non-selective NSAIDs appeared higher in aspirin users than non-users, although not statistically significant. Given the very small number of events, caution is necessary when interpreting these data.

Impact of concomitant gastroprotective agents

Only one trial comparing celecoxib with an NSAID plus a gastroprotective agent was identified. Chan and colleagues[59] compared diclofenac and omeprazole combined versus celecoxib alone in patients with arthritis who had suffered a recent GI haemorrhage on NSAIDs. The 6-month probability of recurrent bleeding

TABLE 24 *MI for celecoxib versus non-selective NSAIDs by low-dose aspirin use*

Subgroup [*N* trials]	Pooled events	Pooled RR (95% CI)[a]	Comparative RR and *p*-value[b]
MI			
User [1]	[**Confidential information removed**]		2.24
Non-user [1]			$p = 0.121$

[a] RR celecoxib vs non-selective NSAID.
[b] Significance of comparative RR ≠ 1.00.

was 4.5 and 5.6% for the celecoxib and diclofenac–omeprazole groups, respectively (not statistically significant). The authors concluded that the two strategies for recurrent ulcer prevention were equivalent.

Summary

- Forty RCTs were included. Studies compared celecoxib (200–800 mg/day) with either placebo or non-selective NSAIDs (naproxen, ibuprofen, diclofenac). Most trials (24) were in OA patients.
- Celecoxib is of similar efficacy to non-selective NSAIDs for the symptomatic treatment of OA and RA.
- The median Jadad score across trials of 5 indicated that trials were generally of 'very good' quality
- Celecoxib was associated with a non-significant reduction in GI adverse events and significantly fewer GI withdrawals compared with non-selective NSAIDs.
- Celecoxib is associated with significantly fewer endoscopic GI ulcers than non-selective NSAIDs. This benefit appears to be independent of low-dose aspirin use, prior GI ulcer history, *H. pylori* status and age, although conclusions are based on limited data.
- Celecoxib is associated with significantly fewer clinical and complicated UGI events than non-selective NSAIDs. This benefit appears to be independent of concomitant low-dose aspirin, but this conclusion is based on small numbers and needs confirmation.
- In people with a recent UGI bleed, celecoxib and diclofenac plus omeprazole may be equivalent, but this is based on a single trial and needs confirmation.
- Celecoxib was associated with a significantly raised risk of MI compared with non-selective NSAIDs (particularly diclofenac). This effect of celecoxib appears to be independent of low-dose aspirin use, although this conclusion is based on limited data and needs confirmation.

Rofecoxib

Description of included trials

Twenty-seven trials met the inclusion criteria. Nine trials compared rofecoxib with another COX-2 selective NSAID: six with celecoxib, two with lumiracoxib and one with valdecoxib. These direct comparisons are described in the section 'Direct comparison of COX-2 selective NSAIDs' (p. 78). In this section we describe 23 of the trials that compared rofecoxib with a non-selective NSAID or placebo: full details are outlined in Appendix 6 and *Table 25*.

The 23 trials recruited a total of 26,406 participants. The median sample size of the trials was 673 patients. The largest were VIGOR and Assessment of Difference Between Vioxx and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness (ADVANTAGE), which recruited over 8000 and 5000 patients, respectively. Most trials lasted for 3 months or less (18 out of 23), but some lasted as long as 1 year and four trials had an extension phase permitting observations up to 3 years after inception. The results from these trial extensions have not been included here, either because the initial randomisation was not maintained or insufficient data were available.

VIGOR

This key multicentre international RCT studied the safety of rofecoxib 50 mg once daily (twice the licensed dose; $n = 4047$) and naproxen 500 mg twice daily ($n = 4029$) in RA patients. Patients, 80% of whom were female with a mean age of 58 years and had had RA for around 11 years, were treated for a median of 9 months. Over 50% of patients were also on oral corticosteroids, around 43% had evidence of *H. pylori* infection and around 8% had had a serious UGI event previously. PPIs were not permitted in this study but standard doses of H2RAs and antacids were allowed. Confirmed PUBs occurred with rofecoxib at a rate of 2.1 per 100 patient years (POB 0.6) and with naproxen at

TABLE 25 *Characteristics and quality of included rofecoxib RCTs*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Rofecoxib	Placebo	NSAID	Efficacy[a]	Safety[a]		
Ehrich, 1999,[229] MSD Study 010	OA (knee)	25 mg/day (25 mg o.d.) (n = 73) 125 mg/day (125 mg o.d.) (n = 74)	n = 72	–	Pain (VAS), patient's global assessment of disease status, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, POBs, dyspepsia, MI, total CV thrombotic, total AE	6	5
Laine, 1999,[37] MSD Study 044/045	OA (not stated)	25 mg/day (25 mg o.d.) (n = 195) 50 mg/day (50 mg o.d.) (n = 186)	n = 177	Ibuprofen 2400 mg/day (800 mg t.d.s.) (n = 183)	Patient's global assessment of disease, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, ulcer (endoscopic, definition: ⩾3 mm), POBs, total AE (clinical)	24	5
Cannon, 2000,[230,231] MSD Study 035	OA (hip, knee)	12.5 mg/day (12.5 mg o.d.) (n = 259) 25 mg/day (25 mg o.d.) (n = 257)	–	Diclofenac 150 mg/day (50 mg t.d.s.) (n = 268)	WOMAC pain, patient's global assessment of therapy response, patient's global assessment of disease status, withdrawal due to lack of efficacy	Withdrawal due to AE (clinical and laboratory), total withdrawal, ulcer (symptomatic), PUBs, MI, CV thromboembolic, total AE, withdrawals due to GI AE	52 (and extended)	5
Day, 2000,[232,233] MSD Study 040	OA (hip, knee)	12.5 mg/day (12.5 mg o.d.) (n = 244) 25 mg/day (25 mg o.d.) (n = 242)	n = 74	Ibuprofen 2400 mg/day (800 mg t.d.s.) (n = 249)	WOMAC pain, patient's global assessment of disease, patient's global assessment of response to therapy, withdrawal due to lack of efficacy	Withdrawal due to 'clinical' AE, total withdrawal, ulcer (symptomatic), total AE	6	5
Hawkey, 2000,[234] MSD Study 044/045	OA (not stated)	25 mg/day (25 mg o.d.) (n = 195) 50 mg/day (50 mg o.d.) (n = 193)	n = 194	Ibuprofen 2400 mg/day (800 mg t.d.s.) (n = 193)	Patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, ulcer (endoscopic), total AE	24	5

continued

TABLE 25 *Characteristics and quality of included rofecoxib RCTs (cont'd)*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Rofecoxib	Placebo	NSAID	Efficacy[a]	Safety[a]		
Saag, 2000a,[235] MSD Study 033	OA (hip, knee)	12.5 mg/day (12.5 mg o.d.) (n = 219) 25 mg/day (25 mg o.d.) (n = 227)	n = 69	Ibuprofen 2400 mg/day (800 mg t.d.s.) (n = 221)	Pain (WOMAC), patient's global assessment of disease, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, total CV thrombotic, withdrawals due to GI AE	6	5
Saag, 2000b,[235] MSD Study 034	OA (hip, knee)	12.5 mg/day (12.5 mg o.d.) (n = 231) 25 mg/day (25 mg o.d.) (n = 232)	–	Diclofenac 150 mg/day (50 mg t.d.s.) (n = 230)	Pain 0–100 VAS, patient's global assessment of disease status, patient's global assessment of response, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia, withdrawals due to GI AE	52	5
Acevedo, 2001,[236] Arthrotec trial, MSD Study 902	OA (not stated)	12.5 mg/day (12.5 mg o.d.) (n = 242)	–	Arthrotec (diclofenac 100 mg + misoprostol 400 μg/day) (diclofenac 50 mg + misoprostol 200 μg b.d.) (n = 241)	Patient's global assessment (VAS 100 mm), withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia, total CV thrombotic, total AE	6	5
Ehrich, 2001,[237–241] MSD Study 029	OA (hip, knee)	5 mg/day (5 mg o.d.) (n = 149) 12.5 mg/day (12.5 mg o.d.) (n = 144) 25 mg/day (25 mg o.d.) (n = 137) 50 mg/day (50 mg o.d.) (n = 97)	n = 145	–	Withdrawal due to lack of efficacy	Withdrawal due to AE	6	3

continued

TABLE 25 *Characteristics and quality of included rofecoxib RCTs (cont'd)*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Rofecoxib	Placebo	NSAID	Efficacy[a]	Safety[a]		
Truitt, 2001a,[242] MSD Study 058	OA (hip, knee)	12.5 mg/day (12.5 mg o.d.) (n = 118) 25 mg/day (25 mg o.d.) (n = 56)	n = 52	Nabumetone 1500 mg/day (1500 mg o.d.) (n = 115)	WOMAC pain subscale, patient's global assessment of disease status, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal	6	5
Myllykangas-Luosujärvi, 2002,[243] MSD Study 901	OA (knee, hip)	Study 1: 12.5 mg/day (12.5 mg o.d.) (n = 242) Study 2: 12.5 mg/day (12.5 mg o.d.) (n = 229)	–	Naproxen Study 1: 1000 mg/day (500 mg b.d.) (n = 240) Study 2: 1000 mg/day (500 mg b.d.) (n = 233)	Pain on walking VAS, patient's global assessment of disease status, patient's global assessment of response to therapy, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, ulcer (symptomatic) 'serious', PUBs, POBs, dyspepsia, total AE	6	5
Niccoli, 2002[228]	OA (hand, hip, knee)	25 mg/day (25 mg o.d.) (n = 30)	–	Diclofenac 150 mg/day (50 mg t.d.s.) (n = 30) Amtolmetin guacyl 600 mg/day[b] (600 mg o.d.) (n = 30)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total AE, withdrawals due to GI AE	2	1
Lisse, 2003,[244] ADVANTAGE MSD Study 102/903	OA (knee, hand, hip, spine)	25 mg/day (25 mg o.d.) (n = 2785)	–	Naproxen 1000 mg/day (500 mg b.d.) (n = 2772)	Patient's global assessment of disease status, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, MI, total CV thrombotic, withdrawals due to GI AE	12	5
Kivitz, 2004,[161] MSD Study 085	OA (knee)	12.5 mg/day (12.5 mg o.d.) (n = 424)	n = 208	Nabumetone 1000 mg/day (1000 mg o.d.) (n = 410)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to clinical AE, total withdrawal, total AE	6	5

continued

TABLE 25 *Characteristics and quality of included rofecoxib RCTs (cont'd)*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Rofecoxib	Placebo	NSAID	Efficacy[a]	Safety[a]		
McKenna, 2001b,[197] Pfizer Study 152	OA (knee)	25 mg/day (25 mg o.d.) (n = 59)	n = 60	Celecoxib[c]	Pain (VAS), withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia, total CV thrombotic, total AE, withdrawals due to GI AE	6	5
Gibofsky, 2003,[202] Pfizer Study 003	OA (knee)	25 mg/day (25 mg o.d.) (n = 190)	n = 96	Celecoxib[c]	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia, total AE	6	5
Sowers, 2003,[206,249] CRESCENT, Pfizer Study 002 (2004 submission)	OA (hip, knee)		–	Naproxen 1000 mg/day (500 mg b.d.) (n = 130) Celecoxib[c]	[**Confidential information removed**]		12	5
Moskowitz, 2003,[245,286] Pfizer Study 143	OA (not stated)	25 mg/day (25 mg o.d.) (n = 208)	n = 110	Valdecoxib[c]	[**Confidential information removed**]		2	5
Novartis Study 0128[280] (2004 submission)	[**Confidential information removed**]							
Schnitzer, 1999,[246] MSD Study 068	RA	5 mg/day (5 mg o.d.) (n = 158) 25 mg/day (25 mg o.d.) (n = 171) 50 mg/day (50 mg o.d.) (n = 161)	n = 168	–	Pain – global (100 mm VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia, withdrawals due to GI AE	8	5
Bombardier, 2000,[39,44,66] VIGOR	RA	50 mg/day (50 mg o.d.) (n = 4047)	–	Naproxen 1000 mg/day (500 mg b.d.) (n = 4029)	Patient global assessment	Ulcer (symptomatic), dyspepsia, MI, total CV thrombotic, withdrawal due to GI AE	38 median (9 months)	5

continued

TABLE 25 *Characteristics and quality of included rofecoxib RCTs (cont'd)*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Rofecoxib	Placebo	NSAID	Efficacy[a]	Safety[a]		
Guesens, 2002,[247] MSD Study 097	RA	25 mg/day (25 mg o.d.) (n = 306) 50 mg/day (50 mg o.d.) (n = 286)	n = 289	Naproxen 1000 mg/day (500 mg b.d.) (n = 142)	Patient's global assessment of disease activity	Withdrawal due to AE, total withdrawal, dyspepsia, MI, total CV thrombotic, total AE, withdrawal due to GI AE	12	5
Hawkey, 2003,[248] MSD Study 098/103	RA	50 mg/day (50 mg o.d.) (n = 219)	n = 221	Naproxen 1000 mg/day (500 mg b.d.) (n = 220)	Withdrawal due to lack of efficacy	Withdrawal due to AE, ulcer (endoscopic), dyspepsia, total AE, withdrawals due to GI AE	12	5

MSD, Merck Sharp and Dohme.
[a] Only the outcomes which were included in meta-analyses are listed.
[b] 1200 mg/day (600 mg twice daily) for the first three days.
[c] See the section 'Direct comparison of COX-2 selective NSAIDs' (p. 78).

4.5 per 100 patient years (POB 1.4). MIs occurred in 0.1% of patients treated with naproxen compared with 0.4% of rofecoxib patients (RR 0.2, 95% CI 0.1 to 0.7). Many analyses including *post hoc* comparisons of the rate of MIs in those eligible for aspirin and those not, and reviews of the potential beneficial CV effects of naproxen have been carried out in the wake of this finding.

ADVANTAGE

This double-blind RCT compared cessation of treatment for GI adverse effects of rofecoxib 25 mg once daily (n = 2799) with naproxen 500 mg twice daily (n = 2787) in OA patients. It was conducted in primary care practices, principally in the USA. Use of medication to treat GI symptoms was allowed and was used as a secondary end-point, as were other safety outcomes, efficacy and quality of life. The quality of the study was judged to be high (Jadad score 5) but the study duration was only 12 weeks. Discontinuations for GI symptoms occurred in 5.9% of rofecoxib patients compared with 8.1% of naproxen patients (p = 0.005), two POB events occurred with rofecoxib compared with nine for naproxen and five presumed MIs occurred with rofecoxib compared with one for naproxen.

Patient characteristics

Nineteen trials included patients with OA, mostly of hip or knee. Four trials included RA patients and none of the trials included both OA and RA patients. Mean age of the patients ranged from 52 to 83 years. More than 80% of patients had prior use of NSAIDs in 13 of the trials. History of previous GI ulcers was not well reported. At least nine of the trials excluded patients on low-dose aspirin.

Assessment of the quality of included trials

Twenty-one of the 23 studies were judged to be of good quality (Jadad score 5). A small, single-blind trial[228] had a Jadad score of 1. Quality assessments of individual trials are summarised in Appendix 7.

Assessment of rofecoxib efficacy

The efficacy results across trials are summarised in *Table 26*.

Patient's assessment of arthritis pain

Rofecoxib is of comparable efficacy to non-selective NSAIDs for pain relief in OA patients. One trial[247] compared rofecoxib 25 and 50 mg/day with naproxen in RA patients and was marginally favourable to naproxen, but this was not statistically significant.

Patient's assessment of global efficacy

Rofecoxib of equivalent efficacy to non-selective NSAIDs, but there was considerable heterogeneity across trials.

ACR-20 responder

Rofecoxib was equivalent to naproxen in one trial that reported this outcome.[247]

Withdrawals due to lack of efficacy

Similar proportions of patients treated with rofecoxib and non-selective NSAIDs withdrew from trials for lack of efficacy.

Rofecoxib tolerability

Adverse events

Total adverse events with rofecoxib were similar to those with non-selective NSAIDs (*Table 27*).

It was not possible to compare the risk of total GI adverse events between rofecoxib and placebo due to insufficient data. One trial[243] that compared rofecoxib 12.5 mg/day with naproxen 1000 mg/day found a significant reduction in the risk of GI adverse events with rofecoxib.

Withdrawals

Withdrawals from all adverse events and GI adverse events with rofecoxib were significantly more common with non-selective NSAIDs than rofecoxib (*Table 28*). Fewer patients withdrew for any reason compared with non-selective NSAIDs, although differences did not reach statistical significance. Substantial heterogeneity was observed between trials for this outcome.

Safety of rofecoxib

Endoscopic ulcers

Endoscopic ulcers were assessed in two OA studies[37,234] and one RA study[248] after up to 24 weeks of treatment. Cumulative incidences of ulcers were calculated using survival analysis methods, taking account of patient withdrawals. Between 5 and 7% of patients did not have a second endoscopy, after baseline, and were excluded from analysis. There were significantly fewer endoscopic gastroduodenal ulcers compared with non-selective NSAIDs.

Clinical UGI events (PUBs) and complicated UGI events (POBs)

Rofecoxib was associated with significantly fewer POBs (RR 0.40, 95% CI 0.23 to 0.70; NNT 198, 95% CI 155 to 397) and PUBs (RR 0.43, 95% CI 0.32 to 0.57; NNT 81, 95% CI 96 to 128) than with non-selective NSAIDs combined (*Table 29* and *Figures 9* and *10*).

TABLE 26 *Summary of efficacy results for rofecoxib versus placebo and NSAIDs*

	Placebo				NSAIDs			
	VAS pain difference: mean (95% CI)	**Global efficacy difference: mean (95% CI)**	**ACR-20: RR (95% CI)**	**Withdrawals due to lack of efficacy: RR (95% CI)**	**VAS pain difference: mean (95% CI)**	**Global efficacy difference: mean (95% CI)**	**ACR-20: RR (95% CI)**	**Withdrawals due to lack of efficacy: RR (95% CI)**
12.5 mg/day	*–14.88 (–15.18 to –14.58) [3]*	*–0.72 (–0.96 to –0.48) [1]*	No trials	*0.34 (0.25 to 0.45) [5]*	–0.77 (–4.21 to 2.68)[a] [4]	–0.06 (–0.22 to 0.10) [1]	No trials	0.78 (0.61 to 1.00) [7]
25 mg/day	*–12.51 (–18.53 to –6.48)[a] [4]*	*–0.81 (–1.36 to –0.26)[a] [3]*	*1.41 (1.08 to 1.82) [1]*	*0.28 (0.19 to 0.41) [6]*	0.62 (–1.39 to 2.64) [4]	–0.06 (–0.38 to 0.25)[a] [2]	[1][b]	0.99 (0.85 to 1.16) [8]
>25 mg/day	No trials	0.07 (–0.14 to 0.28)[a] [2]	*1.55 (1.20 to 1.99) [1]*	*0.26 (0.17 to 0.40) [6]*	[1][b]	–0.07 (–0.28 to 0.14)[a] [2]	[1][b]	0.95 (0.81 to 1.11) [5]
OA only	*–14.74 (–17.93 to –11.54)[a] [4]*	*–0.87 (–1.36 to –0.38)[a] [3]*	Not applicable	*0.28 (0.22 to 0.35) [8]*	0.09 (–2.92 to 3.10)[a] [6]	–0.01 (–0.18 to 0.16)[a] [3]	No trials	0.92 (0.79 to 1.06) [10]
RA only	*–7.03 (–11.60 to –2.46) [1]*	[2][b]	*1.47 (1.17 to 1.86) [1]*	*0.44 (0.27 to 0.72) [2]*	[1][b]	0.02 (–0.02 to 0.06) [1]	[1][b]	0.97 (0.83 to 1.14) [3]
All trials	***–13.11 (–16.96 to -9.25)[a] [5]***	***–0.87 (–1.36 to –0.38)[a] [3]***	***1.47 (1.17 to 1.86) [1]***	***0.31 (0.25 to 0.38) [10]***	**0.09 (–2.92 to 3.10)[a] [6]**	**0.00 (–0.09 to 0.10)[a] [4]**	**[1][b]**	**0.94 (0.85 to 1.05) [13]**

[a] Significant statistical heterogeneity ($p < 0.10$) – random effects meta-analysis.
[b] Insufficient data for meta-analysis; [ ], no. of trials.

TABLE 27 *Summary of adverse events for rofecoxib versus placebo and NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
All adverse events		
12.5 mg/day	1.05 (0.91 to 1.22) [2]	0.98 (0.92 to 1.04) [4]
25 mg/day	*1.10 (1.03 to 1.18) [5]*	1.01 (0.96 to 1.06) [6]
>25 mg/day	*1.10 (1.03 to 1.17) [5]*	1.01 (0.95 to 1.08) [4]
OA only	*1.07 (1.01 to 1.15) [5]*	1.00 (0.96 to 1.04) [7]
RA only	*1.10 (1.01 to 1.20) [2]*	0.98 (0.89 to 1.08) [2]
All trials	***1.08 (1.03 to 1.14) [7]***	**1.00 (0.96 to1.04) [9]**
GI adverse events		
12.5 mg/day	Not reported	*0.55 (0.42 to 0.73) [1]*
25 mg/day	Not reported	Not reported
>25 mg/day	Not reported	Not reported
OA only	Not reported	*0.55 (0.42 to 0.73) [1]*
RA only	Not reported	Not reported
All trials	Not reported	***0.55 (0.42 to 0.73) [1]***

TABLE 28 *Summary of withdrawals for rofecoxib versus placebo and NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
All adverse event withdrawals		
12.5 mg/day	*1.94 (1.11 to 3.41) [5]*	*0.72 (0.59 to 0.89) [7]*
25 mg/day	1.27 (0.93 to 1.73) [9]	*0.69 (0.48 to 0.99)[a] [10]*
>25 mg/day	*1.86 (1.40 to 2.47) [7]*	0.84 (0.50 to 1.22)[a] [5]
OA only	*1.66 (1.23 to 2.23) [8]*	*0.75 (0.57 to 0.98)[a] [11]*
RA only	1.41 (0.91 to 2.21) [3]	1.00 (0.90 to 1.10) [3]
All trials	***1.58 (1.24 to 2.02) [11]***	***0.78 (0.64 to 0.95)[a] [14]***
All GI withdrawals		
12.5 mg/day	0.79 (0.16 to 3.97) [1]	*0.58 (0.38 to 0.89) [4]*
25 mg/day	1.12 (0.61 to 2.06) [4]	*0.57 (0.34 to 0.95)[a] [6]*
>25 mg/day	*2.07 (1.18 to 3.63) [3][b]*	*0.59 (0.36 to 0.96)[a] [4]*
OA only	1.32 (0.70 to 2.46) [2]	*0.55 (0.34 to 0.88)[a] [6]*
RA only	2.02 (0.91 to 4.46) [3]	*0.73 (0.64 to 0.85) [3]*
All trials	**1.56 (0.96 to 2.55) [5]**	***0.59 (0.45 to 0.78)[a] [9]***
All withdrawals		
12.5 mg/day	*0.57 (0.45 to 0.72 [3]*	0.91 (0.81 to 1.03) [6]
25 mg/day	0.69 (0.45 to 1.06)[a] [6]	0.72 (0.47 to 1.09)[a] [8]
>25 mg/day	0.93 (0.60 to 1.42)[a] [4]	0.70 (0.44 to 1.12) [3]
OA only	0.72 (0.48 to 1.08)[a] [6]	0.76 (0.55 to 1.05)[a] [10]
RA only	0.71 (0.49 to 1.04) [1]	1.03 (0.96 to 1.10) [1]
All trials	**0.72 (0.51 to 1.02)[a] [7]**	**0.79 (0.57 to 1.08)[a] [11]**

[a] Significant statistical heterogeneity ($p < 0.10$) – random effects meta-analysis.
[b] One trial reported zero events in both arms.

Myocardial infarctions and serious cardiovascular thrombotic events

Pooled results from three trials including VIGOR and ADVANTAGE indicated that rofecoxib significantly increases the risk of MI compared with non-selective NSAIDs [RR 2.92, 95% CI 1.36 to 6.28; number-needed-to-harm (NNH) 526, 95% CI 180 to 3482] but that the occurrence of serious CV thrombotic events is comparable (*Table 30* and *Figure 11*). This increased MI risk appears to be specific to comparison against naproxen.

Subgroup analysis

Several studies investigated the role of various risk factors on clinical outcomes. These are summarised below.

TABLE 29 *Summary of endoscopic GI ulcers and clinical and complicated UGI events (PUBs and POBs) for rofecoxib versus placebo or NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	**NSAIDs: RR (95% CI) [*N* trials]**
Endoscopic GI ulcers		
12.5 mg/day	No trial	No trial
25 mg/day	[2][g]	[2][g]
>25 mg/day	[3][g]	[3][g]
OA only	[2][g]	[2][g]
RA only	[1][g]	[1][g]
All trials	**[3][g]**	***[3][g]***
PUBs		
12.5 mg/day	[b]	0.39 (0.09 to 1.68) [2][230,243 b]
25 mg/day	[e]	*0.24 (0.09 to 0.65) [3]*[230,244,247 a]
>25 mg/day	2.36 (0.35 to 15.88) [2][247,248 a]	*0.45 (0.33 to 0.61) [3]*[66,247,248]
OA only	[d]	*0.32 (0.12 to 0.84) [3]*[230,243,244 b]
RA only	1.80 (0.27 to 12.14) [2][247,248 a]	*0.44 (0.33 to 0.60) [3]*[66,247,248]
vs ibuprofen	–	No trials
vs diclofenac	–	0.69 (0.16 to 3.07) [1][230]
vs naproxen	–	*0.42 (0.31 to 0.57) [5]*[66,243,244,247,248]
vs other NSAIDs	–	[b]
All trials	**1.80 (0.27 to 12.14) [2][247,248 e]**	***0.43 (0.32 to 0.57) [6]*[66,230,243,244,247,248 b]**
POBs		
12.5 mg/day	[b]	0.33 (0.01 to 8.20) [1][243 c]
25 mg/day	0.56 (0.12 to 2.68) [3][37,202,234 f]	0.41 (0.06 to 2.77) [2][37,234 c]
>25 mg/day	0.99 (0.14 to 7.03) [2][229,234 b]	*0.41 (0.23 to 0.73) [3]*[37,66,234]
OA only	0.49 (0.12 to 1.97) [4][37,202,229,234 e]	0.24 (0.05 to 1.22) [3][37,234,243 d]
RA only	[a]	*0.43 (0.24 to 0.77) [1]*[66]
vs ibuprofen	–	0.21 (0.03 to 1.41) [2][37,234]
vs diclofenac	–	[a]
vs naproxen	–	*0.43 (0.24 to 0.76) [2]*[66,243 a]
vs other NSAIDs	–	[b]
All trials	**0.49 (0.12 to 1.97) [4][37,202,229,234 f]**	***0.40 (0.23 to 0.70) [4]*[37,66,234,243 d]**

Additional trial(s) reporting zero events in both arms: [a] one trial; [b] two trials; [c] three trials; [d] four trials; [e] five trials; [f] six trials.
[g] Meta-analysis not carried out as it was not possible to calculate RR or hazard ratio from survival analysis data.

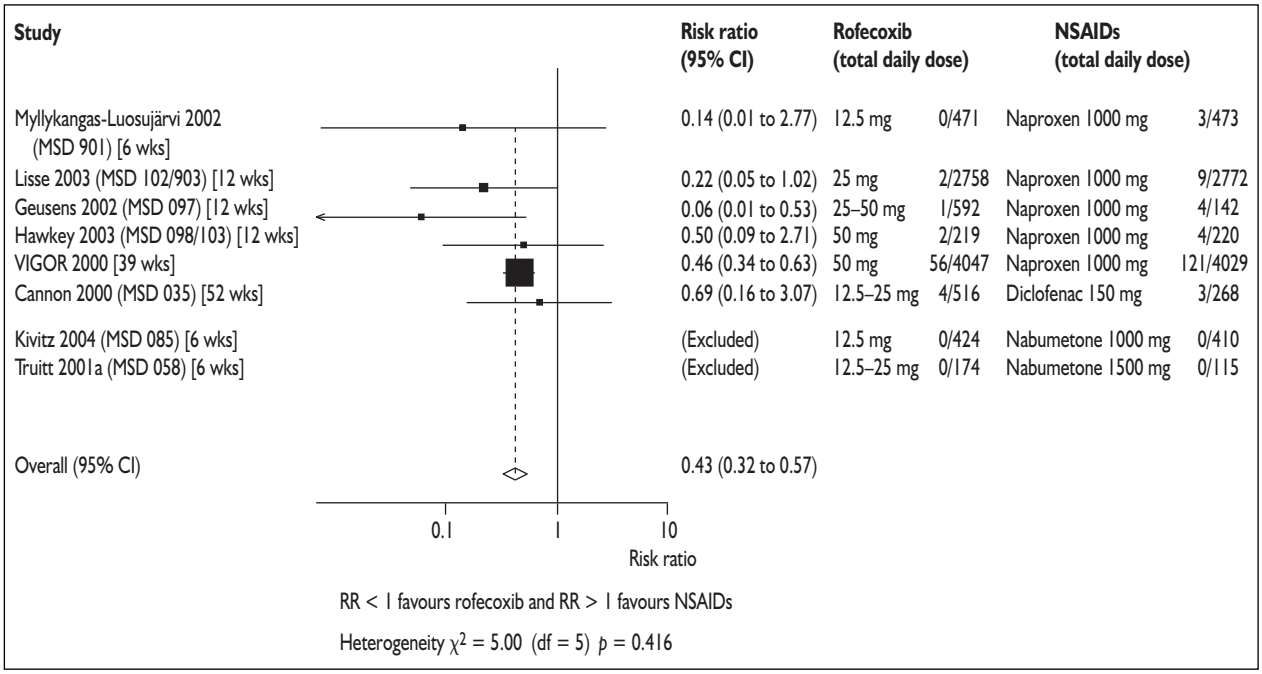


FIGURE 9 *Risk of PUBs with rofecoxib (all doses) versus NSAIDs (all drugs)*

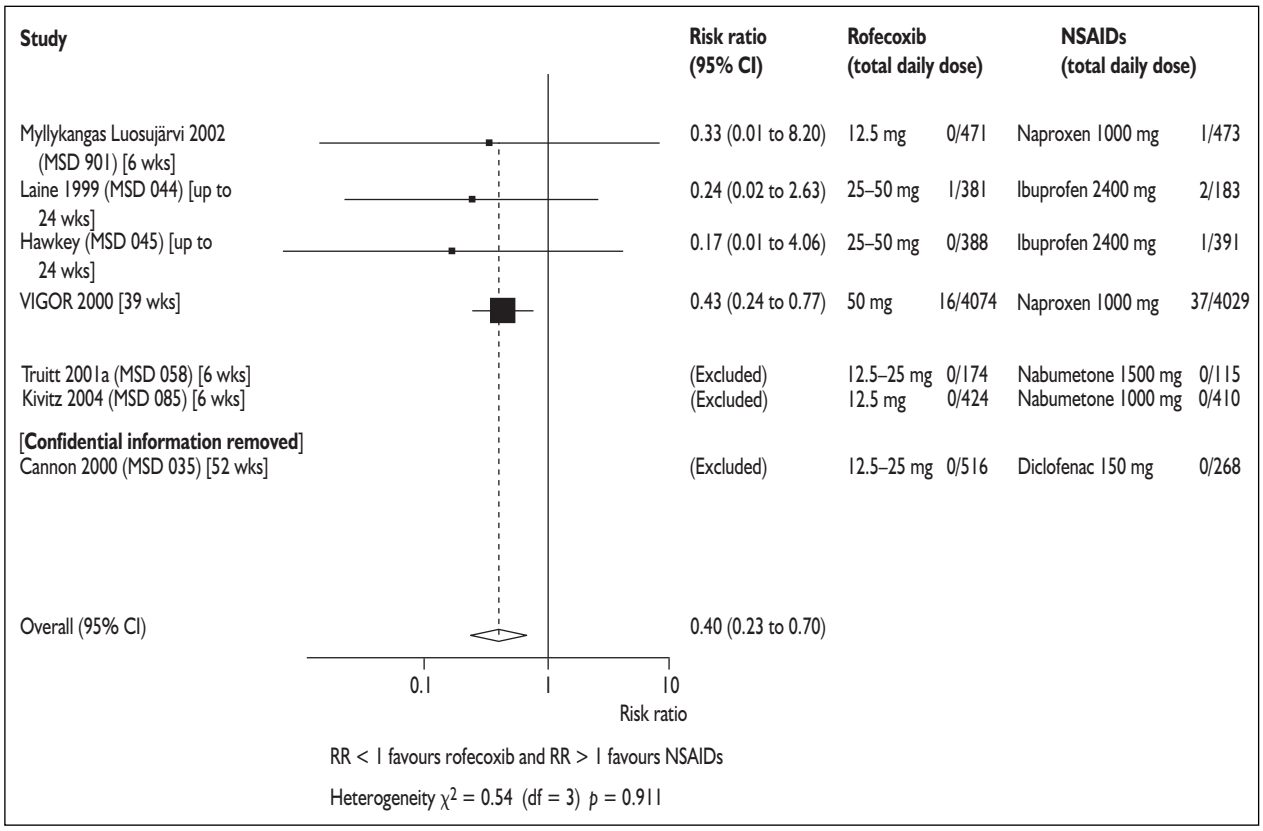


FIGURE 10 *Risk of POBs with rofecoxib (all doses) versus NSAIDs (all drugs)*

TABLE 30 *Summary of myocardial infarction and serious cardiovascular thrombotic events for rofecoxib versus placebo or NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAID: RR (95% CI) [*N* trials]
MI		
12.5 mg/day	1.48 (0.06 to 36.06) [1][161]	1.01 (0.17 to 5.86) [2][161,230 a]
25 mg/day	[d]	2.16 (0.60 to 7.72) [3][230,244,249 a]
>25 mg/day	[b]	*3.98 (1.33 to 11.90) [1]*[66 a]
OA only	1.48 (0.06 to 36.06) [1][161 c]	2.00 (0.67 to 5.99) [4][161,230,244,249 a]
RA only	[a]	*3.98 (1.33 to 11.90) [1]*[66 a]
vs ibuprofen	–	No trials
vs diclofenac	–	0.52 (0.07 to 3.67) [1][230]
vs naproxen	–	*4.06 (1.60 to 10.31) [3]*[66,244,249 b]
vs other NSAIDs	–	2.90 (0.12 to 71.01) [1][161]
All trials	**1.48 (0.06 to 36.06) [1][161 d]**	***2.92 (1.36 to 6.28) [5]*****[66,161,230,244,249 b]**
Serious CV thrombotic events		
12.5 mg/day	Not reported	0.50 (0.14 to 1.47) [1][a]
25 mg/day	[b]	1.02 (0.51 to 2.03) [2][a]
>25 mg/day	[b]	*2.36 (1.38 to 4.02) [1]*[a]
OA only	[a]	0.89 (0.47 to 1.69) [2][a]
RA only	[a]	*2.36 (1.38 to 4.02) [1]*
All trials	**[b]**	**1.31 (0.56 to 3.09)[e] [3][b]**

Additional trial(s) reporting zero events in both arms: [a] one trial; [b] two trials; [c] five trials; [d] six trials.
[e] Significant statistical heterogeneity ($p < 0.10$) – random effects meta-analysis.

[**Confidential information removed**]

FIGURE 11 *Risk of MI with rofecoxib (all doses) versus NSAIDs (all drugs) [figure confidential except pooled estimate]*

H. pylori *status*

Data from VIGOR[66] indicated that the benefits of rofecoxib over naproxen were not influenced by evidence of *H. pylori* infection but that the risks of PUBs were significantly greater in *H. pylori*-positive patients ($p = 0.04$)). However, two endoscopic studies did not find *H. pylori* to be an independent risk factor for gastroduodenal ulcers,[37,248] and neither study found a relationship between outcomes of treatment, in terms of toxicity, and *H. pylori* status.

Low-dose aspirin

Withdrawals due to adverse GI events and use of GI medications remained lower with rofecoxib than with naproxen regardless of aspirin use.[244] Kivitz and colleagues[161] found that concurrent use of low-dose aspirin did not contribute to an increase in adverse events with rofecoxib or nabumetone.

Age

The benefits of rofecoxib over non-selective agents are maintained regardless of age and studies also confirmed that age over 65 years was a risk factor for gastroduodenal ulcers.[37,248] Drugs were similarly efficacious across different age groups.[230,232]

History of prior GI events

Data from VIGOR[66] indicated that the benefits of rofecoxib over naproxen in terms of clinical GI events were similar among patients with (RR 0.4, 95% CI 0.2 to 0.8) or without (RR 0.5, 95% CI 0.3 to 0.7) prior GI events. Endoscopic studies confirmed that a past history of GI events was was a risk factor of gastroduodenal ulcers[37,248] and the advantage of rofecoxib was maintained in patients with and those without prior GI events.[37]

Steroids and other DMARDs

Patients on steroids in VIGOR appeared to benefit more from rofecoxib in that they had a lesser risk of PUBs, compared with naproxen, than those not on steroids: RR 0.4 (95% CI 0.2 to 0.6) for steroid users compared with RR 0.7 (95% CI 0.4 to 1.2) for non-users. Geusens and colleagues[247] observed no unique efficacy or safety findings or trends in subgroups of patients on low-dose corticosteroids, methotrexate or other DMARDs.

Impact of concomitant gastroprotective agents

One study, by Acevedo and colleagues,[236] was the only trial included in this review that compared a COX-2 selective NSAID with a non-selective NSAID combined with misoprostol. In this double-blind, multicentre RCT, rofecoxib 12.5 mg once daily was compared with Arthrotec (diclofenac 50 mg plus misoprostol 0.2 mg) twice daily in 483 OA patients for 6 weeks. The primary end-point in this trial was self-reported diarrhoea. The quality of the trial was judged to be high (Jadad score 5). Unsurprisingly, far more patients on Arthrotec developed diarrhoea (16.2%) and other GI symptoms compared with rofecoxib (6.2% diarrhoea; $p < 0.001$), since both misoprostol and diclofenac have a propensity to cause diarrhoea and abdominal cramping. This trial was not powered to study peptic ulcers or ulcer complications.

Summary

Merck announced voluntary worldwide withdrawal of rofecoxib in September 2004 (see the section 'Safety of COX-2 selective NSAIDs', p. 133) due to its increased risk of serious CV events compared with placebo.

Based on this systematic review and meta-analyses it is concluded that:

- Twenty-three RCTs of rofecoxib compared with either placebo or non-selective NSAID were included. Studies compared rofecoxib (12.5–50 mg/day) with either placebo or non-selective NSAIDs (naproxen, ibuprofen, Arthrotec or nabumetone). Nineteen trials were exclusively in OA patients and four in RA patients.
- Rofecoxib is of similar efficacy to non-selective NSAIDs in the symptomatic treatment of OA and RA.
- Twenty-one of the 23 studies were judged to be of good quality (Jadad score 5).
- Rofecoxib was associated with significantly fewer withdrawals from all adverse events and from GI adverse events compared with non-selective NSAIDs.
- Rofecoxib was associated with significantly fewer endoscopic gastroduodenal ulcers than non-selective NSAIDs and subgroup analyses suggest that the benefit is independent of *H. pylori* infection, age, aspirin use and prior history of GI events, but this conclusion is based on small numbers and needs confirmation.
- Rofecoxib was associated with significantly fewer POBs and PUBs compared with non-selective NSAIDs.
- MIs occurred significantly more commonly in patients treated with rofecoxib than those treated with naproxen.
- Fewer people treated with rofecoxib experience diarrhoea compared with Arthrotec.

Etoricoxib

Description of included trials

Seven trials of etoricoxib met the inclusion criteria. Full details of these trials are outlined in Appendix 6, and summarised in *Table 31*. Trials were relatively small and no trial recruited over 1000 patients. Trials ranged from 6 weeks to 14 months.

Patient characteristics

Four trials recruited only OA, two trials RA and one trial both OA and RA patients. The mean age of trial patients ranged from 52 to 63 years; 66–82% were female and of functional class I–III (the most severely disabled people, class IV, were excluded, in common with most NSAID trials). Patient characteristics were relatively well reported: 8–10% of participants had experienced a previous GI ulcer, 0–7% were taking low-dose aspirin, 32–59% were taking oral corticosteroids and 57–60% were *H. pylori* positive. In three of the trials, all included patients were already taking NSAIDs at the time of recruitment.

Study interventions

Etoricoxib at licensed doses (60 and 90 mg/day) was studied in five trials and two trials included supra-licensed doses (120 mg/day). Six trials compared etoricoxib with placebo and all compared etoricoxib with non-selective NSAIDs: diclofenac (2/7), naproxen (4/7) and ibuprofen (1/7).

Assessment of the quality of included trials

The median Jadad score across trials was 4, indicating that the trials were generally of 'moderate' to 'good' quality (*Table 31*). A full summary of the quality of trials is provided in Appendix 7.

The three trials that scored poorly (Jadad score 3) did so because of poor reporting of trial methods. Four trials provided adequate details of randomisation and concealment, six were double blind and four described ITT analysis. Loss to follow-up, where reported, ranged from <5 to 17%. As with other COX-2 selective drugs, a large proportion of withdrawals and a higher level in the non-selective NSAID arm of trials led to the potential for bias in favour of non-selective NSAIDs.

Assessment of etoricoxib efficacy

The efficacy results across trials are summarised in *Table 32*.

Patient's assessment of arthritis pain

In comparison with non-selective NSAIDs, etoricoxib was equivalent in pain relief. These results appeared relatively consistent across etoricoxib doses and with both OA and RA patients.

Patient's assessment of global efficacy

Global efficacy for etoricoxib was equivalent to that for non-selective NSAIDs. These results appeared to be consistent across etoricoxib doses and with both OA and RA patients.

ACR-20 responder

ACR-20 was equivalent for etoricoxib to non-selective NSAIDs.

Withdrawals due to lack of efficacy

A similar number of patients on etoricoxib withdrew due to lack of efficacy compared with non-selective NSAIDs. These results appeared to be consistent to both OA and RA patients and across etoricoxib doses.

Etoricoxib tolerability

Adverse events

There was no significant difference in overall adverse events for etoricoxib compared with placebo or non-selective NSAID. Specific data on GI-related adverse events were not reported (*Table 33*).

Withdrawals

Etoricoxib significantly reduced the level of both overall and GI-specific withdrawals compared with non-selective NSAIDs (*Table 34*).

Safety of etoricoxib

Outcomes such as PUBs, POBs, MIs and serious CV thrombotic events were reported in four trials (*Tables 35* and *36* and *Figures 12* and *13*).

Endoscopic GI ulcers

Endoscopic ulcers were assessed in two 12-week studies.[253,257] Both studies used etoricoxib 120 mg/day (supra-licensed dose), one included OA patients and another included both OA and RA patients. Cumulative incidences of ulcers were calculated using survival analysis methods, taking into account patient withdrawals. Results showed that etoricoxib was associated with significantly fewer endoscopic gastroduodenal ulcers compared with non-selective NSAIDs.[253,257]

Clinical and complicated UGI events (PUBs and POBs)

There was no significant difference in PUBs and POBs compared with non-selective NSAIDs.

TABLE 31 *Characteristics and quality of included etoricoxib RCTs*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Etoricoxib	Placebo	NSAID	Efficacy[a]	Safety[a]		
Gottesdiener, 2002,[250,251] MSD Study 007	OA (knee)	5 mg/day (5 mg o.d.) (n = 117) 10 mg/day (10 mg o.d.) (n = 114) 30 mg/day (30 mg o.d.) (n = 102) 60 mg/day (60 mg o.d.) (n = 112) 90 mg/day (90 mg o.d.) (n = 112)	n = 60	–	Pain (WOMAC), patient's global assessment (response to therapy), withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia, total AE	6	5
Leung, 2002,[252] MSD Study 019	OA (knee or hip)	60 mg/day (60 mg o.d.) (n = 224)	n = 56	Naproxen 1000 mg/day (500 mg b.d.) (n = 221)	WOMAC pain, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, dyspepsia, total AE, withdrawal due to GI AE	12	5
Hunt, 2003a,[253] MSD Study 029	OA (site not stated)	120 mg/day (120 mg o.d.) (n = 221)	n = 233	Ibuprofen 2400 mg/day (800 mg t.d.s.) (n = 226)	Withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, ulcer (endoscopic, definition: ⩾3 mm), POBs, total AE, withdrawal due to GI AE	12	3
Zacher, 2003,[254] MSD Study 805	OA (knee or hip)	60 mg/day (60 mg o.d.) (n = 256)	–	Diclofenac 150 mg/day (50 mg t.d.s.) (n = 260)	Pain (VAS), patient's global assessment	Withdrawal due to AE	6	4
Collantes, 2002,[255] MSD Study 025	RA	90 mg/day (90 mg o.d.) (n = 353)	n = 357	Naproxen 1000 mg/day (500 mg b.d.) (n = 181)	Pain – patient's global (VAS), patient's global assessment of disease activity, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, total CV thrombotic, total AE, withdrawal due to GI AE	12	3

continued

TABLE 31 *Characteristics and quality of included etoricoxib RCTs (cont'd)*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Etoricoxib	Placebo	NSAID	Efficacy[a]	Safety[a]		
Matsumoto, 2002,[256] MSD Study 024	RA	90 mg/day (90 mg o.d.) (n = 323)	n = 323	Naproxen 1000 mg/day (500 mg b.d.) (n = 170)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, POBs, dyspepsia, MI, total CV thrombotic, total AE, withdrawals due to GI AE	12	3
Hunt, 2003b,[257] MSD Study 026	OA (site not stated) or RA	120 mg/day (120 mg o.d.) (n = 251)	n = 247	Naproxen 1000 mg/day (500 mg b.d.) (n = 244)	Withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, ulcer (endoscopic, definition: ⩾3 mm), withdrawals due to GI AE	12	5

MSD, Merck Sharp and Dohme.
[a] Only the outcomes which were included in meta-analyses are listed.

TABLE 32 *Summary of efficacy results for etoricoxib versus placebo and NSAIDs*

	Placebo				NSAIDs			
	VAS pain difference: mean (95% CI)	**Global efficacy (VAS) difference: mean (95% CI)**	**ACR-20: RR (95% CI)**	**Withdrawals due to lack of efficacy: RR (95% CI)**	**VAS pain difference: mean (95% CI)**	**Global efficacy (VAS) difference: mean (95% CI)**	**ACR-20: RR (95% CI)**	**Withdrawals due to lack of efficacy: RR (95% CI)**
60 mg/day	*–15.81 (–26.66 to –4.97)[a] [2]*	*–9.34 (–15.72 to –2.96) [1]*	No trials	*0.33 (0.14 to 0.76) [2]*	–0.42 (–3.65 to 2.85) [2]	–1.75 (–5.91 to 2.41) [1]	No trials	1.61 (0.22 to 11.70)[a] [2]
90 mg/day	*–16.29 (–19.28 to –13.30)* [2]	*–13.25 (–21.78 to –4.73)[a] [2]*	*1.73 (1.18 to 2.52)[a] [2]*	*0.50 (0.41 to 0.60) [3]*	*–6.7 (–10.6 to –2.8) [1]*	–2.61 (–10.06 to 4.83)[a] [2]	*1.44 (1.26 to 1.63) [2]*	0.81 (0.41 to 1.61)[a] [2]
>90 mg/day	No trials	No trials	No trials	*0.40 (0.18 to 0.90) [2]*	No trials	No trials	No trials	1.32 (0.46 to 3.79) [2]
OA only	*–15.24 (–24.86 to –5.62)[a] [2]*	*–9.34 (–15.72 to –2.96) [1]*	No trials	*0.25 (0.12 to 0.50) [3]*	–0.42 (–2.94 to 2.10) [2]	–1.75 (–5.91 to 2.41) [1]	No trials	0.90 (0.37 to 2.18) [2]
RA only	*–15.8 (–19.1 to –12.6) [1]*	*–13.25 (–21.78 to –4.73)[a]* [2]	1.22 (0.87 to 1.70)[a] [2]	*0.43 (0.36 to 0.52) [2]*	*–6.7 (–10.6 to –2.8) [1]*	–2.61 (–10.06 to 4.83)[a] [2]	1.11 (0.99 to 1.25) [2]	0.81 (0.41 to 1.61)[a] [2]
All trials	***–15.48 (–20.50 to –10.46)[a] [3]***	***–12.10 (–18.05 to –6.15)[a] [3]***	**1.22 (0.87 to 1.70)[a] [2]**	***0.42 (0.35 to 0.50) [6]***	**–2.50 (–6.55 to 1.56)[a] [3]**	**–2.24 (–6.36 to 1.88)[a] [3]**	**1.11 (0.99 to 1.25) [2]**	**1.06 (0.53 to 2.11)[a] [5]**

[a] Significant statistical heterogeneity ($p < 0.10$) – random effects meta-analysis.

TABLE 33 *Summary of adverse events for etoricoxib versus placebo and NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
All adverse events		
60 mg/day	Not reported	Not reported
90 mg/day	Not reported	Not reported
120 mg/day	1.05 (0.89 to 1.25) [1]	0.98 (0.83 to 1.15) [1]
OA only	1.05 (0.89 to 1.25) [1]	0.98 (0.83 to 1.15) [1]
RA only	Not reported	Not reported
All trials	**1.05 (0.89 to 1.25) [1]**	**0.98 (0.83 to 1.15) [1]**
GI adverse events	No trials[a]	No trials[a]

[a] Specific GI AEs reported but not overall GI AEs.

TABLE 34 *Summary of withdrawals for etoricoxib versus placebo and NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
All adverse event withdrawals		
60 mg/day	*0.34 (0.13 to 0.84)* [2]	0.58 (0.08 to 4.34)[a] [2]
90 mg/day	1.03 (0.59 to 1.80) [3]	0.80 (0.40 to 1.59) [2]
120 mg/day	1.43 (0.87 to 2.34) [2]	0.87 (0.56 to 1.34) [2]
OA only	0.79 (0.19 to 3.23)[a] [3]	0.78 (0.24 to 2.48)[a] [3]
RA only	0.96 (0.52 to 1.75) [2]	0.80 (0.40 to 1.59) [2]
All trials	**0.95 (0.56 to 1.60)[a] [7]**	**0.67 (0.39 to 1.15)[a] [6]**
All GI withdrawals		
60 mg/day	0.75 (0.08 to 7.07) [1]	*0.20 (0.06 to 0.67)* [1]
90 mg/day	0.84 (0.26 to 2.72) [2]	0.43 (0.13 to 1.41) [2]
120 mg/day	*9.84 (1.27 to 76.3)* [1]	*0.44 (0.21 to 0.91)* [1]
OA only	0.75 (0.08 to 7.07) [1]	*0.20 (0.06 to 0.67)* [1]
RA only	0.96 (0.52 to 1.75) [2]	0.38 (0.12 to 1.24) [2]
All trials	**1.88 (0.83 to 4.27) [4]**	***0.36 (0.21 to 0.62)* [4]**
All withdrawals		
60 mg/day	*0.44 (0.26 to 0.74)* [2]	*0.53 (0.32 to 0.89)* [1]
90 mg/day	*0.49 (0.42 to 0.57)* [3]	0.79 (0.52 to 1.20) [2]
120 mg/day	0.82 (0.60 to 1.11) [2]	0.89 (0.54 to 1.45) [1]
OA only	*0.61 (0.44 to 0.85)* [3]	0.79 (0.52 to 1.20) [2]
RA only	*0.49 (0.41 to 0.57)* [2]	*0.69 (0.49 to 0.98)* [2]
All trials	***0.57 (0.45 to 0.71)[a] [6]***	***0.76 (0.64 to 0.90)[a] [5]***

[a] Significant statistical heterogeneity ($p < 0.10$) – random effects meta-analysis.

Myocardial infarctions and serious cardiovascular thrombotic events

Only one trial reported MIs and serious CV thrombotic events.[256] There was insufficient evidence to compare etoricoxib and non-selective NSAIDs.

Subgroup analyses

One trial found that age and functional status did not affect the degree of pain relief obtained with etoricoxib (60 mg/day) or diclofenac (50 mg three times per day).[254] No subgroup analyses for adverse effects were available.

Impact of concomitant gastroprotective agents

No relevant trials were identified.

Summary

Based on the systematic review and meta-analysis, it is concluded that:

- Seven RCTs were included. Studies compared etoricoxib (60–120 mg/day) with either placebo or non-selective NSAIDs (naproxen, diclofenac and ibuprofen). Four trials recruited only OA, two trials RA and one trial both OA and RA patients.

TABLE 35 *Summary of endoscopic GI ulcers and clinical and complicated UGI events (PUBs and POBs) for etoricoxib versus placebo and NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
Endoscopic ulcer		
60 mg/day	No trials	No trials
90 mg/day	No trials	No trials
>90 mg/day	[2][e]	[2][e]
OA only	[1][e]	[1][e]
RA only	No trials	No trial
All trials	**[2][e]**	**[2][e]**
PUBs		
60 mg/day	[b]	0.09 (0.00 to 1.61) [1][252]
90 mg/day	3.03 (0.12 to 74.22) [1][255 b]	0.52 (0.07 to 3.70) [2][255,256]
>90 mg/day	Not reported	Not reported
OA only	[b]	0.09 (0.00 to 1.61) [1][252]
RA only	3.03 (0.12 to 74.22) [1][255 a]	0.52 (0.07 to 3.70) [2][255,256]
vs ibuprofen	–	Not reported
vs diclofenac	–	Not reported
vs naproxen	–	0.23 (0.05 to 1.08) [3][252,255,256]
vs other NSAIDs	–	No trial
All trials	**3.03 (0.12 to 74.22) [1][255 c]**	**0.23 (0.05 to 1.08) [3][252,255,256]**
POBs		
60 mg/day	[b]	Not reported
90 mg/day	[c]	0.18 (0.01 to 4.30) [1][256 a]
>90 mg/day	3.16 (0.13 to 77.21) [1][253]	1.02 (0.06 to 16.25) [1][253]
OA only	3.16 (0.13 to 77.21) [1][253 b]	1.02 (0.06 to 16.25) [1][253]
RA only	[b]	0.18 (0.01 to 4.30) [1][256 a]
vs ibuprofen	–	1.02 (0.06 to 16.25) [1][253]
vs diclofenac	–	Not reported
vs naproxen	–	0.18 (0.01 to 4.30) [1][256 a]
vs other NSAIDs	–	No trial
All trials	**3.16 (0.13 to 77.21) [1][253 d]**	**0.46 (0.07 to 3.10) [2][253,256 a]**

Additional trial(s) reporting zero events in both arms: [a] one trial; [b] two trials; [c] three trials; [d] four trials.
[e] Meta-analysis not carried out as it was not possible to calculate RR or hazard ratio from survival analysis data reported by trials.

TABLE 36 *Summary of MI and serious CV thrombotic events for etoricoxib versus placebo and NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
MI		
60 mg/day	[b]	[a]
90 mg/day	3.00 (0.12 to 73.37)[1][256 b]	1.58 (0.06 to 38.66) [1][256 a]
>90 mg/day	Not reported	Not reported
OA only	[b]	[a]
RA only	3.00 (0.12 to 73.37) [1][256 a]	1.58 (0.06 to 38.66) [1][256 a]
vs ibuprofen	–	Not reported
vs diclofenac	–	Not reported
vs naproxen	–	1.58 (0.06 to 38.66) [1][256 b]
vs other NSAIDs	–	No trial
All trials	**3.00 (0.12 to 73.37) [1][256 c]**	**1.58 (0.06 to 38.66) [1][256 b]**
Serious CV thrombotic events		
60 mg/day	[b]	[a]
90 mg/day	3.00 (0.12 to 73.37) [1][b]	1.58 (0.06 to 38.66) [1][a]
>90 mg/day	Not reported	Not reported
OA only	[b]	[a]
RA only	3.00 (0.12 to 73.37) [1][a]	1.58 (0.06 to 38.66) [1][a]
All trials	**3.00 (0.12 to 73.37) [1][c]**	**1.58 (0.06 to 38.66) [1][b]**

Additional trial(s) reporting zero events in both arms: [a] one trial; [b] two trials; [c] three trials.

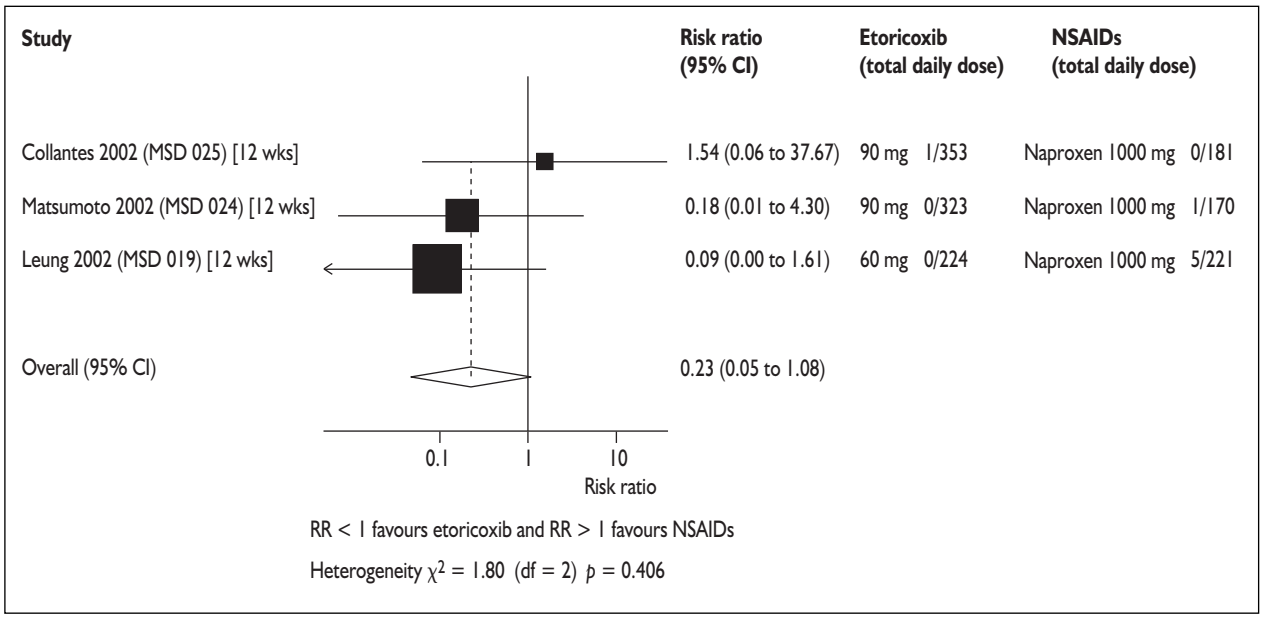


FIGURE 12 *Risk of PUBs with etoricoxib (all doses) versus NSAIDs (all drugs)*

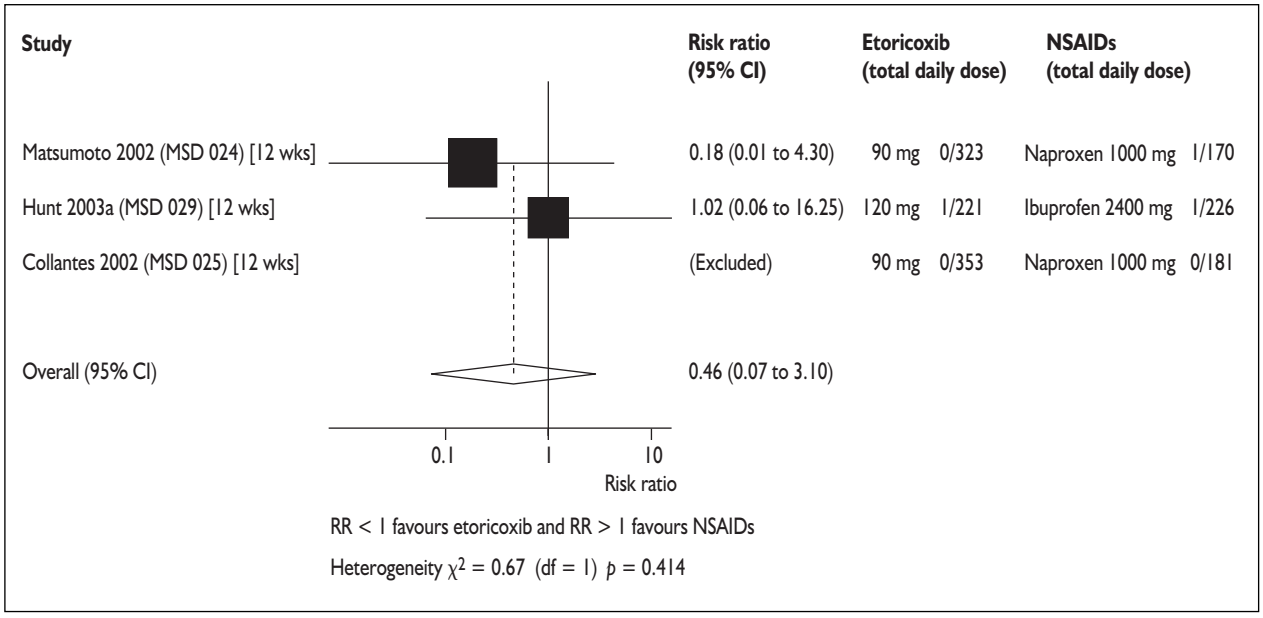


FIGURE 13 *Risk of POBs with etoricoxib (all doses) versus NSAIDs (all drugs)*

- The median Jadad score across trials was 4, indicating that the trials were generally of 'moderate' to 'good' quality.
- Etoricoxib is of equivalent efficacy to non-selective NSAIDs in the symptomatic treatment of OA and RA.
- Etoricoxib is associated with significantly fewer GI-related withdrawals compared with non-selective NSAIDs.
- Only a very small number of POBs and PUBs were reported. There was no significant difference between etoricoxib and non-selective NSAIDs, although there was a trend of reduced PUBs for etoricoxib.
- There is currently insufficient trial evidence to determine whether the incidence of MIs and serious CV thrombotic events is different between etoricoxib and non-selective NSAIDs.
- No trial evidence was found examining the relative benefits of etoricoxib in patients taking low-dose aspirin or anticoagulants or with *H. pylori* infection. Also, no trial has compared etoricoxib with non-selective NSAIDs combined with a gastroprotective agent.

Valdecoxib

Description of included trials

Trials considered confidential in Table 37 *may have subsequently been published.*

Eleven trials of valdecoxib recruiting a total of 9293 participants met the inclusion criteria, nine trials had placebo controls and 10 used one or two non-selective NSAIDs as comparators (naproxen seven, ibuprofen one, diclofenac three). One trial compared valdecoxib with rofecoxib and placebo. The direct comparison with rofecoxib is described in the section 'Direct comparison of COX-2 selective NSAIDs' (p. 78) whereas the comparison with placebo is included in this section. Full details of the 11 trials are outlined in Appendix 6 and summarised in *Table 37*. Sample sizes of trials ranged from 467 to 1218 (median 782) patients. Trials lasted from 2 weeks to 6 months: a majority (8/11) lasted 3 months or less.

Patient characteristics

Six trials recruited exclusively OA patients, four trials RA patients and one trial both OA and RA patients. The mean age of patients was between 55 and 64 years. Low-dose aspirin was permitted in most trials but the proportion of patients on aspirin was not well reported.

Assessment of the quality of included trials

Included trials were generally of good quality; eight out of 11 scored 5 on the Jadad scale. A full summary of the quality of the trials is provided in Appendix 7.

Assessment of valdecoxib efficacy

Efficacy results across trials are summarised in *Table 38*.

Patient's assessment of arthritis pain

Valdecoxib is marginally less efficacious than non-selective NSAIDs at licensed doses. This effect appeared to vary across dose and indication.

Patient's assessment of global efficacy

Valdecoxib was marginally less effective than non-selective NSAIDs. These differences were observed across various doses.

ACR-20 responder

Valdecoxib and non-selective NSAIDs led to similar ACR-20 responses.

Withdrawals due to lack of efficacy

Significantly more patients on valdecoxib withdrew from lack of efficacy compared with non-selective NSAIDs. Significant differences were noted between valdecoxib 10 mg and non-selective NSAIDs in OA patients, but not at higher doses or in RA trials.

Valdecoxib tolerability

Adverse events

Valdecoxib caused significantly fewer GI-related adverse events and adverse events overall compared with non-selective NSAIDs (*Table 39*). These differences were observed across all doses and for OA and RA.

Withdrawals

Withdrawals from all adverse events and from GI-related adverse events were significantly fewer for valdecoxib compared with non-selective NSAIDs (*Table 40*). Withdrawals for any reason were significantly less likely with valdecoxib than with non-selective NSAIDs.

Safety of valdecoxib

Endoscopic GI ulcers

Valdecoxib caused significantly fewer endoscopic ulcers compared with non-selective NSAIDs.

Clinical UGI events (PUBs) and complicated UGI events (POBs)

Valdecoxib reduced the risk of PUBs (RR 0.20, 95% CI 0.03 to 1.46) and POBs (RR 0.43, 95% CI 0.19 to 0.97; NNT 193, 95% CI 136 to 3661) compared with non-selective NSAIDs, although the reduction in PUBs is not statistically significant (*Table 41* and *Figures 14* and *15*).

Myocardial infarctions and serious cardiovascular thrombotic events

Too few serious CV events occurred in valdecoxib trials to draw any sensible conclusions (*Table 42* and *Figure 16*). Pooled results showed two events in valdecoxib patients compared with four events in non-selective NSAID arms of trials (RR 0.25, 95% CI 0.06 to 1.00). Serious CV thrombotic events were also not well reported.

Subgroup analyses

Pavelka and colleagues[265] reported that *H. pylori* status, low-dose aspirin and age had no significant effect on gastroduodenal ulcer rates between valdecoxib 20 and 40 mg and diclofenac150 mg treatment groups ($p \geq 0.51$), but no details were given. Sikes and colleagues[261] and Pfizer Study 047[263] provided numerical data. Pooled results from these two trials are summarised in *Table 43*.

TABLE 37 *Characteristic and quality of included valdecoxib RCTs*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Valdecoxib	Placebo	NSAID	Efficacy[a]	Safety[a]		
Fiechtner, 2001,[258,268] Pfizer Study 015	OA (knee)	1 mg/day (0.5 mg b.d.) (*n* = [**Confidential information removed**]) 2.5 mg/day (1.25 mg b.d.) (*n* = [**Confidential information removed**]) 5 mg/day (2.5 mg b.d.) (*n* = [**Confidential information removed**]) 10 mg/day (5 mg b.d.) (*n* = [**Confidential information removed**]) 10 mg/day (10 mg o.d.) (*n* = [**Confidential information removed**]) 20 mg/day (10 mg b.d.) (*n* = [**Confidential information removed**])	*n* = [**Confidential information removed**]	Naproxen 1000 mg/day (500 mg b.d.) (*n* = [**Confidential information removed**])	[**Confidential information removed**]		6	5
Kivitz, 2002,[259] Pfizer Study 053	OA (knee)	5 mg/day (5 mg o.d.) (*n* = 201) 10 mg/day (10 mg o.d.) (*n* = 206) 20 mg/day (20 mg o.d.) (*n* = 202)	*n* = 205	Naproxen 1000 mg/day (500 mg b.d.) (*n* = 205)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, ulcer (endoscopic, definition: >5 mm), dyspepsia, Total AE	12	5
Makarowski, 2002,[260] Pfizer Study 049	OA (hip)	5 mg/day (5 mg o.d.) (*n* = 120) 10 mg/day (10 mg o.d.) (*n* = 111)	*n* = 118	Naproxen 1000 mg/day (500 mg b.d.) (*n* = 118)	Pain (VAS), patient's global assessment of arthritis, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia, total AE, withdrawal due to GI AE	12	3

continued

TABLE 37 *Characteristic and quality of included valdecoxib RCTs (cont'd)*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Valdecoxib	Placebo	NSAID	Efficacy[a]	Safety[a]		
Sikes, 2002,[261] Pfizer Study 048	OA (not stated)	10 mg/day (10 mg od) (n = 204) 20 mg/day (20 mg o.d.) (n = 219)	n = 210	Diclofenac 150 mg/day (75 mg b.d.) (n = 212), ibuprofen 2400 mg/day (800 mg t.d.s.) (n = 207)	Patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, ulcer (endoscopic, definition: ⩾3 mm), dyspepsia, total CV thrombotic, total AE	12	4
Moskowitz, 2003,[245,286] Pfizer Study 143	OA (not stated)	10 mg/day (10 mg o.d.) (n = 212)	n = 110	Rofecoxib[b]	[**Confidential information removed**]		2	5
Pfizer Study 063[262]	[**Confidential information removed**]							
Pfizer Study 047[263]	[**Confidential information removed**]							
Bensen, 2002,[264] Pfizer Study 60	RA	10 mg/day (10 mg o.d.) (n = 209) 20 mg/day (20 mg o.d.) (n = 212) 40 mg/day (40 mg o.d.) (n = 221)	n = 222	Naproxen 1000 mg/day (500 mg b.d.) (n = 226)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia, total CV thrombotic, total AE	12	3
Pavelka, 2003,[265] Pfizer Study 62	RA	20 mg/day (20 mg o.d.) (n = 246) 40 mg/day (40 mg o.d.) (n = 237)	–	Diclofenac 150 mg/day (75 mg b.d.) (n = 239)	Pain (VAS 100 mm), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, ulcer (endoscopic, definition: ⩾3 mm), POBs, dyspepsia, total AE, withdrawals due to GI AE	26	5
Pfizer Study 016[266]	[**Confidential information removed**]							
Pfizer Study 061[267]	[**Confidential information removed**]							

[a] Only the outcomes which were included in meta-analyses are listed.
[b] See the section 'Direct comparison of COX-2 selective NSAIDs' (p. 78).

TABLE 38 *Summary of efficacy results for valdecoxib versus placebo and NSAIDs*

	Placebo				NSAIDs			
	VAS pain difference: mean (95% CI)	**Global efficacy difference: mean (95% CI)**	**ACR-20: RR (95% CI)**	**Withdrawals due to lack of efficacy: RR (95% CI)**	**VAS pain difference: mean (95% CI)**	**Global efficacy difference: mean (95% CI)**	**ACR-20: RR (95% CI)**	**Withdrawals due to lack of efficacy: RR (95% CI)**
10 mg/day	*–10.05 (–13.98 to –6.13)[a] [5]*	*–0.40 (–0.60 to –0.20) [1]*	*1.41 (1.20 to 1.66) [3]*	*0.50 (0.39 to 0.63)[a] [8]*	*3.20 (0.81 to 5.58) [5]*	*0.23 (0.12 to 0.34) [2]*	0.99 (0.86 to 1.13) [3]	*1.25 (1.05 to 1.49) [8]*
20 mg/day	*–10.20 (–15.73 to –4.67)[a] [4]*	*–0.50 (–0.71 to –0.29) [1]*	*1.42 (1.21 to 1.67) [3]*	*0.50 (0.42 to 0.59) [6]*	*2.81 (0.31 to 5.30) [5]*	*0.20 (0.09 to 0.31) [2]*	0.96 (0.85 to 1.08) [4]	1.17 (0.98 to 1.40) [8]
>20 mg/day	*–11.7 (–17.06 to –6.34) [1]*	*–0.4 (–0.61 to –0.19) [1]*	*1.48 (1.26 to 1.76) [2]*	*0.55 (0.45 to 0.67) [2]*	4.40 (–0.89 to 9.69) [1]	*0.3 (0.10 to 0.50) [1]*	0.96 (0.85 to 1.09) [3]	1.03 (0.85 to 1.25) [4]
OA only	*–11.39 (–18.06 to –4.72)[a] [3]*	No trials	No trials	*0.39 (0.24 to 0.63)[a] [5]*	–6.05 (–18.28 to 6.17)[a] [3]	*0.20 (0.08 to 0.32) [1]*	No trials	*1.36 (1.06 to 1.75) [5]*
RA only	*–9.11 (–12.67 to –5.55) [2]*	*–0.43 (–0.60 to –0.26) [1]*	*1.43 (1.24 to 1.64) [3]*	*0.56 (0.49 to 0.64) [3]*	*4.64 (1.11 to 8.18) [2]*	*0.27 (0.11 to 0.43) [1]*	0.96 (0.87 to 1.07) [4]	0.99 (0.95 to 1.02) [4]
All trials	***–10.01 (–13.94 to –6.09)[a] [5]***	***–0.43 (–0.60 to –0.26) [1]***	***1.43 (1.24 to 1.64) [3]***	***0.49 (0.39 to 0.61)[a] [8]***	**–1.89 (–10.71 to 6.93)[a] [5]**	***0.22 (0.14 to 0.32) [2]***	**0.96 (0.87 to 1.07) [4]**	***1.16 (1.01 to 1.33) [10]***

[a] Significant statistical heterogeneity ($p < 0.10$) – random effects meta-analysis.

TABLE 39 *Summary of adverse events for valdecoxib versus placebo and NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
All adverse events		
10 mg/day	1.07 (0.99 to 1.15) [8]	*0.88 (0.83 to 0.94) [8]*
20 mg/day	*1.15 (1.06 to 1.25) [6]*	*0.90 (0.86 to 0.96) [8]*
>20 mg/day	*1.25 (1.10 to 1.42) [2]*	*0.94 (0.90 to 0.99) [4]*
OA only	1.02 (0.94 to 1.11) [5]	*0.88 (0.82 to 0.93) [5]*
RA only	1.03 (0.71 to 1.49)[a] [3]	0.83 (0.62 to 1.11)[a] [4]
All trials	**1.00 (0.87 to 1.15)[a] [8]**	***0.87 (0.78 to 0.97)[a] [10]***
GI adverse events		
10 mg/day	1.15 (0.99 to 1.34) [6]	*0.78 (0.69 to 0.88) [6]*
20 mg/day	1.09 (0.92 to 1.29) [5]	*0.73 (0.66 to 0.82) [7]*
>20 mg/day	*1.33 (1.09 to 1.64) [2]*	*0.84 (0.76 to 0.92) [4]*
OA only	1.05 (0.72 to 1.52)[a] [3]	*0.84 (0.71 to 0.98) [2]*
RA only	0.98 (0.71 to 1.36)[a] [3]	*0.69 (0.55 to 0.87)[a] [4]*
All trials	**1.02 (0.82 to 1.26)[a] [6]**	***0.74 (0.66 to 0.84)[a] [8]***

[a] Significant statistical heterogeneity ($p < 0.10$) – random effects meta-analysis.

TABLE 40 *Summary of withdrawals for valdecoxib versus placebo and NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
All adverse event withdrawals		
10 mg/day	1.17 (0.87 to 1.58) [8]	*0.65 (0.51 to 0.81) [8]*
20 mg/day	1.04 (0.74 to 1.46) [6]	*0.58 (0.46 to 0.73) [8]*
>20 mg/day	1.73 (0.99 to 3.00) [2]	0.91 (0.73 to 1.13) [4]
OA only	1.07 (0.77 to 1.49) [5]	*0.57 (0.46 to 0.71) [5]*
RA only	1.17 (0.75 to 1.82) [3]	0.73 (0.39 to 1.39)[a] [4]
All trials	**1.11 (0.85 to 1.44) [8]**	***0.66 (0.51 to 0.86)[a] [10]***
All GI withdrawals		
10 mg/day	1.61 (0.79 to 3.28) [4]	*0.44 (0.29 to 0.68) [5]*
20 mg/day	0.91 (0.37 to 2.28) [3]	*0.35 (0.23 to 0.54) [5]*
>20 mg/day	1.68 (0.56 to 5.07) [1]	*0.56 (0.41 to 0.77) [3]*
OA only	1.43 (0.53 to 3.82) [2]	*0.36 (0.23 to 0.57) [3]*
RA only	1.05 (0.44 to 2.50) [2]	*0.40 (0.27 to 0.59) [3]*
All trials	**1.20 (0.63 to 2.30) [4]**	***0.47 (0.38 to 0.59) [7]***
All withdrawals		
10 mg/day	*0.66 (0.59 to 0.73) [8]*	0.99 (0.89 to 1.10) [8]
20 mg/day	*0.64 (0.54 to 0.77)[a] [6]*	0.90 (0.76 to 1.08)[a] [8]
>20 mg/day	*0.65 (0.56 to 0.75) [2]*	0.94 (0.84 to 1.06) [4]
OA only	*0.58 (0.43 to 0.77)[a] [5]*	0.86 (0.71 to 1.04)[a] [5]
RA only	*0.56 (0.38 to 0.84)[a] [3]*	0.88 (0.68 to 1.13)[a] [4]
All trials	***0.57 (0.45 to 0.71)[a] [8]***	***0.88 (0.77 to 0.99)[a] [10]***

[a] Significant statistical heterogeneity ($p < 0.10$) – random effects meta-analysis.

No trials reported subgroup analyses for clinical UGI events, complicated UGI events or serious CV events.

H. pylori *status*

Both studies reported a non-significant trend towards higher endoscopic ulcer rates among patients who were tested *H. pylori* positive.[261,263] The risk reduction for patients treated with valdecoxib compared with non-selective NSAIDs does not appear to be affected by *H. pylori* status.

Low-dose aspirin

No consistent results were observed; Sikes and colleagues found that aspirin increased endoscopic gastroduodenal ulcer rates with valdecoxib 10 mg, diclofenac and ibuprofen, but not with valdecoxib

TABLE 41 *Summary of endoscopic GI ulcers and clinical and complicated UGI events (PUBs and POBs) for valdecoxib versus placebo or NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	**NSAIDs: RR (95% CI) [*N* trials]**
Endoscopic GI ulcers		
10 mg/day	0.73 (0.35 to 1.53) [2]	*0.28 (0.15 to 0.51) [2]*
20 mg/day	0.99 (0.51 to 1.93) [2]	*0.35 (0.24 to 0.53) [3]*
>20 mg/day	Not reported	*0.35 (0.24 to 0.51) [2]*
OA only	0.87 (0.48 to 1.57) [2]	*0.32 (0.21 to 0.49) [2]*
RA only	Not reported	*0.29 (0.17 to 0.48) [1]*
All trials	**0.87 (0.48 to 1.57) [2]**	***0.32 (0.25 to 0.41) [4]***
PUBs		
10 mg/day	[b]	0.23 (0.02 to 2.09) [2][267,268]
20 mg/day	[b]	0.32 (0.03 to 3.10) [2][267,268]
>20 mg/day	[**Confidential information removed**][267]	[**Confidential information removed**][267]
OA only	[a]	[**Confidential information removed**][268]
RA only	[**Confidential information removed**][267]	[**Confidential information removed**][267]
vs ibuprofen	–	No trials
vs diclofenac	–	No trials
vs naproxen	–	0.20 (0.03 to 1.46) [2][267,268]
vs other NSAIDs	–	No trials
All trials	[**Confidential information removed**][267] [a]	0.20 (0.03 to 1.46) [2][267,268]
POBs		
10 mg/day	[c]	0.23 (0.02 to 2.09) [2][267,268] [a]
20 mg/day	[b]	0.72 (0.24 to 2.14) [4][262,265,267,268]
>20 mg/day	[**Confidential information removed**][267]	0.41 (0.15 to 1.14) [3][263,265,267]
OA only	[b]	0.88 (0.18 to 4.29) [2][262,268]
RA only	[**Confidential information removed**][267]	0.26 (0.06 to 1.12) [2][265,267]
vs ibuprofen	–	No trials
vs diclofenac	–	0.61 (0.18 to 2.09) [2][262,265]
vs naproxen	–	*0.33 (0.11 to 0.99) [3]*[263,267,268]
vs other NSAIDs	–	No trials
All trials	[**Confidential information removed**][267] [b]	***0.43 (0.19 to 0.97) [5]***[262,263,265,267,268]

Additional trial(s) reporting zero events in both arms: [a] one trial; [b] two trials; [c] three trials.

[**Confidential information removed**]

FIGURE 14 *Risk of PUBs with valdecoxib (all doses) versus NSAIDs (all drugs) [figure confidential except pooled estimate]*

[**Confidential information removed**]

FIGURE 15 *Risk of POBs with valdecoxib (all doses) versus NSAIDs (all drugs) [figure confidential except pooled estimate]*

TABLE 42 *Summary of myocardial infarction and serious CV thrombotic events for valdecoxib versus placebo or NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
MI		
10 mg/day	1.02 (0.15 to 7.04) [2][266,267 b]	0.48 (0.11 to 2.09)[3][262,266,267 a]
20 mg/day	0.33 (0.01 to 8.18) [1][267 b]	0.20 (0.02 to 1.71) [2][262,267 b]
>20 mg/day	0.35 (0.01 to 8.56) [1][267]	0.35 (0.01 to 8.52) [1][267]
OA only	[b]	0.07 (0.00 to 1.39) [1][262 a]
RA only	0.52 (0.09 to 3.08) [2][266,267]	0.52 (0.09 to 3.07) [2][266,267]
vs ibuprofen	–	No trials
vs diclofenac	–	0.07 (0.00 to 1.39) [1][262]
vs naproxen	–	0.52 (0.09 to 3.07) [2][266,267 a]
vs other NSAIDs	–	No trials
All trials	**0.52 (0.09 to 3.08) [2][266,267 b]**	**0.25 (0.06 to 1.00) [3][262,266,267 a]**
Serious CV thrombotic events		
10 mg/day	0.19 (0.13 to 77.77) [1][b]	[a]
20 mg/day	3.14 (0.13 to 76.68) [1][a]	[a]
>20 mg/day	3.01 (0.12 to 73.58) [1]	No trials
OA only	[b]	[a]
RA only	2.43 (0.13 to 46.81) [1]	No trials
All trials	2.43 (0.13 to 46.81) [1][b]	[a]

Additional trial(s) reporting zero events in both arms: [a] one trial; [b] two trials.

[**Confidential information removed**]

FIGURE 16 *Risk of MI with valdecoxib (all doses) versus NSAIDs (all drugs) [figure confidential except pooled estimate]*

TABLE 43 *Endoscopic ulcers for valdecoxib versus non-selective NSAIDs by subgroups*

Subgroup [*N* trials]	Pooled events valdecoxib vs NSAID	Pooled RR (95% CI)[a]	Comparative RR
H. pylori status:			
Positive [2]	[**Confidential information removed**]	[**Confidential information removed**]	0.97
Negative [2]			
Low-dose aspirin:			
User [2]	[**Confidential information removed**]	[**Confidential information removed**]	3.00
Non-user [2]			
Age:			
⩾65 years [2]	[**Confidential information removed**]	[**Confidential information removed**]	1.63
<65 years [2]			
Prior GI ulcer:			
Present [1]	[**Confidential information removed**]	[**Confidential information removed**]	1.63
Not present [1]			

[a] RR valdecoxib versus non-selective NSAIDs.

20 mg and placebo. In contrast, the Pfizer Study 047 found [**Confidential information removed**].

Age

Both studies[261,263] reported a higher incidence of endoscopic ulcers among patients aged 65 years and over compared with younger patients. The risk reduction for patients treated with valdecoxib compared with non-selective NSAIDs does not appear to be affected by age.

Prior GI ulcers

No consistent result was reported: Sikes and colleagues found that a prior ulcer history had no effect on ulcer incidence in any treatment group; the Pfizer Study 047 reported [**Confidential information removed**].

Impact of concomitant gastroprotective agents

No relevant trials were identified.

Summary

Pfizer suspended the sale of valdecoxib in April 2005 following FDA and EMEA reviews that highlighted serious skin reactions associated with this drug (see the section 'Safety of COX-2 selective NSAIDs', p. 133).

Based on the systematic review and meta-analysis, it is concluded that:

- Eleven RCTs were included. Studies compared valdecoxib (10–80 mg/day) with either placebo or non-selective NSAIDs (naproxen or diclofenac). Six trials recruited exclusively OA patients, four trials RA patients and one trial both OA and RA patients.
- Included trials were generally of good quality; eight out of 11 scored 5 on the Jadad scale
- Valdecoxib is equivalent to or marginally inferior in efficacy, particularly in RA patients, compared with non-selective NSAIDs.
- Valdecoxib is associated with significantly fewer total and GI-related adverse events and withdrawals as a result of adverse events than non-selective NSAIDs.
- Valdecoxib is associated with significantly fewer endoscopic ulcers than non-selective NSAIDs.
- Based on short-term trials (6 months or less), valdecoxib was associated with fewer clinical and complicated UGI events than non-selective NSAIDs. There are insufficient data on the occurrence of MIs and the effect of *H. pylori*, aspirin, age, anticoagulants and concomitant low-dose aspirin to draw any conclusions about the benefits or hazards of valdecoxib. Also, no trial compared valdecoxib with non-selective NSAIDs with a gastroprotective agent.

Lumiracoxib

Quantity of research available

A few trials considered confidential in Table 44 *have subsequently been published.*

Fifteen trials met the inclusion criteria: a detailed summary of their characteristics is given in Appendix 6 and summarised in *Table 44*. Most trials lasted 3 months or less and only two trials lasted 6 months or longer. The median sample size of trials was 893 patients. A key study, the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), was randomised over 18,000 patients.

TARGET

TARGET was a double-blind RCT of patients with OA who were randomised, in two identical substudies, to receive lumiracoxib (400 mg/day, $n = 9156$), naproxen (1 g/day, $n = 4754$) in study 0117 or ibuprofen (2.4 g/day, $n = 4415$) in study 2332. The trial was designed to test the hypothesis that lumiracoxib reduced the risk of serious UGI complications compared with non-selective NSAIDs. A secondary objective was to compare CV morbidity and mortality between agents. Patients were stratified by age and use of low-dose aspirin. The original protocol for TARGET was amended and patients with RA were excluded because [**Confidential information removed**].

Description of included trials

Patients' characteristics

Most trials studied patients with OA (nine studies), usually of the hip or knee. The average age of patients across trials ranged from 50 to 65 years and 63–84% were female. Details of baseline risk characteristics such as *H. pylori* status or previous peptic ulcers were either not reported or not collected in many trials, but where reported, patients were of functional class I–III, 0–7% had experienced a previous GI ulcer, 0–24% were taking low-dose aspirin and over 57% needed NSAIDs long-term.

Study interventions

Included trials studied lumiracoxib for a wide range of doses (100–1200 mg/day). Lumiracoxib was compared with placebo in 10 studies and with non-selective NSAIDs in eight: naproxen 1 g/day ($n = 4$), diclofenac 150 mg/day ($n = 2$), or ibuprofen 2.4 g/day ($n = 3$). Seven studies compared lumiracoxib with a COX-2 selective NSAID: celecoxib 200 or 400 mg/day ($n = 5$) or rofecoxib 25 mg once daily ($n = 2$). These direct

TABLE 44 *Characteristics and quality of included lumiracoxib RCTs*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Lumiracoxib	Placebo	NSAID	Efficacy[a]	Safety[a]		
Schnitzer, 2004,[270,438] Novartis Study 0104	[**Confidential information removed**]							
Hawkey, 2004,[207,287] Novartis Study 0126	[**Confidential information removed**]							
Benevolenskaya, 2003,[271,441] Novartis Study 2316	[**Confidential information removed**]							
Fleischmann, 2003,[208,209] Novartis Study 0109	OA (knee)	200 mg/day (200 mg o.d.) (n = 465) 400 mg/day (400 mg o.d.) (n = 465)	n = 232	Celecoxib[b]	[**Confidential information removed**]		13	5
Grifka, 2003,[272,442] Novartis Study 2319	[**Confidential information removed**]							
Tannenbaum, 2004,[210] Novartis Study 0112	OA (knee)	200 mg/day (200 mg o.d.) (n = 487) 400 mg/day (400 mg o.d.) (n = 491)	n = 243	Celecoxib[b]	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, POBs, dyspepsia, MI, total CV thrombotic, total AE, withdrawal due to GI AE	13	5
Novartis Study 0128[280] (2004 submission)	[**Confidential information removed**]							
Novartis Study 2307[288] (2004 submission)	[**Confidential information removed**]							
TARGET,[273–275] Novartis Study 0117 + A2332	OA (hip, knee, hand, cervical or lumbar spine)	400 mg/day (400 mg o.d.) (n = 9156)	–	Naproxen 1000 mg/day (500 mg b.d.) or ibuprofen 2400 mg/day (800 mg t.d.s.) (n = 9169)	Patient's global assessment, withdrawal due to lack of efficacy	Total withdrawal, PUBs, POBs, dyspepsia, MI, total CV thrombotic, total AE, withdrawal due to GI AE	52	5

continued

TABLE 44 *Characteristics and quality of included lumiracoxib RCTs (cont'd)*

Author, year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Lumiracoxib	Placebo	NSAID	Efficacy[a]	Safety[a]		
Guesens, 2003,[276,443] Novartis Study 0111	[**Confidential information removed**]							
Kivitz, 2004,[214] Novartis Study 0110	RA	400 mg/day (400 mg o.d.) (n = 227) 800 mg/day (800 mg o.d.) (n = 227)	–	Celecoxib[b] ibuprofen 2400 mg/day (800 mg t.d.s.) (n = 216)	Patient's global assessment, withdrawal due to lack of efficacy	Total withdrawal, ulcer (endoscopic, definition: ⩾3 mm), dyspepsia, total AE	13	4
Scott, 2003,[277,281] Novartis Study 2312	[**Confidential information removed**]							
Novartis Study 0105[279] (2004 submission)	[**Confidential information removed**]							
Novartis Study 0114[222] (2004 submission)	[**Confidential information removed**]							
Novartis Study A2335[278] (2004 submission)	[**Confidential information removed**]							

[a] Only the outcomes which were included in meta-analyses are listed.
[b] See the section 'Direct comparison of COX-2 selective NSAIDs' (p. 78).

comparisons between COX-2 selective NSAIDs are not included here but are described in the section 'Direct comparison of COX-2 selective NSAIDs' (p. 78).

Assessment of quality of included trials

Trials were of high quality as judged by the Jadad scale, with a median score of 5. A detailed summary of scores is provided in Appendix 7. It was possible, because of access to full trial reports for most trials, to assess trial design in detail. The majority of trials were properly randomised (11/15) and described methods of concealment well (11/15). All trials were double blind, stated ITT analysis (often a modified ITT), and all reported small losses to follow up (<5%).

Assessment of lumiracoxib efficacy

Efficacy results are summarised in *Table 45*.

Patients' assessment of arthritis pain

There was no statistically significant improvement in pain over non-selective NSAIDs. This was true for OA and RA patients, different doses of lumiracoxib and choice of comparator NSAID, although the number of trials overall was small.

Patients' assessment of global efficacy

There was evidence of a greater improvement in global efficacy with non-selective NSAIDs compared with lumiracoxib. However, the number of reporting trials was small.

ACR-20 responder

ACR-20 was reported in only three trials of RA patients. Lumiracoxib was no better than comparator NSAIDs. This result appeared to be consistent for lumiracoxib dose and choice of comparator.

Withdrawals due to lack of efficacy

There was no difference in withdrawal rates on comparing lumiracoxib with non-selective NSAIDs. This was true for OA and RA patients, lumiracoxib dose and choice of NSAID comparator.

Lumiracoxib tolerability

Adverse events

Adverse events are separated into two categories: all adverse events and GI-related adverse events (*Table 46*). Both overall and GI-specific adverse events were reduced with lumiracoxib compared with non-selective NSAIDs. There was evidence of significant statistical heterogeneity across trials. These results appeared to be consistent across type of arthritis and dose of lumiracoxib.

Withdrawals

Withdrawals are considered at three levels: withdrawal from the trials for any reason (including loss to follow-up, lack of efficacy or adverse events), withdrawal due to adverse events and withdrawal due to GI-specific adverse events (*Table 47*).

The proportion of withdrawal due to all adverse events and GI-specific adverse events with lumiracoxib was lower than with non-selective NSAIDs. There was no significant difference in withdrawals for any reason. There was evidence of statistical heterogeneity across all withdrawal outcomes. Results appeared to be consistent across dose of lumiracoxib and type of arthritis.

Safety of lumiracoxib

The safety of lumiracoxib was evaluated by considering the development of endoscopic GI ulcers, clinical UGI events (PUBs), complicated UGI event (POBs), clinical MIs and serious CV thrombotic events (see *Tables 48* and *49*).

Endoscopic ulcers

In the two trials that reported endoscopic ulcers, there was a statistically significant reduction in ulcers with lumiracoxib compared with non-selective NSAIDs. There is insufficient evidence to comment on the effect of lumiracoxib dose and type of arthritis on endoscopic ulcers.

Clinical UGI events (PUBs)

A statistically significant reduction in PUBs with lumiracoxib compared with non-selective NSAIDs was reported in the TARGET trial, which included only OA patients. There is insufficient evidence to comment on the effect of lumiracoxib dose and type of arthritis.

Complicated UGI events (POBs)

In the two trials that reported POBs, there was a statistically significant reduction in the risk of POBs with lumiracoxib compared with non-selective NSAIDs. There is insufficient evidence to comment on the effect of lumiracoxib dose and type of arthritis. Again, virtually all events come from TARGET (*Figure 17*).

Myocardial infarctions and serious cardiovascular thrombotic events

In the trials that reported MI, there was an increase in the number of clinical events with

TABLE 45 *Summary of efficacy results for lumiracoxib versus placebo and NSAIDs*

	Placebo				NSAIDs			
	VAS pain difference: mean (95% CI)	**VAS global efficacy difference: mean (95% CI)**	**ACR-20: RR (95% CI)**	**Withdrawals due to lack of efficacy: RR (95% CI)**	**VAS pain difference: mean (95% CI)**	**VAS global efficacy difference: mean (95% CI)[a]**	**ACR-20: RR (95% CI)**	**Withdrawals due to lack of efficacy: RR (95% CI)**
100 mg/day	*–7.20 (–10.65 to –3.75) [3]*	*–8.57 (–12.18 to –4.97) [3]*	1.31 (0.79 to 2.18) [1]	*0.20 (0.06 to 0.62) [3]*	1.07 (–3.10 to 5.25) [2]	2.78 (–1.60 to 7.16) [2]	1.05 (0.65 to 1.69) [1]	2.88 (0.12 to 69.80)[b] [1]
200 mg/day	*–6.32 (–7.83 to –4.80) [8]*	*–6.69 (–8.24 to –5.14) [8]*	*1.24 (1.12 to 1.37) [4]*	*0.59 (0.51 to 0.68) [8]*	1.77 (–1.89 to 5.44)[c] [4]	*2.57 (0.16 to 4.98) [4]*	0.97 (0.86 to 1.10) [3]	*1.48 (1.13 to 1.94) [5]*
>200 mg/day	*–7.52 (–9.10 to –5.95) [8]*	*–8.54 (–10.81 to –6.27)[c] [8]*	*1.18 (1.03 to 1.35) [3]*	*0.55 (0.46 to 0.65) [8]*	–0.18 (–2.91 to 2.55) [3]	0.51 (–2.36 to 3.38) [3]	0.98 (0.81 to 1.18) [2]	1.03 (0.94 to 1.13) [7]
OA only	*–8.11 (–9.80 to –6.42) [6]*	*–9.24 (–11.00 to –7.48) [6]*	No trials	*0.44 (0.34 to 0.59) [6]*	–0.02 (–4.23 to 4.19) [1]	2.01 (–2.54 to 6.56) [1]	No trials	1.03 (0.93 to 1.13) [3]
RA only	*–5.46 (–7.36 to –3.57) [4]*	*-5.24 (–7.16 to –3.31) [4]*	*1.22 (1.11 to 1.34) [4]*	*0.61 (0.53 to 0.69) [4]*	1.71 (–2.24 to 5.67)[c] [3]	2.13 (–1.88 to 6.14)[c] [3]	0.96 (0.86 to 1.08) [3]	1.23 (0.74 to 2.03)[c] [5]
All trials	***–6.94 (–8.20 to –5.67) [10]***	***–7.51 (–9.27 to –5.76)[c] [10]***	***1.22 (1.11 to 1.34) [4]***	***0.53 (0.44 to 0.65) [10]***	**1.13 (–0.93 to 3.18) [4]**	***2.25 (0.14 to 4.37) [4]***	**0.96 (0.86 to 1.08) [3]**	**1.13 (0.85 to 1.50) [8]**

[a] Assessed using 100 mm VAS scale.
[b] One trial reported zero events in both arms.
[c] Significant statistical heterogeneity ($p < 0.10$) – random effects meta-analysis; [ ], no. of trials.

TABLE 46 *Summary of adverse events for lumiracoxib versus placebo and NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
All adverse events		
100 mg/day	1.07 (0.85 to 1.34) [2]	0.97 (0.77 to 1.23) [1]
200 mg/day	*1.07 (1.00 to 1.14) [7]*	*0.91 (0.85 to 0.99) [4]*
>200 mg/day	1.05 (0.98 to 1.12) [7]	0.95 (0.89 to 1.01)[a] [6]
OA only	1.06 (0.98 to 1.14) [5]	0.99 (0.98 to 1.01) [2]
RA only	1.07 (0.99 to 1.16) [4]	*0.91 (0.86 to 0.98) [5]*
All trials	***1.07 (1.01 to 1.13) [9]***	**0.94 (0.89 to 1.00)[a] [7]**
All GI adverse events		
100 mg/day	1.12 (0.62 to 2.03)[a] [3]	*0.51 (0.37 to 0.69) [2]*
200 mg/day	*1.30 (1.13 to 1.50) [8]*	*0.69 (0.53 to 0.90)[a] [5]*
>200 mg/day	*1.41 (1.22 to 1.62) [8]*	*0.84 (0.75 to 0.94)[a] [7]*
OA only	*1.47 (1.24 to 1.74) [6]*	*0.84 (0.72 to 0.99)[a] [3]*
RA only	*1.20 (1.01 to 1.43) [4]*	*0.75 (0.59 to 0.95)[a] [5]*
All trials	***1.34 (1.19 to 1.51) [10]***	***0.79 (0.70 to 0.90)[a] [8]***

[a] Significant statistical heterogeneity ($p < 0.10$) – random effects meta-analysis.

TABLE 47 *Summary of withdrawals for lumiracoxib versus placebo and NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
All adverse event withdrawals		
100 mg/day	0.86 (0.43 to 1.71) [3]	*0.39 (0.21 to 0.75) [2]*
200 mg/day	1.04 (0.82 to 1.31) [8]	*0.60 (0.45 to 0.80) [5]*
>200 mg/day	1.15 (0.92 to 1.44) [8]	*0.65 (0.46 to 0.90)[a] [7]*
OA only	1.05 (0.80 to 1.37) [6]	0.51 (0.26 to 1.02)[a] [3]
RA only	1.16 (0.88 to 1.53) [4]	*0.74 (0.58 to 0.95) [5]*
All trials	**1.10 (0.91 to 1.34) [10]**	***0.64 (0.48 to 0.86)[a] [8]***
All GI withdrawals		
100 mg/day	0.98 (0.25 to 3.84) [2]	0.30 (0.08 to 1.07) [1]
200 mg/day	1.29 (0.78 to 2.12) [5]	*0.39 (0.23 to 0.66) [3]*
>200 mg/day	1.59 (0.97 to 2.60) [5]	*0.70 (0.64 to 0.77) [4]*
OA only	1.57 (0.92 to 2.69) [4]	*0.60 (0.39 to 0.94)[a] [2]*
RA only	1.16 (0.59 to 2.28) [3]	*0.35 (0.18 to 0.69) [3]*
All trials	**1.41 (0.92 to 2.14) [7]**	***0.50 (0.32 to 0.79)[a] [5]***
All withdrawals		
100 mg/day	0.65 (0.41 to 1.02) [3]	0.60 (0.36 to 1.01) [2]
200 mg/day	*0.75 (0.68 to 0.82) [8]*	0.85 (0.57 to 1.27)[a] [5]
>200 mg/day	*0.81 (0.73 to 0.91) [8]*	0.83 (0.68 to 1.01)[a] [7]
OA only	*0.79 (0.68 to 0.92) [6]*	0.70 (0.47 to 1.05)[a] [3]
RA only	*0.75 (0.68 to 0.83) [4]*	1.02 (0.73 to 1.42)[a] [5]
All trials	***0.77 (0.70 to 0.83) [10]***	**0.88 (0.72 to 1.07)[a] [8]**

[a] Significant statistical heterogeneity ($p < 0.10$) – random effects meta-analysis.

lumiracoxib compared with non-selective NSAIDs, although this failed to reach statistical significance. When compared against naproxen, there was evidence of a significant increase in MI risk. There was no significant difference in CV thrombotic events on comparing lumiracoxib and non-selective NSAIDs. There is insufficient evidence to comment on the effect of different lumiracoxib doses and types of arthritis. As before, the majority events come from TARGET (*Figure 18*).

Hepatotoxicity

Data on hepatotoxicity was not included in our protocol for systematic review. However, TARGET indicates that lumiracoxib is associated with

TABLE 48 *Summary of endoscopic GI ulcers and clinical and complicated UGI events (PUBs and POBs) for lumiracoxib versus placebo and NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
Endoscopic GI ulcers		
100 mg/day	No trials	No trials
200 mg/day	No trials	*0.27 (0.14 to 0.52) [1]*
>200 mg/day	No trials	*0.26 (0.16 to 0.41) [2]*
OA only	No trials	*0.26 (0.16 to 0.44) [1]*
RA only	No trials	*0.26 (0.14 to 0.48) [1]*
All trials	No trials	***0.26 (0.18 to 0.39) [2]***
PUBs		
100 mg/day	[a]	Not reported
200 mg/day	1.12 (0.21 to 5.92) [3][209,210,278 b]	[a]
>200 mg/day	2.26 (0.37 to 13.64) [3][209,210,222 b]	*0.47 (0.37 to 0.61)* [1][274 a]
OA only	1.75 (0.22 to 14.18) [2][209,210 c]	0.47 (0.37 to 0.61) [1][274]
RA only	0.69 (0.08 to 5.75) [2][222,278]	[b]
vs ibuprofen	–	*0.48 (0.32 to 0.72)* [1][274]
vs diclofenac	–	Not reported
vs naproxen	–	*0.46 (0.34 to 0.64)* [1][274 b]
vs other NSAIDs	–	No trials
All trials	**1.14 (0.27 to 4.88) [4][209,210,222,278 c]**	***0.47 (0.37 to 0.61) [1][274 b]***
POBs		
100 mg/day	[b]	0.30 (0.01 to 7.22) [1][279]
200 mg/day	1.50 (0.06 to 36.69) [1][210 e]	0.31 (0.01 to 7.58) [1][279 a]
>200 mg/day	1.99 (0.22 to 17.78) [2][209,210 d]	*0.35 (0.23 to 0.52)* [2][274,279 a]
OA only	1.25 (0.15 to 10.67) [2][209,210 c]	*0.35 (0.23 to 0.53)* [1][274]
RA only	[c]	0.08 (0.00 to 1.96) [1][279 b]
vs ibuprofen	–	*0.30 (0.15 to 0.62)* [1][274]
vs diclofenac	–	0.08 (0.00 to 1.96) [1][279]
vs naproxen	–	*0.38 (0.22 to 0.64)* [1][274 b]
vs other NSAIDs	–	No trials
All trials	**1.25 (0.15 to 10.67) [2][209,210 f]**	***0.34 (0.23 to 0.52) [2][274,279 b]***

Additional trial(s) reporting zero events in both arms: [a] one trial; [b] two trials; [c] three trials; [d] four trials; [e] five trials; [f] six trials.

TABLE 49 *Summary of myocardial infarction and serious CV thrombotic events for lumiracoxib versus placebo and NSAIDs*

	Placebo: RR (95% CI) [*N* trials]	NSAIDs: RR (95% CI) [*N* trials]
MI		
100 mg/day	[b]	[a]
200 mg/day	3.03 (0.37 to 25.13) [2][209,278 d]	2.49 (0.12 to 51.75) [1][278 a]
>200 mg/day	2.13 (0.23 to 19.74) [2][210,280 d]	1.66 (0.83 to 3.34) [2][273,281 a]
OA only	1.28 (0.22 to 7.43) [3][209,210,280 b]	1.67 (0.82 to 3.41) [1][273]
RA only	5.08 (0.24 to 105.45) [1][278 b]	2.04 (0.23 to 18.15) [2][278,281 a]
vs ibuprofen	–	1.00 (0.29 to 3.47) [1][273]
vs diclofenac	–	[a]
vs naproxen	–	2.12 (0.93 to 4.87) [3][273,278,281]
vs other NSAIDs	–	No trials
All trials	**2.01 (0.47 to 8.67) [4][278 d]**	**1.71 (0.86 to 3.37) [3][273,278,281 a]**
Serious CV thrombotic events		
100 mg/day	[b]	[a]
200 mg/day	2.47 (0.43 to 14.13) [3][c]	1.00 (0.09 to 10.92) [1][a]
>200 mg/day	1.59 (0.21 to 11.80) [2][d]	1.19 (0.82 to 1.72) [2][a]
OA only	1.15 (0.21 to 6.26) [3][b]	1.18 (0.81 to 1.72) [1]
RA only	5.08 (0.24 to 105.45) [1][b]	1.19 (0.18 to 7.95) [2][a]
All trials	**1.78 (0.44 to 7.27) [4][d]**	**1.18 (0.82 to 1.71) [3][a]**

Additional trial(s) reporting zero events in both arms: [a] one trial; [b] two trials; [c] three trials; [d] four trials.

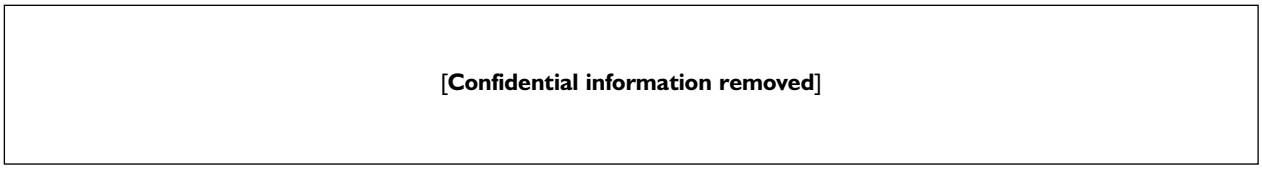


FIGURE 17 *Risk of POBs with lumiracoxib (all doses) versus NSAIDs (all drugs) [figure confidential except pooled estimate]*

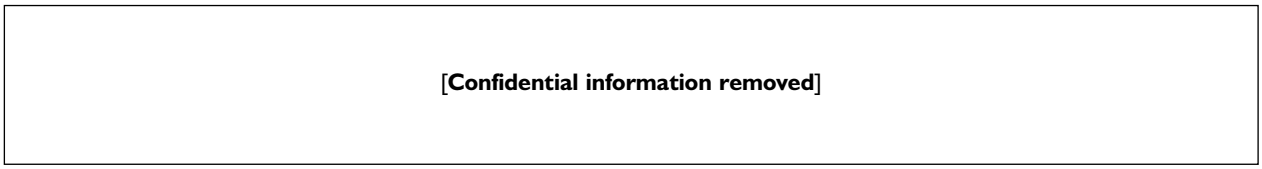


FIGURE 18 *Risk of MI with lumiracoxib (all doses) versus NSAIDs (all drugs) [figure confidential except pooled estimate]*

TABLE 50 *Endoscopic ulcer for lumiracoxib versus non-selective NSAID by subgroups*

Subgroup [*N* trials]	Pooled events lumiracoxib vs NSAID	RR (95% CI)[a]	*p*-Value[b]
H. pylori status:			
Positive [1]	8/179 vs 14/91	0.29 (0.13 to 0.67)	0.65
Negative [1]	6/219 vs 12/96	0.20 (0.08 to 0.51)	

[a] RR lumiracoxib vs non-selective NSAID.
[b] χ^2 test of heterogeneity.

significant hepatotoxicity: 2.7% of 9156 patients randomised to lumiracoxib had hepatitis, defined as a rise in transaminases of three times above the upper limit of normal, compared with 0.5% for naproxen and 1% for ibuprofen. There were nine events of severe hepatitis, defined as a five-fold increase in transaminases and a bilirubin of more than 51 mmol/l, with lumiracoxib and one case of hepatic failure.

Subgroup analyses

Stratified analyses of endoscopic ulcers according to *H. pylori* status were reported in Novartis Study 0110,[214] and TARGET reported subgroup analyses of POBs and MIs by low-dose aspirin use. None of the identified trials reported subgroup analyses for age, prior GI status or steroid or anticoagulant use.

Endoscopic ulcers

Stratified pooled RRs for endoscopically detected ulcers with lumiracoxib compared with non-selective NSAIDs are summarised in *Table 50*.

There are few events in these subgroups and results should be interpreted with caution.

Lumiracoxib significantly reduced endoscopic events compared with non-selective NSAIDs in each subgroup pair.

POBs

The subgroup analyses for aspirin users from the TARGET trial are summarised in *Table 51*.

Analysis suggests that lumiracoxib is less beneficial in aspirin users in terms of POBs, compared with the pronounced reduction seen in non-aspirin users. However, given the very small number of events observed, these data need confirmation. TARGET reported a significant reduction in POBs with lumiracoxib compared with non-selective NSAID regardless of *H. pylori* status, although the numbers were not reported.

Myocardial infarction

Subgroup analysis for low-dose aspirin on MI (clinically confirmed) rates from the TARGET trial are summarised in *Table 52*.

The increase in risk of clinically confirmed MI with lumiracoxib compared with non-selective NSAIDs appeared higher in [**Confidential information removed**]. Given the relatively small

TABLE 51 *POBs for lumiracoxib versus non-selective NSAID by low-dose aspirin use*

Subgroup [*N* trials]	Pooled events	Pooled RR (95% CI)[a]	*p*-Value[b]
POBs:			
User [1]	15/2167 vs 19/2159	0.78 (0.40 to 1.54)	0.005
Non-user [1]	14/6950 vs 64/6968	0.22 (0.12 to 0.40)	

[a] RR lumiracoxib vs non-selective NSAID.
[b] χ^2 test of heterogeneity.

TABLE 52 *MI for lumiracoxib versus non-selective NSAID by low-dose aspirin use*

Subgroup [*N* trials]	Pooled events	Pooled RR (95% CI)[a]	*p*-Value[b]
MI:			
User [1]	[**Confidential information removed**]	[**Confidential information removed**]	[**Confidential information removed**]
Non-user [1]			

[a] RR lumiracoxib vs non-selective NSAID.
[b] χ^2 test of heterogeneity.

number of events, caution is necessary when interpreting these data.

Impact of concomitant gastroprotective agents

No relevant trials were identified.

Summary

In December 2007 EMEA recommended the withdrawal of the marketing authorisations for lumiracoxib due to the risk of serious side-effects affecting the liver.

- Fifteen RCTs were included. Studies compared lumiracoxib (100–1200 mg/day) with either placebo, non-selective NSAIDs (diclofenac, ibuprofen or naproxen) or COX-2 selective NSAIDs (celecoxib or rofecoxib).
- Most trials studied patients with OA (nine studies), usually of the hip or knee.
- Trials were of high quality as judged by the Jadad scale, with a median score of 5.
- Lumiracoxib was of similar efficacy to non-selective NSAIDs for the symptomatic treatment of OA and RA, although the amount of trial evidence is small.
- Lumiracoxib is associated with significantly fewer GI-related adverse events and related withdrawals compared with non-selective NSAIDs, except for hepatotoxicity, which, in TARGET, was significantly increased for lumiracoxib compared with naproxen and ibuprofen.
- Lumiracoxib is associated with significantly fewer endoscopic ulcers than non-selective NSAIDs. This appears to be independent of patients' *H. pylori* status and is based on small numbers of events.
- Lumiracoxib is associated with significantly fewer clinical and complicated GI events than non-selective NSAIDs in OA patients. This benefit of lumiracoxib appeared to be limited to patients not taking low-dose aspirin, but this conclusion is based on small numbers and requires confirmation.
- In the TARGET trial (from which the majority of the events come), non-aspirin users treated with naproxen had significantly fewer clinical MI events than non-aspirin users treated with lumiracoxib. No difference in the risk of MI was observed between patients treated with ibuprofen and those treated with lumiracoxib.
- Lumiracoxib has not been compared with non-selective NSAIDs combined with a gastroprotective agent.

Direct comparison of COX-2 selective NSAIDs

Description of included trials, patients' characteristics and trial quality

Direct comparisons of two COX-2 selective NSAIDs are reported in 14 trials: six compared celecoxib with rofecoxib in OA over 6–12 weeks. Patients were randomised to celecoxib 200 mg/day

or rofecoxib 25 mg/day and one trial also included a rofecoxib 12.5 mg/day arm. A further trial compared valdecoxib (10 mg/day; $n = 212$) with rofecoxib (25 mg/day; $n = 208$) in patients with OA over 2 weeks (Moskowtiz and colleagues, Pfizer 143).[245] Seven trials compared lumiracoxib with another COX-2 selective NSAID: five with celecoxib and two with rofecoxib. Two trials compared lumiracoxib 200–800 mg/day with celecoxib 400 mg/day in RA patients. The remaining trials compared lumiracoxib 200–400 mg/day with either celecoxib 200 mg/day or rofecoxib 25 mg/day in OA patients. The characteristics of the 14 trials are summarised in *Table 53*.

All but one of the 14 trials scored 5 on the Jadad scale, indicating high quality. All trials were of relatively short duration (≤3 months). Five of the six trials that compared celecoxib with rofecoxib were of 6 weeks duration only. Six of the seven lumiracoxib trials were of 13 weeks duration.

Efficacy

Patients' assessment of arthritis pain

Celecoxib and rofecoxib reduced pain, assessed by VAS in four of six trials, equally well (*Figure 19*). Similarly [**Confidential information removed**].

Substantial heterogeneity exists between the three trials which compared lumiracoxib with celecoxib and reported VAS pain (*Figure 20*). There were no significant differences between lumiracoxib 200–400 mg/day and celecoxib 200 mg/day in OA patients.[209,210] However, celecoxib 400 mg/day was [**Confidential information removed**].

One trial (Study 0128) found [**Confidential information removed**].

Patients' assessment of global efficacy

One trial compared celecoxib 200 mg/day with rofecoxib 25 mg/day (Pfizer 002).[206,249] [**Confidential information removed**]. A similar finding was reported in a comparison of valdecoxib 10 mg/day with rofecoxib 25 mg/day (Pfizer 143)[245,286] [**Confidential information removed**].

For lumiracoxib, the results of patients' assessment of global efficacy mirrored the results for pain: lumiracoxib 200-400 mg/day was equally efficacious to celecoxib 200 mg/day in OA patients, but was less efficacious than celecoxib 400 mg/day in RA patients (*Figure 21*). One trial (Novartis 0128) found [**Confidential information removed**].

ACR-20 responder

One trial (Novartis 0114) reported [**Confidential information removed**].

Withdrawal due to lack of efficacy

No significant difference in withdrawals due to lack of efficacy was found between celecoxib 200 mg/day and rofecoxib 12.5–25 mg/day in pooled analysis (*Figure 22*). In Pfizer Study 143 [**Confidential information removed**].

Overall there was no significant difference in withdrawals due to lack of efficacy between lumiracoxib and celecoxib (*Figure 23*). However, significantly more patients [**Confidential information removed**]. There was no difference between lumiracoxib 400 mg/day and rofecoxib 25 mg/day in OA (*Figure 24*).

Tolerability

Total adverse events

There was no evidence of a difference in overall adverse events between celecoxib-treated and rofecoxib-treated patients (*Figure 25*). In Pfizer Study 143, [**Confidential information removed**]. There were no significant differences in total adverse events between lumiracoxib and celecoxib or between lumiracoxib and rofecoxib (*Figures 26* and *27*).

GI adverse events

Overall there appeared to be no difference in the level of GI-related adverse events between celecoxib and rofecoxib groups (*Figure 28*). However, one study, by McKenna and colleagues,[197] did report a significantly lower level of GI-related adverse events with celecoxib (RR 0.33, 95% CI 0.15 to 0.72). In Pfizer Study 143, [**Confidential information removed**]. No significant differences were observed in GI-related adverse events between lumiracoxib and celecoxib or between lumiracoxib and rofecoxib, although the pooled estimates showed slight trends in favour of celecoxib and rofecoxib (*Figures 29* and *30*).

Withdrawals due to adverse events

Overall, withdrawals due to adverse events appeared equivalent between celecoxib and rofecoxib (*Figure 31*). This outcome was not reported in the valdecoxib versus rofecoxib trial. There were no significant differences in withdrawal due to adverse events between lumiracoxib and celecoxib or between lumiracoxib and rofecoxib (*Figures 32* and *33*).

TABLE 53 *Characteristic and quality of included head-to-head COX-2 selective NSAID trials*

Author, year, trial name	RA/OA (location)	COX-2s, dose and no. randomised		Outcomes		Duration (weeks)	Jadad score
		COX-2	Comparator COX-2	Efficacy[a]	Safety[a]		
McKenna, 2001b,[197] Pfizer Study 152	OA (knee)	**Celecoxib** 200 mg/day (200 mg o.d.) (n = 63)	**Rofecoxib** 25 mg/day (25 mg o.d.) (n = 59)	Pain (VAS), withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia, total AE, withdrawals due to GI AE	6	5
Whelton, 2001,[282,283] SUCCESS-VI, Pfizer Study 149	OA (hip, hand, knee)	**Celecoxib** 200 mg/day (200 mg o.d.) (n = 411)	**Rofecoxib** 25 mg/day (25 mg o.d.) (n = 399)	–	Withdrawal due to AE, dyspepsia, total AE	6	5
Whelton, 2002a,[284] SUCCESS-VII, Pfizer Study 181	OA (hip, knee, hand)	**Celecoxib** 200 mg/day (200 mg o.d.) (n = 549)	**Rofecoxib** 25 mg/day (25 mg o.d.) (n = 543)	Withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, total AE	6	5
Gibofsky, 2003,[202] Pfizer Study 003	OA (knee)	**Celecoxib** 200 mg/day (200 mg o.d.) (n = 189)	**Rofecoxib** 25 mg/day (25 mg o.d.) (n = 190)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, dyspepsia, total AE	6	5
Sowers, 2003,[206,249] CRESCENT, Pfizer Study 002 (2004 submission)	OA (hip, knee)	**Celecoxib** 200 mg/day (200 mg o.d.) (n = 136)	**Rofecoxib** 25 mg/day (25 mg o.d.) (n = 138)	[**Confidential information removed**]		12	5
Geba, 2002,[285] VACT-1	OA (knee)	**Celecoxib** 200 mg/day (200 mg o.d.) (n = 97)	**Rofecoxib** 12.5 mg/day (12.5 mg o.d.) (n = 96) 25 mg/day (25 mg o.d.) (n = 95)	Pain (WOMAC), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, ulcer (endoscopic, clinical or symptomatic), dyspepsia, total AE, withdrawals due to GI AE	6	5
Moskowitz, 2003,[245,286] Pfizer Study 143 (2004 submission)	OA (knee)	**Valdecoxib** 10 mg/day (10 mg o.d.) (n = 212)	**Rofecoxib** 25 mg/day (25 mg o.d.) (n = 208)	[**Confidential information removed**]		2	5
Hawkey, 2004,[207,287] Novartis Study 0126	OA (hip, knee or hand)	**Lumiracoxib** 200 mg/day (200 mg o.d.) (n = 264) 400 mg/day (400 mg o.d.) (n = 260)	**Celecoxib** 200 mg/day (200 mg o.d.) (n = 258)	Withdrawal due to lack of efficacy	Total withdrawal, ulcer (endoscopic, definition: ⩾3 mm), dyspepsia, total AE, withdrawals due to GI AE	13	5

continued

TABLE 53 *Characteristic and quality of included head-to-head COX-2 selective NSAID trials (cont'd)*

Author, year, trial name	RA/OA (location)	COX-2s, dose and no. randomised		Outcomes		Duration (weeks)	Jadad score
		COX-2	Comparator COX-2	Efficacy[a]	Safety[a]		
Fleischmann, 2003,[208,209] Novartis Study 0109	OA (knee)	**Lumiracoxib** 200 mg/day (200 mg o.d.) (n = 465) 400 mg/day (400 mg o.d.) (n = 465)	**Celecoxib** 200 mg/day (200 mg o.d.) (n = 446)	[**Confidential information removed**]		13	5
Tannenbaum, 2004,[210] Novartis Study 0112	OA (knee)	**Lumiracoxib** 200 mg/day (200 mg o.d.) (n = 487) 400 mg/day (400 mg o.d.) (n = 491)	**Celecoxib** 200 mg/day (200 mg o.d.) (n = 481)	Pain (VAS), patient's global assessment, withdrawal due to lack of efficacy	Withdrawal due to AE, total withdrawal, PUBs, POBs, dyspepsia, total AE, withdrawal due to GI AE	13	5
Novartis Study 0128[280] (2004 submission)	[**Confidential information removed**]						
Novartis Study 2307[288] (2004 submission)	[**Confidential information removed**]						
Kivitz, 2004,[214] Novartis Study 0110	RA	**Lumiracoxib** 400 mg/day (400 mg o.d.) (n = 227) 800 mg/day (800 mg o.d.) (n = 227)	**Celecoxib** 400 mg/day (200 mg b.d.) (n = 223)	Patient's global assessment, withdrawal due to lack of efficacy	Total withdrawal, ulcer (endoscopic, definition: ⩾3 mm), dyspepsia, total AE	13	4
Novartis Study 0114[222] (2004 submission)	[**Confidential information removed**]						

VACT, Vioxx, Acetaminophen, Celecoxib Trial.
[a] Only the outcomes which were included in meta-analyses are listed.

[**Confidential information removed**]

FIGURE 19 *Comparison of change in VAS pain between celecoxib (200 mg/day) and rofecoxib (12.5–25 mg/day) [figure confidential except pooled estimate]*

[**Confidential information removed**]

FIGURE 20 *Comparison of change in VAS pain between lumiracoxib (all doses) and celecoxib (all doses) [figure confidential except pooled estimate]*

[**Confidential information removed**]

FIGURE 21 *Comparison of change in patient's global assessment (VAS) between lumiracoxib (all doses) and celecoxib (all doses) [figure confidential except pooled estimate]*

[**Confidential information removed**]

FIGURE 22 *Comparison of level of withdrawal due to lack of efficacy in celecoxib (200 mg/day) and rofecoxib (12.5–25 mg/day) [figure confidential except pooled estimate]*

[**Confidential information removed**]

FIGURE 23 *Comparison of level of withdrawal due to lack of efficacy in lumiracoxib (all doses) and celecoxib (all doses) [figure confidential except pooled estimate]*

[**Confidential information removed**]

FIGURE 24 *Comparison of level of withdrawal due to lack of efficacy in lumiracoxib 400 mg/day and rofecoxib 25 mg/day [figure confidential except pooled estimate]*

[**Confidential information removed**]

FIGURE 25 *Comparison of overall adverse events with celecoxib (200 mg/day) and rofecoxib (12.5–25 mg/day) [figure confidential except pooled estimate]*

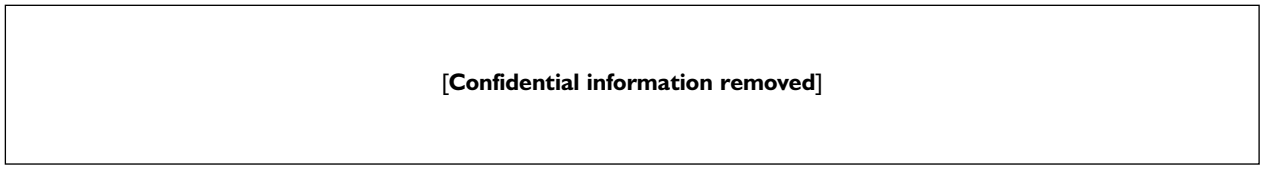


FIGURE 26 *Comparison of overall adverse events with lumiracoxib (all doses) and celecoxib (all doses) [figure confidential except pooled estimate]*

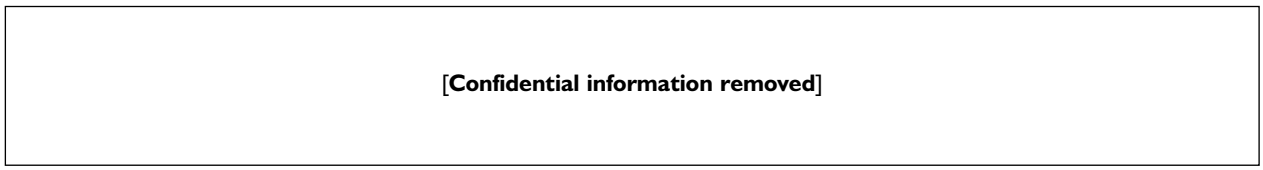


FIGURE 27 *Comparison of overall adverse events with lumiracoxib (400 mg/day) and rofecoxib (25 mg/day) [figure confidential except pooled estimate]*

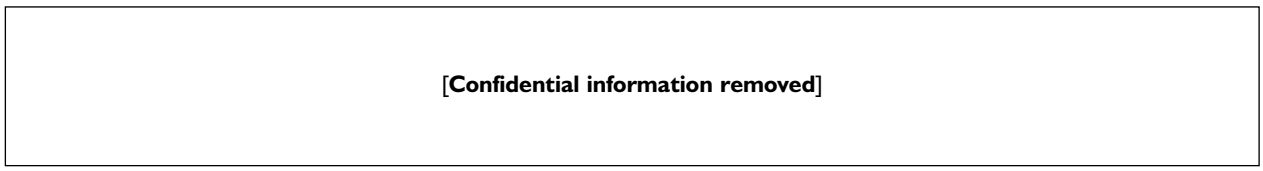


FIGURE 28 *Comparison of GI-related adverse events with celecoxib (200 mg/day) and rofecoxib (12.5–25 mg/day) [figure confidential except pooled estimate]*

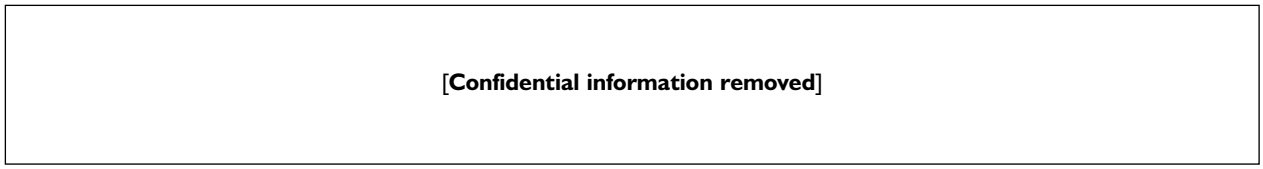


FIGURE 29 *Comparison of GI-related adverse events with lumiracoxib (all doses) and celecoxib (all doses) [figure confidential except pooled estimate]*

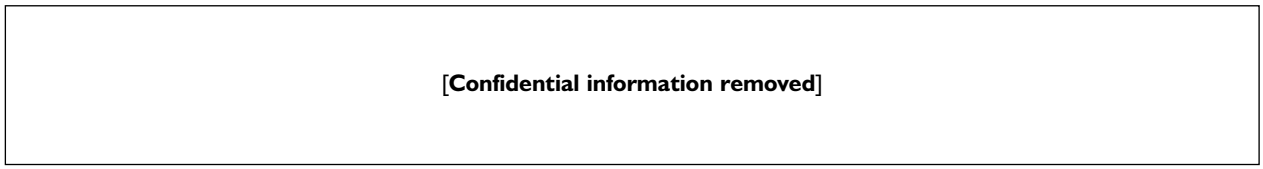


FIGURE 30 *Comparison of GI-related adverse events with lumiracoxib (400 mg/day) and rofecoxib (25 mg/day) [figure confidential except pooled estimate]*

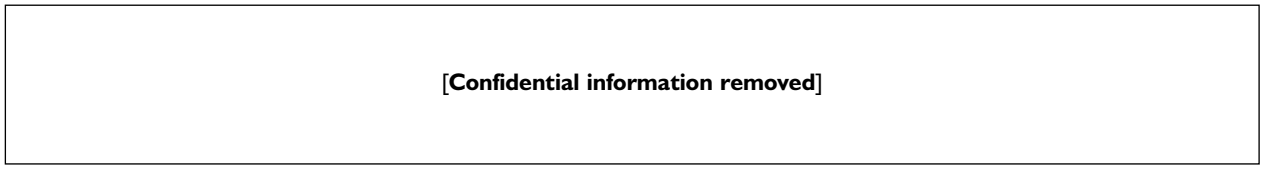


FIGURE 31 *Comparison of withdrawals due to adverse events with celecoxib (200 mg/day) and rofecoxib (12.5–25 mg/day) [figure confidential except pooled estimate]*

[**Confidential information removed**]

FIGURE 32 *Comparison of withdrawals due to adverse events with lumiracoxib (all doses) and celecoxib (all doses) [figure confidential except pooled estimate]*

[**Confidential information removed**]

FIGURE 33 *Comparison of withdrawals due to adverse events with lumiracoxib (400 mg/day) and rofecoxib (25 mg/day) [figure confidential except pooled estimate]*

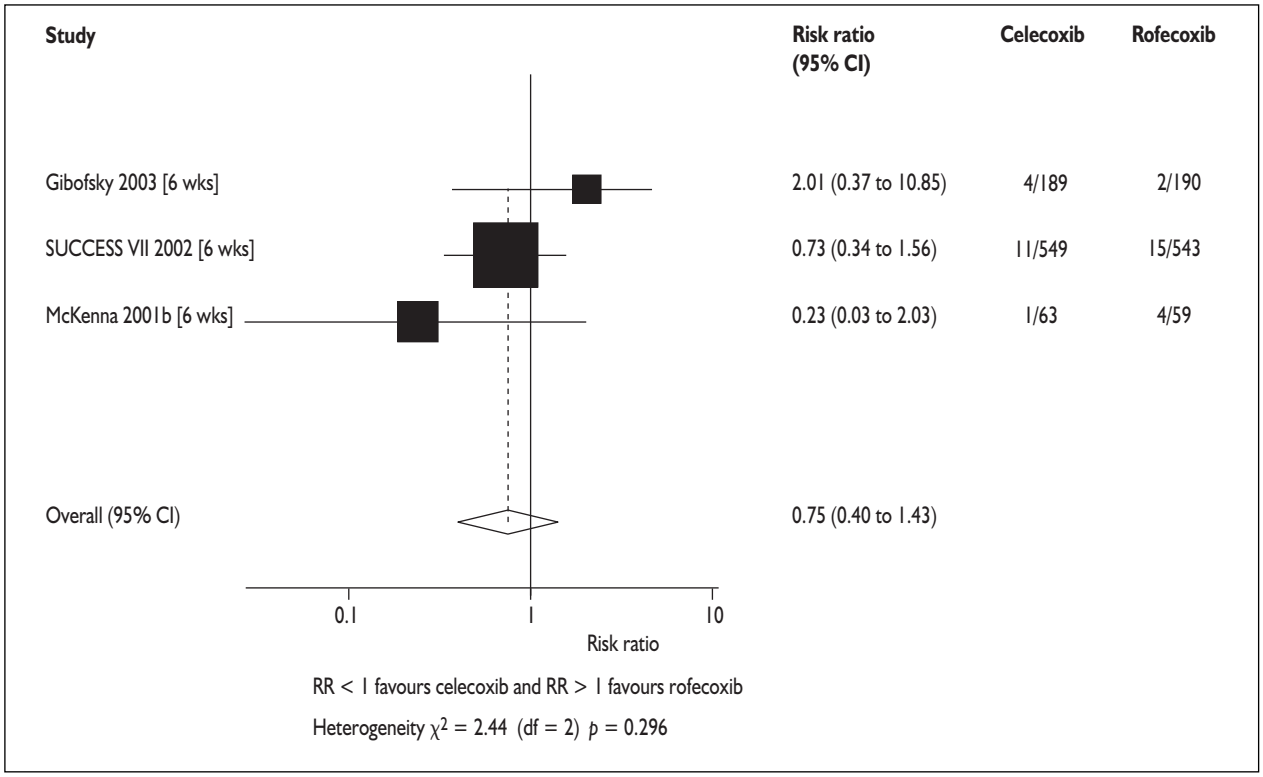


FIGURE 34 *Comparison of withdrawals due to GI-related adverse events with celecoxib (200 mg/day) and rofecoxib (25 mg/day)*

[**Confidential information removed**]

FIGURE 35 *Comparison of withdrawals due to GI-related adverse events with lumiracoxib (all doses) and celecoxib (all doses) [figure confidential except pooled estimate]*

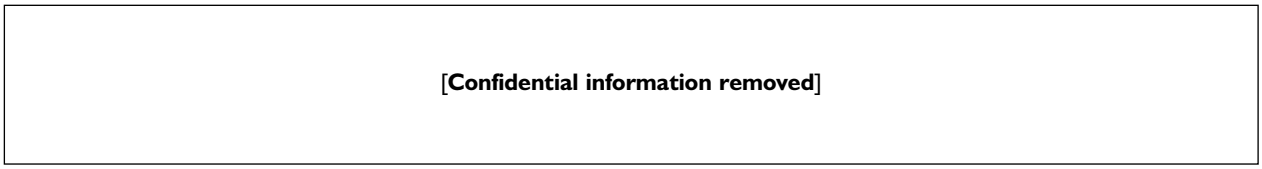


FIGURE 36 *Comparison of withdrawals due to GI adverse events with lumiracoxib (400 mg/day) and rofecoxib (25 mg/day) [figure confidential except pooled estimate]*

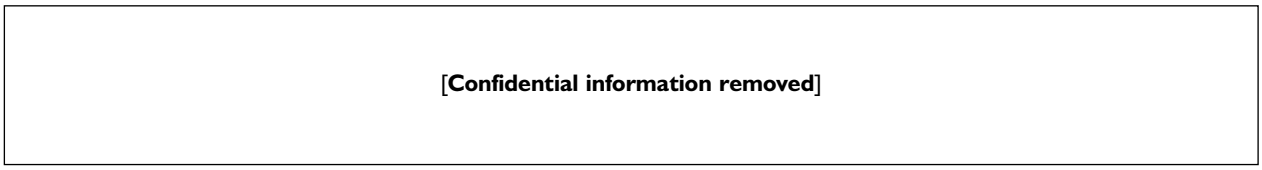


FIGURE 37 *Comparison of overall withdrawals with lumiracoxib (all doses) and celecoxib (all doses) [figure confidential except pooled estimate]*

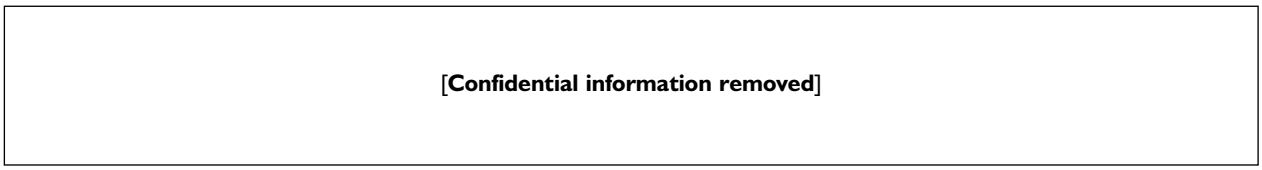


FIGURE 38 *Comparison of overall withdrawals with lumiracoxib (400 mg/day) and rofecoxib (25 mg/day) [figure confidential except pooled estimate]*

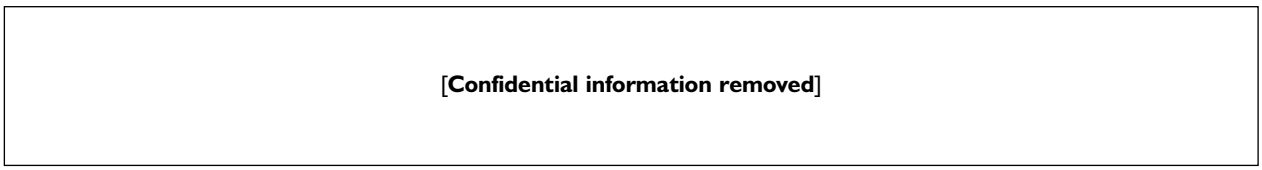


FIGURE 39 *Comparison of endoscopic ulcers with lumiracoxib (all doses) and celecoxib (all doses) [figure confidential except pooled estimate]*

Withdrawals due to GI events

The level of withdrawal due to GI-related adverse events appeared equivalent between celecoxib and rofecoxib across the three trials where it was reported (*Figure 34*). Similarly, no significant differences were found between lumiracoxib and celecoxib or between lumiracoxib and rofecoxib (*Figures 35* and *36*). Withdrawals due to GI-specific adverse events were not reported in the valdecoxib versus rofecoxib trial.

Total withdrawals

Overall, withdrawals for any reason were similar between lumiracoxib treatment groups and celecoxib or rofecoxib groups (*Figures 37* and *38*). Nevertheless, Kivitz and colleagues[214] reported significantly more withdrawals for any reason in the lumiracoxib 400–800 mg/day arms than in the celecoxib 400 mg/day arm.

Safety

Direct head-to-head trials on the safety of COX-2s in terms of their GI (endoscopic ulcers, PUBs or POBs) or CV effects were available for lumiracoxib compared with celecoxib and rofecoxib.

Endoscopic GI ulcers

Two trials reported [**Confidential information removed**] endoscopically detected ulcers between lumiracoxib and celecoxib treatment arms (*Figure 39*). No trial which compared lumiracoxib and rofecoxib reported this outcome.

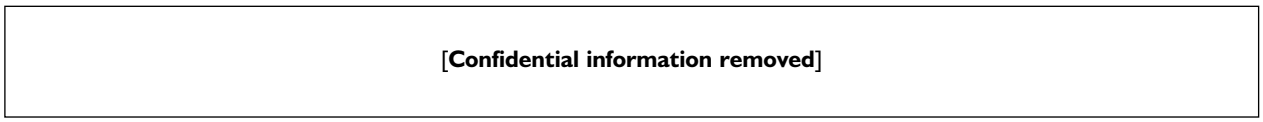


FIGURE 40 *Comparison of PUBs with lumiracoxib (all doses) and celecoxib (all doses) [figure confidential except pooled estimate]*

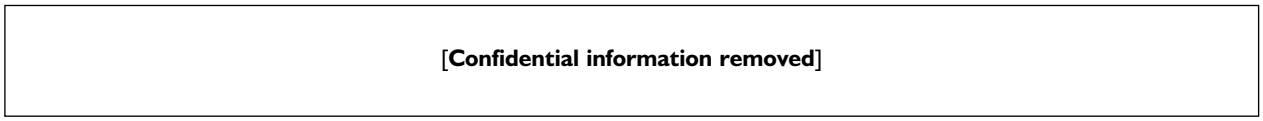


FIGURE 41 *Comparison of POBs with lumiracoxib (all doses) and celecoxib (all doses) [figure confidential except pooled estimate]*

FIGURE 42 *Comparison of MI with lumiracoxib (all doses) and celecoxib (all doses) [figure confidential except pooled estimate]*

FIGURE 43 *Comparison of serious CV thrombotic events with lumiracoxib (all doses) and celecoxib (all doses) [figure confidential except pooled estimate]*

Clinical UGI events (PUBs) and complicated UGI events (POBs)

Three trials comparing lumiracoxib to celecoxib reported a total of [**Confidential information removed**] (*Figures 40* and *41*). There were [**Confidential information removed**] although the number of events was too small to draw any conclusion. One trial comparing lumiracoxib with rofecoxib reported [**Confidential information removed**].

Myocardial infarctions and cardiovascular thrombotic events

Two trials comparing lumiracoxib with celecoxib reported [**Confidential information removed**] (*Figure 42*). Three trials reported a total of [**Confidential information removed**] (*Figure 43*). Overall there was [**Confidential information removed**] the number of events was too small to allow sensible comparison. One of the two trials comparing lumiracoxib with rofecoxib reported [**Confidential information removed**].

Summary

Based on this systematic review and meta-analyses it is concluded that:

- A total of 14 'head-to-head' trials have directly compared COX-2 selective NSAIDs in OA and RA patients over 2–13 weeks.
- Seven of the trials compared the maximum licensed dose of rofecoxib (25 mg/day) with either celecoxib (200 mg/day) or valdecoxib (10 mg/day), both at half of their maximum licensed doses. Only one of the trials [Vioxx, Acetaminophen, Celecoxib Trial 1 (VACT-1)] included rofecoxib 12.5 mg/day. Other trials compared lumiracoxib at 200–800 mg/day with celecoxib 200–400 mg/day or rofecoxib 25 mg/day.
- The efficacy and tolerability of rofecoxib appeared to be similar to those of both celecoxib and valdecoxib but, in view of the limited evidence base and because these comparisons are underpowered and at potentially non-equivalent doses, caution is needed in this interpretation. The efficacy of lumiracoxib compared with celecoxib and rofecoxib appears to be dose dependent. There is no significant difference between these COX-2 selective NSAIDs in terms of tolerability and safety based on short-term trials.
- There is insufficient evidence from direct head-to-head trials (for lumiracoxib relative to celecoxib and rofecoxib) on the relative safety of COX-2s in terms of their serious GI (POBs or PUBs) or CV effects.

Chapter 5
Health economics

Introduction

The aim of this chapter is to assess the cost-effectiveness of celecoxib, rofecoxib, etodolac, meloxicam, etoricoxib, valdecoxib and lumiracoxib for OA or RA from an NHS perspective. We include a systematic review of the published literature on the cost-effectiveness of COX-2 selective NSAIDs, a review of economic analyses submitted by manufacturers and a description of our own modelling and economic analyses.

Systematic review of published cost-effectiveness literature

The searches for this systematic review were carried out in January 2004.

Methods for the systematic review

A systematic literature search was undertaken to identify economic evaluations where the cost-effectiveness of one or more of the COX-2 drugs was investigated.

For all COX-2 selective NSAIDs, the searches for clinical effectiveness were amplified to identify any existing economic models and information on costs, cost effectiveness and quality of life from the following sources:

- bibliographic databases: MEDLINE, pre-MEDLINE, EMBASE, NHS EED, DARE, HEED
- Internet sites of national economic units
- Internet sites of regulating authorities, such as FDA and EMEA.

Databases were searched from the inception date of the databases for all drugs.

Full details of the search terms used and the overall search strategy are given in Appendix 2.

The inclusion and exclusion criteria applied for the economic searches are shown in *Table 54*.

An experienced health economist (SB) identified included studies by applying inclusion and exclusion criteria and screening titles, abstracts and full text, if appropriate, of bibliographic searches.

A reviewer using a predesigned data extraction form extracted data from included studies. Data were extracted on the following:

- study characteristics such as form of economic analysis, population, interventions, comparators, perspective, time horizon and modelling used
- effectiveness and cost parameters such as effectiveness data, health state valuations (utilities), resource use data, unit cost data, price year, discounting and key assumptions
- results and sensitivity analyses.

These characteristics and main results of included economic evaluations are summarised in a table. The quality of included studies was assessed using the Drummond and Jefferson checklist.[289] The study question, selection of alternatives, form of evaluation, effectiveness data, costs, benefit measurement and valuation, decision modelling, discounting, allowance for uncertainty and

TABLE 54 *Inclusion criteria for the review on cost-effectiveness*

Study design	Cost–consequence analysis, cost-minimisation analysis, cost–benefit analysis, cost-effectiveness analysis, cost–utility analysis; cost studies (UK only), quality of life studies
Population	People with OA or RA; other forms of arthritis are excluded
Intervention	Celecoxib, rofecoxib, meloxicam, etodolac, etoricoxib, valdecoxib and lumiracoxib, with or without aspirin
Comparator	Non-COX-2 NSAIDs with or without gastroprotective agents, COX-2 selective NSAIDs with or without gastroprotective agents
Outcome	Quality of life estimates, cost estimates, cost-effectiveness

presentation of results were all evaluated as part of this process.

Results of the cost-effectiveness systematic review

Fifteen published studies meeting the criteria for inclusion were identified. In addition, three manufacturers (Boehringer Ingelheim, Merck Sharp and Dohme and Pfizer) submitted economic analyses and models. These submissions are reviewed in detail in the section 'Review of industry cost-effectiveness submissions' (p. 93).

Details of the 15 studies (presented using a simplified version of the Drummond and Jefferson checklist)[289] are reported in Appendix 8. Of these 15, three were sponsored by Merck and considered rofecoxib only in comparison with an unnamed non-selective or conventional NSAID (*Table 55*). All three studies were cost-effectiveness analyses, with the cost-effectiveness ratio being in the form of either cost per PUB avoided or cost per life-year gained. Results universally indicated that the incremental cost of rofecoxib is positive; however, in all cases it was concluded that the associated benefits lead support for more widespread use of rofecoxib in OA. All three studies used a very similar simple decision tree model structure. These models did not include the possibility of drug-related MI.

Five of the 15 identified published studies report an economic analysis of celecoxib alone (*Table 56*), four of which were sponsored by the manufacturer (either Pfizer or Pharmacia). All four of the company-sponsored analyses used a simple decision tree that was either the same as the Arthritis Cost Consequences Evaluation System (ACCES) model (for more details see the section 'Pfizer submission', p. 93) or was a slight modification of it. Against the range of comparators explored [ranging from conventional NSAID as monotherapy to NSAIDs with various gastroprotective agents (GPAs)], the most common result was that celecoxib dominated the alternatives; hence celecoxib costs less and was more effective. Unsurprisingly, these reports recommended more widespread use of celecoxib in people with arthritis. Incremental cost-effectiveness ratios (ICERs) in two other comparisons of celecoxib with NSAID monotherapy, by Zabinski and colleagues[293] and Haglund and Svarvar,[294] were Can$1800 and SEK780 per GI event avoided, respectively.

A study sponsored by US Veterans Affairs came to a more cautious conclusion: that celecoxib is only cost-effective in OA patients with a high baseline risk of UGI events. This was again a decision tree model, although the detail of the model was not reported in the paper. None of the five models of celecoxib described above considered MIs in their analyses.

A further five cost-effectiveness studies (all published in 2003) considered both celecoxib and rofecoxib, none of which was funded by a drug manufacturer (*Table 57*). All of these analyses gave results that were less attractive for COX-2 selective NSAIDs. Most of these studies considered a longer time horizon; for example, lifetime in the case of Spiegel and colleagues[298] and 5 years in the cases of Maetzel and colleagues[299] and Rafter and colleagues[300] (see Appendix 8).

Spiegel and colleagues[298] did not distinguish between rofecoxib and celecoxib and assumed that they had the same cost and benefit characteristics. They focused on patients with either OA or RA and used a decision tree model. Detailed base-case results found are given in *Table 58*; costs and quality-adjusted life-year (QALY) estimates are for an average patient over a lifetime.

The ICER for the strategy of restricting use of COX-2s to patients who had a previous ulcer haemorrhage was more attractive (US$55,800 per QALY gained) than unrestricted use (US$275,800 per QALY gained). Nevertheless, the inclusion of CV events would result in COX-2 selective NSAIDs being less cost-effective.

TABLE 55 *Published rofecoxib economic analyses*

Study	Sponsor	Patient group	Comparator(s)	Base-case ICER
Marshall, 2001[290]	Merck	OA	Non-selective NSAID	Can$2,000 per PUB avoided
Pellissier, 2001[291]	Merck	OA	Non-selective NSAID	US$4,700 per PUB avoided US$18,600 per life-year saved
Moore, 2001[292]	Merck	OA	Conventional NSAIDs	£10,700 per PUB avoided £15,600 per life-year saved

TABLE 56 *Published celecoxib economic analyses*

Study	Sponsor	Patient group	Comparator(s)	Base-case ICER
Chancellor, 2001[295]	Pharmacia	Arthritis	5 strategies: NSAID alone NSAID + PPI NSAID + H2RA NSAID + misoprostol Diclofenac/misoprostol	Celecoxib dominant against all comparators (i.e. lower cost and fewer GI events)
Zabinski, 2001[293]	Pfizer and Pharmacia	OA or RA	5 strategies: NSAID alone NSAID + PPI NSAID + H2RA NSAID + misoprostol Diclofenac/misoprostol	Celecoxib vs NSAID alone: Can$1,800 per serious GI event avoided Celecoxib vs all other strategies: celecoxib dominant
Svarvar, 2000[296]	Pfizer	OA and RA analysed separately	2 comparators: NSAID monotherapy Average NSAID use in Norway	For both OA and RA, celecoxib dominant against both comparators
Haglund, 2000[294]	Pfizer	OA or RA analysed separately	2 comparators: NSAID monotherapy Average NSAID use in Sweden	For OA, celecoxib dominant against both comparators For RA, celecoxib vs NSAID monotherapy: SEK780 per GI event avoided For RA, celecoxib vs 'average basket': celecoxib dominant
El-Serag, 2002[297]	US Veterans Affairs	OA	7 strategies: Ibuprofen Ibuprofen + PPI Ibuprofen + misoprostol *H. pylori* treatment + ibuprofen *H. pylori* treatment + ibuprofen + PPI *H. pylori* treatment + ibuprofen + misoprostol *H. pylori* treatment + celecoxib	With 2.5% baseline risk of clinical UGI event with conventional NSAID, US$35,200 per clinical UGI event avoided (celecoxib vs ibuprofen) With 6.5% baseline risk of clinical UGI event with conventional NSAID, celecoxib dominates

Maetzel and colleagues[299] and Rafter and colleagues[300] came to the same broad result. They both used a very similar Markov model (originally developed by Maetzel and colleagues), and considered the use of COX-2 selective NSAIDs in both OA and RA. The detailed base-case results reported by Maetzel and colleagues[299] are given in *Table 59*. The costs and QALY estimates are for an average patient over a 5-year time horizon.

Maetzel and colleagues' results[299] support the use of rofecoxib and celecoxib only in high-risk patients with a previous clinical UGI event, but Rafter and colleagues[300] concluded that neither drug represents value for money: both studies explicitly considered CV events. Kamath and colleagues,[301] using a decision tree, did not find any support for the use of rofecoxib and celecoxib in patients with knee OA. Bae and colleagues[302] used a Markov model and found that comparing COX-2 selective NSAIDs versus a standard NSAID in RA cost US$51,700 per QALY gained.

A study of meloxicam, by Tavakoli,[303] that appears not to have been funded by a manufacturer of meloxicam, is summarised in *Table 60*. This analysis used a simple decision tree and found that meloxicam dominated the alternatives (diclofenac and piroxicam). CV events were included in this analysis.

Fendrick and colleagues[304] considered an unnamed COX-2 (*Table 60*) and from an analysis of a Markov model concluded that although the unrestricted use of COX-2 selective NSAIDs has the potential to provide important clinical benefit in long-term users of NSAIDs, there is a considerable incremental cost. CV events were not included in this analysis.

TABLE 57 *Published rofecoxib and celecoxib economic analyses*

Study	Sponsor	Patient group	Comparator(s)	Base-case ICER
Spiegel, 2003[298]	US National Institute for Health and Veterans Affairs	OA or RA	Non-selective NSAID (i.e. naproxen)	For the average patient, US$275,800 per QALY gained For patients who have had a previous ulcer haemorrhage, US$55,800 per QALY gained
Maetzel, 2003[299]	Canadian Coordinating Office for Health Technology Assessment	OA or RA	For average-risk patients: Naproxen (vs rofecoxib) Diclofenac (vs celecoxib) Ibuprofen (vs celecoxib) For high-risk patients, all comparators also included the addition of PPIs	For average-risk patients: Can$271,000 per QALY gained (rofecoxib vs naproxen) Can$125,000 per QALY gained (celecoxib vs diclofenac) For high-risk patients: Rofecoxib dominates naproxen + PPI Celecoxib dominates ibuprofen + PPI Can$271,000 per QALY gained (celecoxib vs diclofenac + PPI)
Rafter, 2003[300]	Accident Compensation Corporation and Australasian Faculty of Public Health Medicine	OA or RA	3 comparators: Naproxen (vs rofecoxib) Diclofenac (vs celecoxib) Ibuprofen (vs celecoxib)	Naproxen dominates rofecoxib Diclofenac dominates celecoxib Celecoxib vs ibuprofen: NZ$482,000 per QALY gained (average-risk patients) NZ$88,000 per QALY gained (high-risk patients)
Kamath, 2003[301]	McNeil Consumer Healthcare	Symptomatic knee OA	3 comparators: High-dose acetaminophen Ibuprofen Ibuprofen + misoprostol	Acetaminophen dominant against all comparators (i.e. lower cost and fewer GI events)
Bae, 2003[302]	Korean Ministry of Health and Arthritis Foundation	RA	2 comparators: Corticosteroids NSAIDs	US$51,700 per QALY gained (COX-2 vs NSAID) US$137,000 per QALY gained (COX-2 vs corticosteroids)

QALY, quality-adjusted life-year.

TABLE 58 *Base-case study results – Spiegel and colleagues[298]*

	Drug	Cost (US$)	QALYs	ICER (US$)
Base case	Naproxen	4,859	15.2613	
	Coxib	16,443	15.3033	275,800
Including CV events	Naproxen	2,037	15.2539	
	Coxib	16,620	15.2832	395,000
High-risk cohort (previous ulcer haemorrhage)	Naproxen	14,294	14.7235	
	Coxib	19,015	14.8081	55,800

TABLE 59 *Base case study results – Maetzel and colleagues*[299]

	Drug	Cost (Can$)	Complicated UGI events	QALYs	ICER (cost/QALY gained) (Can$)
Average-risk patients	Naproxen	1,576	7.70	2.8938	
	Rofecoxib	3,173	3.39	2.8997	271,000
	Ibuprofen	1,141	6.36	2.8990	
	Diclofenac	2,570	2.68	2.9104	125,000
	Celecoxib	3,371	2.48	2.9095	Dominated by diclofenac
High-risk patients	Rofecoxib	4,090	7.45	2.8851	
	Naproxen + PPI	4,766	11.31	2.8816	Dominated by rofecoxib
	Rofecoxib + PPI	6,486	5.13	2.8936	281,000
	Celecoxib	4,327	5.54	2.9003	
	Ibuprofen + PPI	4,414	9.49	2.8894	Dominated by celecoxib
	Diclofenac + PPI	5,980	4.11	2.9064	271,000
	Celecoxib + PPI	6,746	3.81	2.9057	Dominated by diclofenac

TABLE 60 *Published meloxicam economic analysis and published economic analysis of unnamed COX-2 selective NSAIDs*

Study	Sponsor	Patient group	Comparator(s)	Base-case ICER
Tavakoli, 2003[303]	None	OA	Meloxicam compared with: Diclofenac Piroxicam	Meloxicam dominant against both comparators
Fendrick, 2002[304]	SKB ('unrestricted grant')	Long-term users of NSAIDs	2 strategies compared: Generic NSAID used initially, with safer NSAID used for patients with GI events or intolerance Safer NSAIDs used first line for all patients	For first line use: US$31,900 per symptomatic ulcer avoided US$56,700 per complicated ulcer avoided

Summary

- Results of the published economic evaluations of COX-2 selective and non-selective NSAIDs are highly variable: some analyses suggest dominance and so support the widespread use of COX-2 selective NSAIDs, whereas others report very high ICERs and conclude that use of COX-2 selective NSAIDs cannot be considered an appropriate use of healthcare resources.
- None of the published analyses, where the COX-2 drug name was stated, considered valdecoxib, etoricoxib, etodolac or lumiracoxib.
- Many of the previous analyses are based on clinical estimates that are derived from single trials, or a small number of trials, rather than a formal systematic review and meta-analysis of the evidence.
- Drug manufacturers have sponsored a majority of published analyses; however, government agencies and others have also published economic evaluations of COX-2 selective NSAIDs. Studies not supported by the drug manufacturers are considerably less favourable to COX-2 selective NSAIDs.
- Virtually all economic analyses use a decision analytic model. Published models vary in some important respects, for example, whether switching of therapy is considered, timescale and nature of events considered. This makes direct comparison difficult, but it does appear that those explicitly including CV events found COX-2 selective NSAIDs less attractive.
- Most analyses modelled costs and benefits over a relatively short period (usually between 6 and 12 months) and their results tend to support the widespread use of COX-2 selective NSAIDs. Where a longer time horizon has been modelled (e.g. between 5 years and patient lifetime), ICERs are considerably higher.
- Analyses that consider restricting the use of COX-2 selective NSAIDs to 'high-risk' patients have results that tend to support restriction.

TABLE 61 *Cost-effectiveness information in company submissions*

Manufacturer	Drug	Economic analysis included in submission?	Electronic files of model provided?
Pfizer	Celecoxib Valdecoxib	Yes	Yes
Merck Sharp and Dohme	Rofecoxib Etoricoxib	Yes	Yes
Boehringer Ingelheim	Meloxicam	Yes	Yes
Shire	Etodolac	No	No
Novartis	Lumiracoxib	No	No

TABLE 62 *Summary of methods used in industry economic analyses*

Submission features	Pfizer	Merck Sharp and Dohme	Boehringer Ingelheim
COX-2s considered	Celecoxib Valdecoxib	Rofecoxib (12.5, 25 and 50 mg once daily) Etoricoxib (60, 90 and 120 mg once daily)	Meloxicam (7.5 and 15 mg once daily)
Comparison technologies	Non-selective NSAID alone Non-selective NSAID plus PPI Non-selective NSAID plus H2RA Arthrotec Non-selective NSAID plus misoprostol	Non-selective NSAIDs alone Non-selective NSAIDs plus PPIs Non-selective NSAIDs plus misoprostol Non-selective NSAIDs plus H2RAs	Diclofenac retard (100 mg once daily) Piroxicam (20 mg once daily)
Patients' characteristics	Patients with arthritis Average-risk patient: age 62 years, no history of GI side-effects or complications, no aspirin use and HAQ of 1 High-risk patient: age 72 years, history of GI side-effects, aspirin use and HAQ of 2	Patient with chronic OA/RA	Average patient with OA Patient with previous symptomatic ulcer (without PPI)
Form of economic analysis	Cost-effectiveness analysis (i.e. cost per life-year saved)	Cost–utility analysis	Cost–utility analysis
Model used	Decision tree (based on ACCES model)	Decision tree	Markov model (based on Maetzel model)
Time horizon of model	1 year (but calculation of life years lost considered patient age and expected survival from actuarial life tables)	1 year (but calculation of life-years lost from actuarial life tables)	5 years
Assumption concerning differential effectiveness/efficacy	Equal efficacy for all treatment arms	Equal efficacy for all treatment arms	Equal efficacy for all treatment arms

HAQ, Health Assessment Questionnaire.

Review of industry cost-effectiveness submissions

A detailed summary of the economic analyses and models included in the company submissions has been undertaken and is reported in this section. *Table 61* shows the information that was presented by the companies; no economic analysis for etodolac is available. Analyses presented by Pfizer, Merck Sharp and Dohme and Boehringer Ingelheim will be discussed in turn.

An overview of the methods used in the economic analyses is presented in *Table 62*.

Pfizer submission

Celecoxib or valdecoxib are compared with a generic NSAID (a weighted average of NSAIDs used in the UK); patients with either OA or RA are considered. A direct comparison of celecoxib versus valdecoxib is not reported. Pfizer use the ACCES decision tree, in line with most published economic analyses of celecoxib (supported by Pfizer). The model structure is shown in *Figure 44*. Patients move along the tree from left to right and events cover a 1-year time horizon, but the calculation of life-years gained is undertaken using UK actuarial life tables (assuming a reduction of 1.6 and 3 years for men and women, respectively, with RA). Costs have been discounted at 6% and life-years at 1.5%.

Initial treatment results in one of the eight possible outcomes shown (including therapeutic success, loss of efficacy and death). The outcomes are defined as:

- GI discomfort: moderate to severe dyspepsia, abdominal pain or nausea
- diarrhoea: severe enough to lead to patient withdrawal from trial
- symptomatic ulcers: ulcers treated in outpatient setting but severe enough to lead to NSAID discontinuation
- anaemia: with occult bleeding
- serious GI events: any GI event resulting in hospitalisation.

Patients who achieve therapeutic success on initial therapy remain on that for the remainder of the time in the model. Those who do not find treatment efficacious or have intolerable diarrhoea change immediately to another therapy. The switch is defined according to a set algorithm that depends on the starting NSAID. A reduced version of this algorithm is given in *Table 63*. Patients who experience an adverse GI event have their therapy temporarily withdrawn while the

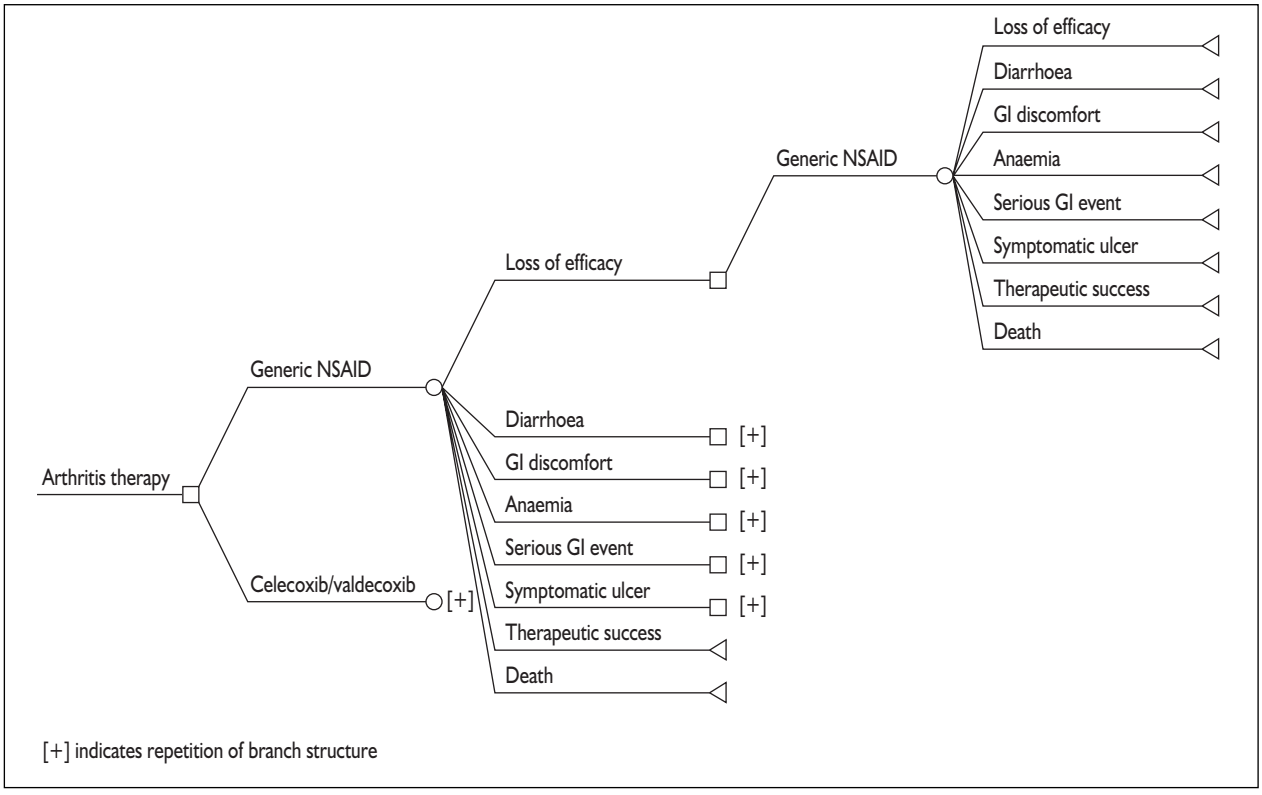


FIGURE 44 *Decision tree used in the Pfizer submission*

TABLE 63 *Reduced version of the algorithm for therapy switching*

Initial therapy	Subsequent therapy after a GI event or loss of efficacy				
	Loss of efficacy	Diarrhoea	GI discomfort	Symptomatic ulcer	Anaemia or serious GI event
NSAID	NSAID	NSAID	NSAID + H2RA	NSAID + H2RA	Arthrotec
Celecoxib	Valdecoxib	Valdecoxib	NSAID + H2RA	NSAID + H2RA	Arthrotec
Valdecoxib	Celecoxib	Celecoxib	NSAID + H2RA	NSAID + H2RA	Arthrotec

TABLE 64 *Event probabilities and relative risks used in Pfizer model (average-risk patients)*

[**Confidential information removed**]

event is treated but are then switched to another therapy.

The analysis assumes that all compared therapies are equivalent in terms of efficacy and rates of CV events and renal events, so neither CV nor renal adverse events are considered in the model structure.

The event probabilities for the non-selective NSAID strategy were taken from a variety of sources:

- GI discomfort: Weibull model to provide a GI discomfort probability adjusted for time of drug exposure, based on "pooled analysis of five, 12-week, placebo and active (naproxen) controlled, randomised, parallel group celecoxib clinical trials" (Bensen and colleagues[94]).
- Serious GI events: based on a predictive equation adapted from the Fries risk calculator, which uses information from the ARAMIS database – the risk calculator gives the baseline NSAID rate of serious GI events for a population described in terms of age, history of GI events, etc.
- Symptomatic ulcers and anaemia: taken from NSAID-only arm of the CLASS trial.
- Diarrhoea and lack of efficacy: taken from Edwards and colleagues' meta-analysis (a commissioned meta-analysis reported in the Pfizer submission).[448]

The RRs for gastrointestinal events were taken from single sources for the two drugs of interest:

- the SUCCESS trial (study 096) for celecoxib[224]
- Edwards and colleagues for valdecoxib.[448]

Edwards and colleagues' analysis was a systematic review commissioned by the manufacturer.[448]

The explanation for the former is that SUCCESS "is the largest study that reports all the inputs to the model at the licensed dose". The source for valdecoxib is stated to be the only source available. *Table 64* gives the event probabilities used in the ACCES model for average risk patients.

Average-risk patients were defined as "age 62, no history of GI side-effects or complications, no aspirin use and HAQ of 1" (i.e. average age of all patients in SUCCESS). High-risk patients were defined as "age 72, history of GI side-effects, aspirin use and HAQ of 2" (i.e. average age of patients over 65 years in SUCCESS). Analyses were run separately for men and women, and for OA and RA.

Resource use information relating to model events was collected by questioning and interviewing physicians who treat OA and RA patients. Unit costs were taken from routine sources and are expressed in 2002–3 prices.

The base-case results for average-risk OA patients are reported in *Table 65* and for high-risk patients in *Table 66*.

Pfizer believe, from their findings, that celecoxib and valdecoxib represent cost-effective uses of NHS resources. Although valdecoxib and celecoxib were not compared directly, there is sufficient detail in their submission to allow an indirect comparison. ICERs for these comparisons are given in the final rows in *Tables 65* and *66* and show that for both average- and high-risk patients

TABLE 65 *Modelled outcomes – 1000 average-risk male OA patients*

[**Confidential information removed**]

TABLE 66 *Modelled outcomes – 1000 high-risk male OA patients*

[**Confidential information removed**]

celecoxib has a higher cost than valdecoxib but is associated with fewer years of life lost. The ICER for changing from valdecoxib to celecoxib is just over £3000 per life-year gained for both average- and high-risk patients. One-way and probabilistic sensitivity analyses were reported. The baseline patient risk had a large impact on the resulting cost-effectiveness and results change considerably with variation in the RR of serious GI events for celecoxib (up to £33,000 per life-year gained). The results of the probabilistic sensitivity analysis are summarised as follows.

"At a ceiling ratio of £30,000 per life-year saved:

- There is a greater than 95% probability for both average- and high-risk patients that celecoxib is cost-effective.
- There is a greater than 95% probability that in the high-risk patients valdecoxib is cost-effective.
- There is approximately 90% probability that in the average-risk patients valdecoxib is cost-effective."

Although not reported, the assertion is made that the general findings of the sensitivity analyses are similar for valdecoxib.

Merck Sharp and Dohme submission

In this submission, rofecoxib or etoricoxib, for patients with either OA or RA, are compared with a range of non-selective NSAID alternatives; rofecoxib and etoricoxib are not compared directly. The alternatives considered are:

- non-selective NSAIDs alone
- non-selective NSAIDs plus PPIs
- non-selective NSAIDs plus misoprostol
- non-selective NSAIDs plus H2RAs.

Merck Sharp and Dohme explore a dose range for rofecoxib and [**Confidential information removed**] and also all doses up to 50 mg based on clinical trials and meta-analyses. For etoricoxib, a similar approach was desired but because of time constraints their analysis used clinical data for all doses up to 120 mg and [**Confidential information removed**].

A decision tree model similar to the published economic analyses of rofecoxib was used (*Figure 45*). Patients move along the tree from left to right. Model events cover a 1-year time horizon but the calculation of life-years gained is undertaken using actuarial life tables (with no differentiation between patients with RA and OA). The cost analysis considered only costs incurred within 1 year and so these were not discounted, but life-years were discounted at a rate of 1.5%.

Events modelled included:

- major GI events (i.e. PUBs)
- lower GI events
- events of sufficient severity to prompt a procedure to exclude a PUB (e.g. endoscopic examination)
- CV events.

Rofecoxib analyses

Analyses only included data on PUBs that related to occurrences at least 7 days before or after any trial protocol scheduled endoscopic procedure, and were confirmed as clinically significant by an outside expert panel. The rationale for this was to ensure that no protocol-driven healthcare costs were included in the analysis. [**Confidential information removed.**] For the all-dose investigation, data were taken from pooled analyses of a larger number of trials, including VIGOR.

The model input probabilities are listed in *Tables 67* and *68*.

TABLE 67 *Model inputs (probabilities and rates) – UGI events [partly confidential]*

	Non-selective NSAID	Rofecoxib
[**Confidential information removed**]		
All-dose study		
GI adverse events	0.3673	0.3302
PUB rate per 100 patients	0.0313	0.0116
PUB, given GI adverse event	0.0853	0.0351
Suspected PUB (per 100 patient years)	0.0039	0.0009
Suspected PUB, given GI adverse event and not major GI problem	0.0038	0.0009
Treatment given non-serious GI adverse event	0.3826	0.2985

TABLE 68 *Model inputs (probabilities and rates) – hospital treatment pathways of PUBs and mortality rate of PUBs*

	Base rate	Range
Hospitalisation given PUB	0.207	0.056–0.67
Inpatient investigation of suspected PUB	0.25	0.24–0.39
Surgery following hospitalisation	0.24	0.09–0.39
Death rate given hospitalisation	0.186	Not varied
Death given PUB	0.039	Not varied
Death given clinically diagnosed ulcer	0.036	Not varied

TABLE 69 *Results – licensed dose investigation*

[**Confidential information removed**]

Probability estimates on pathways and mortality were taken from a variety of published sources. In considering treatment options involving non-selective NSAIDs used in combination with prophylactic GPAs, Merck Sharp and Dohme assumed that no further reduction in UGI PUBs would be seen from the use of H2RAs and a 40% reduction in risk of UGI PUBs was assumed for both misoprostol and PPIs (based on Rostom and colleagues[449]). Estimates of probabilities for CV events were taken from the Antiplatelet Trialists' Collaboration (APTC) end-points observed in rofecoxib clinical trials. For the licensed dose investigation (*Table 69*) there was no statistically significant difference in rates between rofecoxib and non-selective NSAIDs, so the base-case analysis assumed that there was no difference. A sensitivity analyses varied this assumption. Similarly, the base-case analysis assumed no difference in the rate of lower GI events.

Resource use information relating to model events was taken from a variety of published and routine data sources. Unit costs have been taken from routine sources and are expressed in 2003 prices. The QALY calculations made use of Maetzel and colleagues' utility weights.[305] Extensive sensitivity analyses were undertaken, both one-way and probabilistic. A key feature of the sensitivity analyses is that the effect of incorporating lower GI events and CV events was explored.

The base-case results for [**Confidential information removed**] and for the all-dose investigation are given in *Table 70*.

Merck Sharp and Dohme believe, from these findings, that rofecoxib is cost-effective in the treatment of OA and RA when compared with non-selective NSAIDs alone or in combination with other therapies. On comparing a non-selective NSAID plus either a PPI or misoprostol, rofecoxib is dominant. The inclusion of CV events leads to an improved cost-effectiveness for rofecoxib [**Confidential information removed**]. Sensitivity analyses highlight the high degree of sensitivity of the results to variations in the risk of PUB and the cost of PPIs.

TABLE 70 *Results – all-dose investigation*

	NSAID alone	NSAID + PPI	NSAID + H2RA	NSAID + misoprostol	Rofecoxib
Base-case analysis					
Total daily cost (£)	0.40	1.07	0.67	1.03	0.86
QALYs per 10,000 patients	6683	6745	6683	6745	6776
ICER (rofecoxib vs comparator) (£)	17,900	(Saving)	7,159	(Saving)	
Including lower GI effects (from VIGOR)					
Total daily cost (£)	0.43	1.09	0.70	1.06	0.87
QALYs per 10,000 patients	6647	6710	6647	6710	6757
ICER (rofecoxib vs comparator) (£)	14,994	(Saving)	5,834	(Saving)	
Including CV and lower GI effects					
Total daily cost (£)	0.63	1.30	0.91	1.26	1.08
QALYs per 10,000 patients	6261	6324	6261	6324	6406
ICER (rofecoxib vs comparator) (£)	11,192	(Saving)	4,324	(Saving)	

Etoricoxib analysis

This analysis followed the same approach as the economic evaluation of rofecoxib. Exactly the same model structure was used (*Figure 45*). Key differences are the model inputs for UGI events and drug costs.

Estimates for UGI events come from a pooled analysis of 10 Phase IIb or Phase III clinical trials that compared etoricoxib with non-selective NSAIDs in OA, RA and ankylosing spondylitis. Probabilities for UGI events included in the model are given in *Table 71* and pathways for hospital treatment of PUBs including mortality rate are identical with those used in the rofecoxib analysis.

Once again, extensive sensitivity analyses were undertaken, both one-way and probabilistic. A key feature of the sensitivity analysis is that the effect of incorporating lower GI events and CV events was explored.

The base-case results are reported in *Table 72*.

In line with the findings for rofecoxib, Merck Sharp and Dohme believe that etoricoxib is cost-effective in the treatment of OA and RA when compared with non-selective NSAIDs alone or in combination with other therapies. On comparing etoricoxib with a non-selective NSAID plus either a PPI or misoprostol, etoricoxib is dominant. Sensitivity analyses again highlight the importance of variations in the risk of PUB and the costs of PPIs.

Boehringer Ingelheim submission

In this submission, meloxicam (7.5 or 15 mg/day), for patients with OA or RA, is compared with diclofenac retard (100 mg/day) and piroxicam (20 mg/day). An economic evaluation, using a slightly modified version of the Markov model developed by Maetzel and colleagues,[305] is included. The submission indicates that the model used "has been adapted to a UK health care setting", but full details on the nature of the changes made are not given. It is assumed that COX-2 selective and non-selective NSAIDs do not differ in effectiveness but differ in their adverse event profile. *Figure 46* shows the model structure as reported in Maetzel and colleagues[305] and reproduced by Boehringer. The time frame for the model is 5 years.

Clinical information concerning the incidence of GI and MI adverse events was based on two trials, MELISSA and SELECT. It was assumed that the RR reduction for 15 and 7.5 mg of meloxicam was the same, and that "the rate of CV adverse event was not substantially raised compared with those on standard NSAIDs amongst those on meloxicam 15 mg".

Some of the key clinical assumptions and input parameter values used in the analysis are given in *Table 73*.

Resource use information relating to model events was taken from a variety of published and routine data sources. Unit costs were taken from routine sources and are expressed in 2003–4 prices. Costs were discounted at a rate of 6%. Benefits were discounted at 1.5%. QALY calculations made use of Maetzel and colleagues' utility weights.[305]

The base-case result for an average patient with OA, comparing meloxicam (7.5 mg) against piroxicam (20 mg), is £12,383 per QALY gained

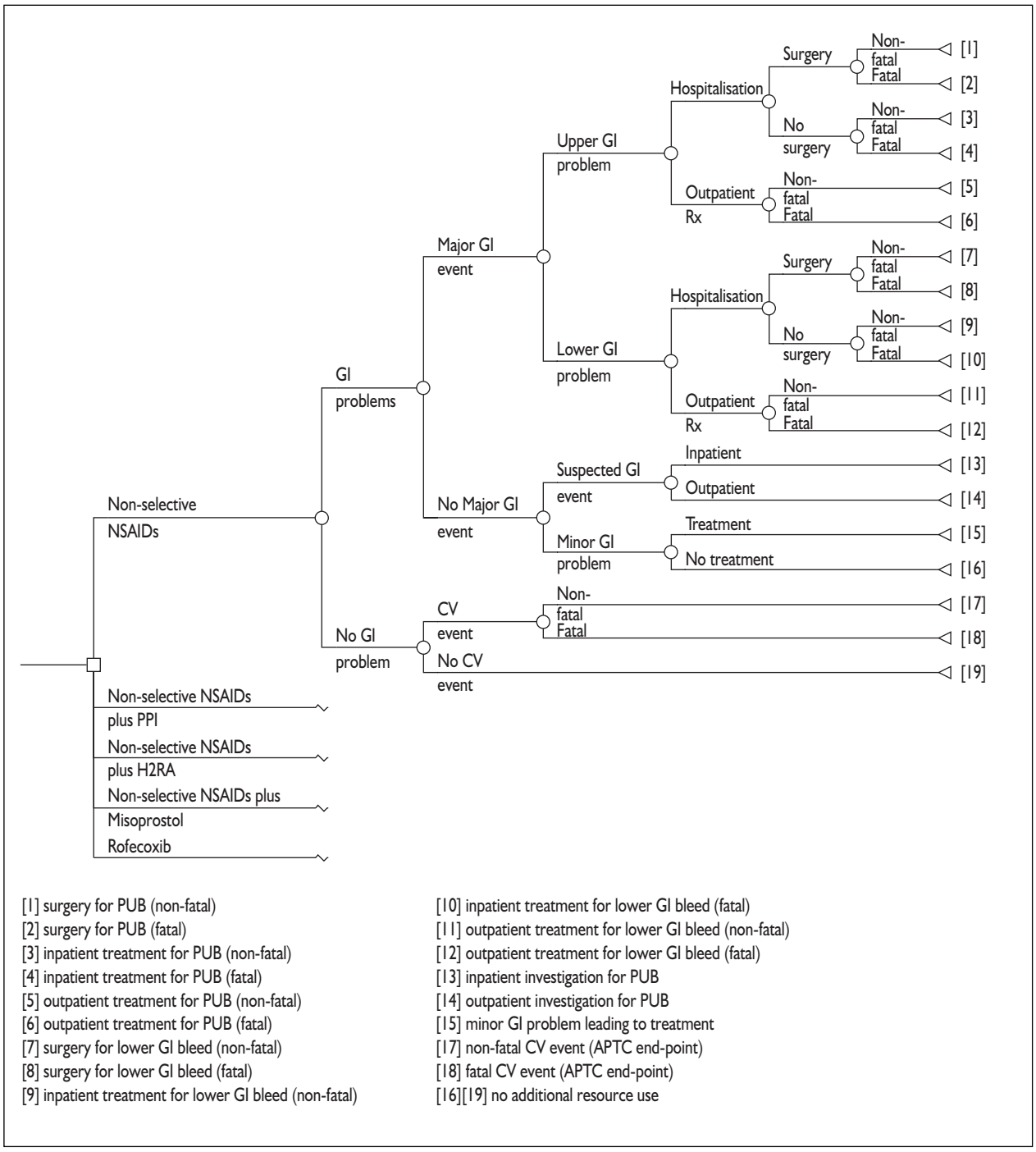


FIGURE 45 *Decision tree used in the Merck Sharp and Dohme submission*

TABLE 71 *Model inputs (probabilities and rates) – UGI events*

	Non-selective NSAID	Etoricoxib
GI adverse events	0.1840	0.1472
PUB rate per 100 patients	0.0294	0.0124
PUB, given GI adverse event	0.1598	0.0842
Suspected PUB (per 100 patient years)	0.0032	0.0022
Suspected PUB, given GI adverse event and not major GI problem	0.0032	0.0024
Treatment given non-serious GI adverse event	0.3341	0.2913

TABLE 72 *Results – base case analysis*

	NSAID alone	NSAID + PPI	NSAID + H2RA	NSAID + misoprostol	Etoricoxib
Base case analysis					
Total daily cost (£)	0.37	1.05	0.65	1.01	0.87
QALYs per 10,000 patients	6705	6769	6705	6769	6802
ICER (etoricoxib vs comparator) (£)	18,972	(Saving)	8,534	(Saving)	
Including CV and lower GI effects					
Total daily cost (£)	0.51	1.18	0.78	1.14	1.01
QALYs per 10,000 patients	6426	6490	6426	6490	6510
ICER (etoricoxib vs comparator) (£)	21,727	(Saving)	9,745	(Saving)	

TABLE 73 *Clinical outcome estimates included in model analysis*

Variable	Base-case value	Source
Dyspepsia requiring medical consultation (%)	10.7	Maetzel, 2001[305]
Hospitalised if complicated UGI event (%)	62.7	Maetzel, 2001[305]
Surgery if hospitalised (%)	8.5	Maetzel, 2001[305]
Mortality in patients with 1st bleed (%)	4.3	Maetzel, 2001[305]
Recurrence of bleed (%)	11.5	Maetzel, 2001[305]
Surgery in patients with 2nd GI bleed (%)	71.1	Maetzel, 2001[305]
Mortality in patient with 2nd bleed (%)	38.7	Maetzel, 2001[305]
% retrying NSAIDs after GI bleed	5.0	Maetzel, 2001[305]
RR increase of clinical UGI event due to prior symptomatic ulcer	2.6	Maetzel, 2001[305]
Mortality after experiencing non-fatal MI (%)	3.5	Maetzel, 2001[305]
Complicated UGI event (3 months) – meloxicam (%)	0.208	MELISSA
Complicated UGI event (3 months) – diclofenac (%)	0.343	MELISSA
Symptomatic ulcer (3 months) – meloxicam (%)	0.139	MELISSA
Symptomatic ulcer (3 months) – diclofenac (%)	0.137	MELISSA
Non fatal MI (3 months) – meloxicam (%)	0.139	MELISSA
Non fatal MI (3 months) – diclofenac (%)	0.274	MELISSA
Complicated UGI event (3 months) – meloxicam (%)	0.372	SELECT
Complicated UGI event (3 months) – piroxicam (%)	0.815	SELECT
Symptomatic ulcer (3 months) – meloxicam (%)	0.149	SELECT
Symptomatic ulcer (3 months) – piroxicam (%)	0.371	SELECT
Non-fatal MI (3 months) – meloxicam (%)	0.149	SELECT
Non-fatal MI (3 months) – piroxicam (%)	0.074	SELECT

(note: the precise definition of the 'average patient' is not clear from the submission). When the 15-mg dose is considered, the ICER increases to £23,448 per QALY gained. These estimates are based on the current branded price for meloxicam. When a generic price is used (assumed to be 60% lower price), meloxicam dominates (i.e. lower cost and higher benefits). For patients with a previous history of symptomatic ulcer (without the use of PPIs), meloxicam dominates all comparisons made. Results from extensive one-way sensitivity analyses do not change the results, in general terms. Unsurprisingly, changes in the reduction in the risk of complicated UGI events bring about the largest change in the overall results.

Boehringer conclude that meloxicam (at both 7.5- and 15-mg doses) is highly cost-effective against diclofenac (100 mg slow-release) and piroxicam in patients at average risk and more so for patients at high risk of GI events. The patent for meloxicam is due to expire in 2005. In a separate analysis assuming drug prices 60% lower than branded prices, an even more favourable result for meloxicam is shown.

Summary

- All three industry submissions that included a formal economic analysis used a decision modelling approach. Models vary in some important aspects, for example, whether switching of therapy is considered, time frame

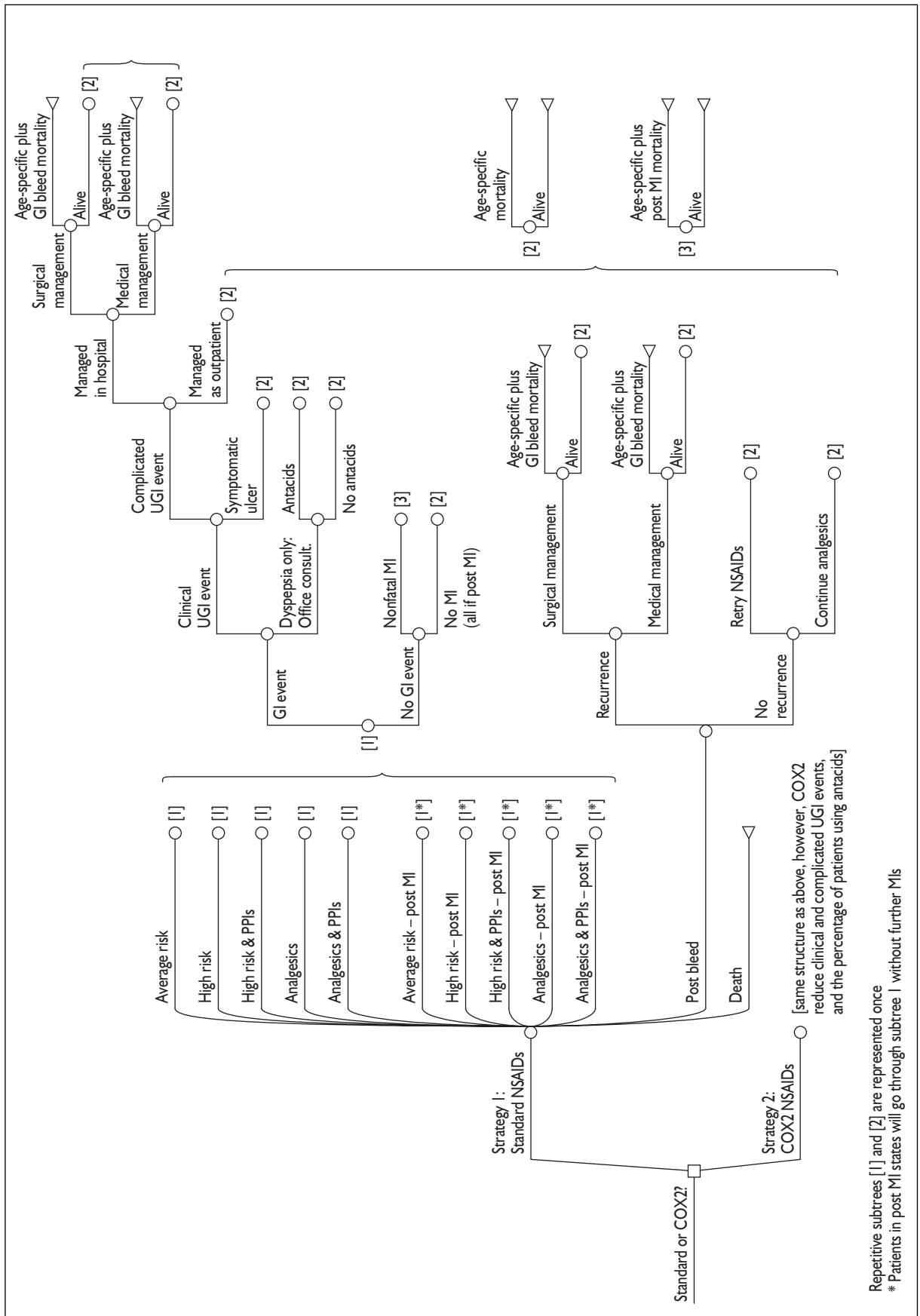


FIGURE 46 *Markov model used in Boehringer Ingelheim submission (diagram of Maetzel model)*

and nature of events considered. This makes direct comparisons difficult.
- All analyses compared individual COX-2 selective NSAIDs with a non-selective agent (in some cases with co-therapy). Manufacturer analyses support the widespread use of celecoxib, rofecoxib, meloxicam, etoricoxib and valdecoxib but none report direct comparisons of COX-2 selective drugs even though this is clearly feasible, especially where manufacturers have more than one product.
- In general terms, the economic analyses presented by the companies are based on clinical estimates derived from single trials, or a small number of trials, rather than a formal systematic review and meta-analysis of the evidence.
- Sensitivity analyses show, consistently, that cost-effectiveness is more favourable when COX-2 selective NSAIDs are restricted to 'high-risk' patients, and when the reduction in the risk of serious GI events is large.

The Assessment Group Model (AGM)

The Assessment Group has undertaken a new modelling exercise that used the Markov model developed originally by Maetzel and colleagues[305] as a starting point (see the section 'Systematic review of published cost-effectiveness literature', p. 87 for a discussion of the published Maetzel model) and built on it in a number of ways, including: (1) introducing an initial cycle where drug switching could take place, (2) revising the model input parameters and (3) using the revised model to consider all COX-2 drugs (for which adequate data were available). The methods and results of this modelling work are reported in this section.

The AGM is a Markov model with a time cycle of 3 months, and runs by default for a time horizon of 5 years. The model was constructed using TreeAge DATA Pro.

The model has been designed to run in two different forms: the 'full AGM', which includes an initial drug switching cycle, and the 'simpler AGM', which has no initial cycle and no opportunity for the patient to switch NSAID.

Both versions of the AGM are designed to compare COX-2 selective NSAIDs individually with non-selective NSAIDs, not to compare non-selective NSAIDs with each other. Therefore, cost-effectiveness results have been obtained for each COX-2, compared with a non-selective NSAID, initially for a general population with no special risk factors but additionally for other patient populations with defined risk factors (e.g. previous GI event).

The full AGM, in our view, has the more appropriate model structure, for two reasons: first, it directly addresses the policy question at hand, and second, it models strategies that are in line with current NSAID-prescribing practice. That is, the full AGM allows for the possibility that patients will, in the short term, switch from an initial NSAID therapy to an alternative.

However, this section of the report initially describes the methods and results for the simpler AGM (with no initial switching cycle). The reason for this is that the simpler model is more directly comparable with previous modelling work and the results can more easily be compared with the results of the company analyses. In broad terms, the results of the simpler version of our model and the fuller model are not very different.

The simpler AGM: broad overview

Simulated patients with arthritis initially start in the model on one NSAID (either a non-selective or a COX-2 selective NSAID) and are immediately at risk of GI and MI events. As time goes on, for each simulated patient, the NSAID that they are receiving may be withdrawn and/or a PPI may be added. There is no provision for switching NSAIDs. Mortality from MI and GI complications is taken into account, in addition to mortality from other causes.

Markov states and cycles

On entry into the model, a patient is in one of the Markov model states. The majority of states are defined by four characteristics (as shown in *Table 74*):

- whether or not an NSAID is being used (NSAID use)
- whether or not a PPI is being used (PPI use)
- whether or not a GI event has been experienced in the past (Post GI)

TABLE 74 *Markov states in the AGM*

NSAID use	PPI	Post GI	Post MI
Yes	No	No	No
No	Yes	Yes	Yes

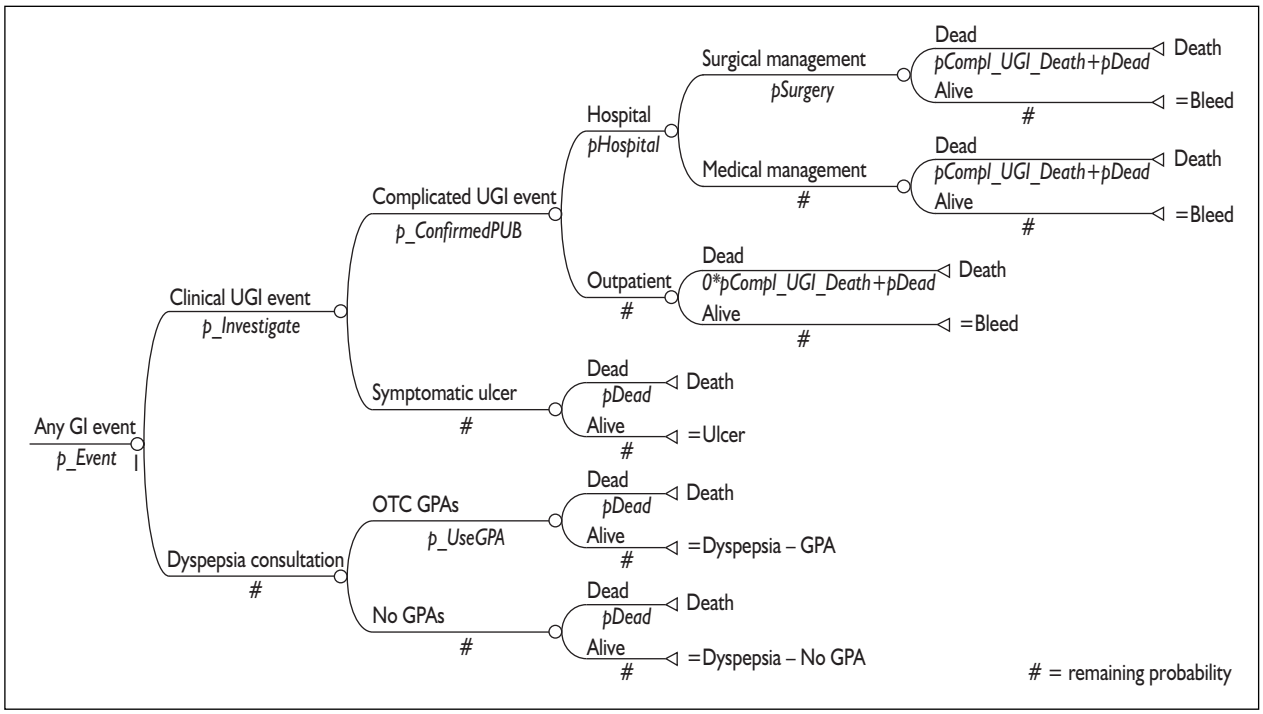


FIGURE 47 *Handling GI events*

- whether or not an MI event has been experienced in the past (Post MI).

For example, a simulated patient might be taking an NSAID with no PPI, having experienced neither a GI nor an MI event. There are also (immediate) Post Bleed states (with or without Post MI) and Death.

NSAIDs may be taken with or without PPI. Patients who have had a previous serious UGI event are in 'Post GI' states, whereas patients with a previous MI are in 'Post MI' states. For patients taking non-selective NSAIDs, it is assumed that if the patient has had a previous serious UGI event then a PPI would always be used. Thus, the combination 'No PPI' with 'Post GI' is not permitted.

Patients may be in the 'Post GI' states as a result of starting in the model having never previously had a GI event but transitions within the model mean that a GI event is experienced. Alternatively, patients may be in the 'Post GI' states simply because the model is being run for a high-risk cohort of patients with previous UGI history, in which case **only** the 'Post GI' states will be used.

We have maintained the assumption in the Maetzel model that only one new event (GI or MI) can occur in any 3-month cycle. We have also maintained the assumption that second MIs are

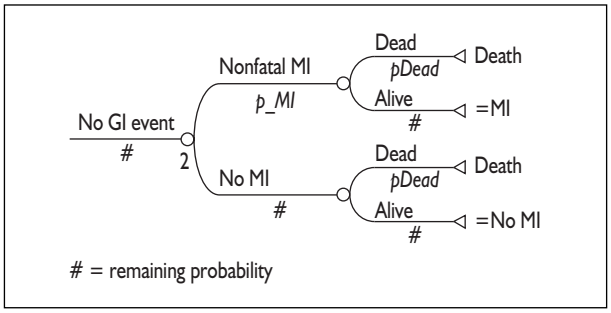


FIGURE 48 *Other events*

fatal; we appreciate that this is not usual. The possibility that the first MI can be fatal is incorporated in the standard mortality tables, and additional probability of death from MI is added in the 'Post MI' states.

Figure 47 shows possible outcomes following a GI event in a Markov cycle in the model. Patients move from left to right through the tree and circles indicate chance nodes. The label below each branch in the figure indicates the probability of a patient following that branch, conditional on them reaching the previous chance node. If there is no GI event in a Markov cycle, the possibilities are shown in *Figure 48*. An exception here is that non-fatal MI is omitted in 'Post MI' states as we assume that a second MI would be fatal. The Markov state reached at the end of the cycle is shown in *Table 75*.

TABLE 75 *Markov transitions*

Event occurring during cycle	Markov state at end of cycle
Death (any cause)	Death
Complicated UGI event (bleed)	Post Bleed ('Post MI' as at start)
Other clinical UGI event (ulcer)	Add PPI and 'Post GI' to starting state
Dyspepsia – GPA used	Add PPI to starting state
Dyspepsia – GPA not used	Same as at start of cycle
MI	Add 'Post MI' to starting state
No event (no MI)	Same as at start of cycle

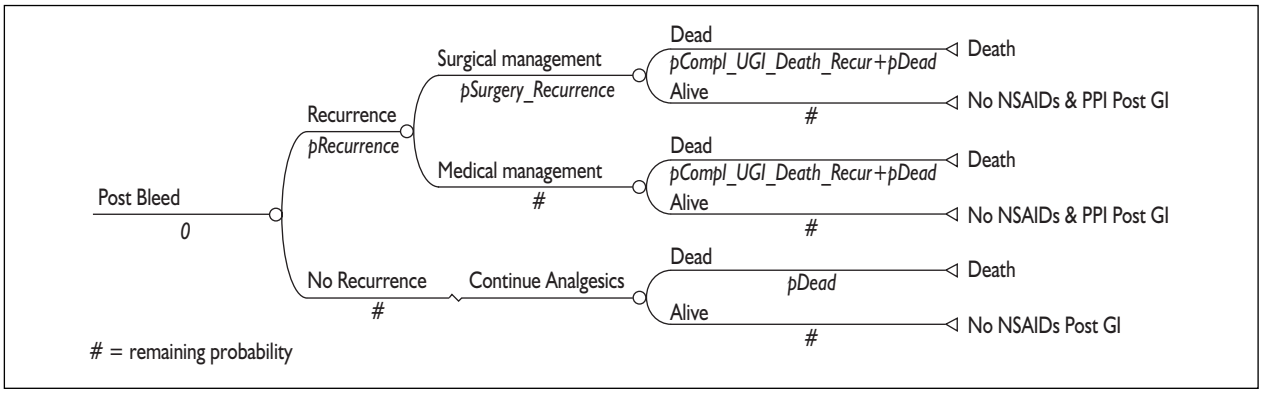


FIGURE 49 *'Post bleed' transitions*

Data inputs to the Markov cycles consist of probabilities of any GI event, clinical GI event, complicated GI event and non-fatal MI. Baseline risks are given for non-selective NSAIDs, with RRs for adding PPI, for COX-2 selective NSAIDs (assumed relative to ibuprofen) and for previous UGI event.

Consider, for example, a patient in state 'NSAID & PPI' at the start of the Markov cycle. If this patient developed an ulcer during the Markov cycle, the patient then moves into the state 'NSAID & PPI, Post GI'.

The only states remaining to be described are the 'Post Bleed' states. The structure for these is shown in *Figure 49*. For a patient who has had an MI and now experiences a bleed (i.e. 'Post Bleed & Post MI'), the possible transitions are equivalent 'Post MI' to those shown in *Figure 49*. In our version of the model (unlike the original Maetzel model), all 'Post Bleed' transitions are to 'No NSAID' states, and therefore no further NSAID will be taken after a bleed. The original Maetzel model allows a small probability of re-trying NSAIDs after a bleed with no recurrence. To include this possibility in a model allowing switching of NSAIDs would require separate 'Post Bleed' states and thus further complicate the model. Our justification for omitting this possibility is also based on the fact that Maetzel and colleagues reported a sensitivity analysis on the probability of re-trying, which shows that it makes very little difference to the results to the model.

Costs

Costs in the model consist of costs of medication (i.e. NSAIDs, analgesics and PPIs) and costs of managing events as they occur. *Table 76* shows the costs in the model.

Utilities

We have maintained the utility structure from the Maetzel model. The utilities actually used are shown in *Table 77*. They represent the (undiscounted) QALYs accruing over one 3-month cycle in which the given event occurs. Note that 0 QALYs are scored if death occurs during the cycle. This may appear unreasonable for 'other causes' death, but the difference is likely to be small, and to cancel out between different arms of the model.

Markov cycle and other model parameters

The probabilities for the later Markov cycles are calculated from the data in *Table 78*. Details of the methods used are given in Appendix 10. Here,

TABLE 76 *Costs included in the AGM*

Item	Per	Value (£)	Source
Ibuprofen	Day	0.11	BNF
Diclofenac	Day	0.13	BNF
Celecoxib (LD)	Day	0.718	BNF
Celecoxib (HD)	Day	1.436	BNF
Etodolac (branded)	Day	0.52	BNF
Etodolac (generic)	Day	0.29	BNF
Etoricoxib	Day	0.82	BNF
Meloxicam (LD)	Day	0.33	BNF
Meloxicam (HD)	Day	0.46	BNF
Rofecoxib	Day	0.77	BNF
Valdecoxib	Day	0.77	BNF
Lumiracoxib	Day	0.57	Novartis
PPI	Day	0.46	BNF
Analgesics	Day	0.05	BNF
Surgical treatment of PUB	Case	3258	BI
Medical treatment of PUB	Case	445	BI
Outpatient treatment of PUB	Case	308	BI
Endoscopy for ulcer	Case	337	BI
Dyspepsia consultation	3 months	28.52	BI
Dyspepsia treatment (H2RA)	Day	0.09	BNF
Non-fatal MI	Case	1383	BI
Bleed follow-up consultation	3 months	87	BI
Post-MI management	3 months	114	BI

BI, company submission (Boehringer Ingelheim); BNF, British National Formulary; HD, high dose; LD, low dose.

TABLE 77 *State utilities used in the model*

Event	Utility weight	QALYs per 3-month cycle
Arthritis	0.688	0.172
Dyspepsia	0.504	0.126
Endoscopy (no ulcer)	0.46	0.115
Endoscopy (ulcer)	0.38	0.095
MI	0	0
PUB (medical management)	0.312	0.078
PUB (outpatient treatment)	0.38	0.095
PUB (surgery)	0	0
Post-MI states	Multiply by 0.97	

absolute risks are given for ibuprofen and diclofenac and RRs for COX-2 selective NSAIDs compared with ibuprofen (note that hepatotoxicity, which is increased with lumiracoxib, is not considered).

Clearly, some important assumptions have been made. Notably, we have assumed that non-selective NSAIDs do not protect against the risk of MI.

Other model parameters are given in *Table 79*.

GI events and previous GI history

The parameter 'RR of GI events for patients with previous GI history' in *Table 79* is applied for risks of clinical and complicated GI events (PUBs and POBs) to patients in all 'Post GI' states in the model. Note that in the model structure described above, patients who have had a bleed during the model are in a 'No NSAID Post GI' state. However, as a result of the new initial 3-month cycle in the AGM model (in contrast to the original Maetzel model), we have some 'No NSAID' states that are not 'Post GI'.

The risk of serious GI events needs to recognise the difference between 'No NSAID Post GI' states and 'No NSAID' states (which are not 'Post GI').[45] For the 'No NSAID' states (which are not 'Post GI'), we have assumed that the risk of GI events is

TABLE 78 *Data for main Markov cycles*[a]

	Absolute or relative risk (95% CI)	Source and comment
Risk of any GI event[b]		
Ibuprofen	31.15 per 100 person years	CLASS[50] [c]
Diclofenac	37.21 per 100 person years	CLASS[50] [c]
Celecoxib	RR 0.84 (0.78 to 0.89)	Assessment group meta-analysis
Etodolac	RR 0.85 (0.72 to 1.01)	Assessment group meta-analysis
Etoricoxib	RR 0.48 (0.24 to 0.96)	Assessment group meta-analysis
Lumiracoxib	RR 0.94 (0.90 to 0.98)	Assessment group meta-analysis
Meloxicam	RR 0.66 (0.58 to 0.75)	Assessment group meta-analysis
Rofecoxib	RR 0.84 (0.45 to 1.60)	Assessment group meta-analysis
Valdecoxib	RR 0.71 (0.62 to 0.82)	Assessment group meta-analysis
No NSAID	RR 0.48	Assumed equivalent to lowest COX-2
Adding PPI	RR 0.40 (0.32 to 0.51)	Rostom *et al.*[125] and Ekstrom *et al.*[306]
Risk of clinical GI event (PUB)		
Ibuprofen	3.2 per 100 person years	CLASS[50] [c]
Diclofenac	1.19 per 100 person years	CLASS[50] [c]
Celecoxib	RR 0.55 (0.40 to 0.76)	Assessment group meta-analysis
Etodolac	RR 0.32 (0.15 to 0.71)	Assessment group meta-analysis
Etoricoxib	RR 0.23 (0.05 to 1.08)	Assessment group meta-analysis
Lumiracoxib	RR 0.47 (0.37 to 0.61)	Assessment group meta-analysis
Meloxicam	RR 0.53 (0.29 to 0.97)	Assessment group meta-analysis
Rofecoxib	RR 0.43 (0.32 to 0.57)	Assessment group meta-analysis
Valdecoxib	RR 0.20 (0.03 to 1.46)	Assessment group meta-analysis
No NSAID	RR 0.20	Assumed equivalent to lowest COX-2
Adding PPI	RR 0.40 (0.32 to 0.51)	Rostom *et al.*[125] and Ekstrom *et al.*[306]
Risk of complicated GI event (POB)		
Ibuprofen	1.14 per 100 person years	CLASS[50] [c]
Diclofenac	0.48 per 100 person years	CLASS[50] [c]
Celecoxib	RR 0.57 (0.35 to 0.95)	Assessment group meta-analysis
Etodolac	RR 0.39 (0.12 to 1.24)	Assessment group meta-analysis
Etoricoxib	RR 0.46 (0.07 to 3.10)	Assessment group meta-analysis
Lumiracoxib	RR 0.34 (0.23 to 0.52)	Assessment group meta-analysis
Meloxicam	RR 0.56 (0.27 to 1.15)	Assessment group meta-analysis
Rofecoxib	RR 0.40 (0.23 to 0.70)	Assessment group meta-analysis
Valdecoxib	RR 0.43 (0.19 to 0.97)	Assessment group meta-analysis
No NSAID	RR 0.34	Assumed equivalent to lowest COX-2
Adding PPI	RR 0.40 (0.32 to 0.51)	Rostom *et al.*[125] and Ekstrom *et al.*[306]
Risk of MI		
Ibuprofen	0.24/100 person years	CLASS[50]
Diclofenac	0.23/100 person years	CLASS[50]
Celecoxib	RR 1.77 (1.00 to 3.11)	Assessment group meta-analysis
Etodolac	RR 1.77 (1.00 to 3.11)	Assumed same as celecoxib
Etoricoxib	RR 1.58 (0.06 to 38.66)	One trial only (Matsumoto *et al.*,[256] vs naproxen)
Lumiracoxib	RR 1.71 (0.86 to 3.37)	Assessment group meta-analysis
Meloxicam	RR 0.33 (0.01 to 8.03)	One trial only (Hosie *et al.*,[170] vs diclofenac)
Rofecoxib	RR 2.92 (1.36 to 6.28)	Assessment group meta-analysis
Valdecoxib	RR 0.25 (0.06 to 1.00)	Assessment group meta-analysis
No NSAID	0.23 per 100 person years	Assumed same as diclofenac
Adding PPI	RR 1	Assumed PPI does not affect MI rates

[a] Effective antiplatelet therapy with aspirin reduces the risk of MI in low-risk patients by about one-third (risk reduction 30%; 95% CI 21 to 38%).[307] Naproxen may provide a similar level of benefit and in a recent case–control study ibuprofen had a protective effect similar to naproxen.[308] We have assumed that ibuprofen and diclofenac may have a similar beneficial effect on MI rate but we have explored the possibility that non-selective NSAIDs have no effect at all on MI rates.
[b] PUBs plus dyspepsia.
[c] Non-aspirin users.

TABLE 79 *Other model parameters*

Parameter	Value	Source
RR of GI events for patients with previous GI history	2.6	Maetzel model[305]
Hospitalisation given complicated GI event	0.432	CLASS:[50] see below
Surgery given hospitalisation	0.085	Maetzel model:[305] see below
Death given complicated GI event	0.03	VIGOR,[66] CLASS,[50] MUCOSA:[56] see below
Recurrence of GI bleed	0.1145	Maetzel model[305]
Surgery given recurrence of GI bleed	0.7113	Maetzel model[305]
Extra mortality risk post-MI	3.5 per 1000 years	Maetzel model[305]

equivalent to the best COX-2 selective NSAID. For the 'No NSAID Post GI' states, we have again assumed that the risk of GI events is equivalent to the best COX-2 selective NSAID but have applied the additional previous GI history risk.

The Maetzel model assumes that the risk for 'No NSAIDs Post GI' is the same as the risk for COX-2 selective NSAIDs without the additional 'Post GI' risk.[45]

Hospitalisation

Maetzel and colleagues[305] quote a figure of 62.7% for hospitalisation of patients with a complicated UGI event, based on the MUCOSA study of RA patients. Since RA patients are likely to be sicker and MUCOSA was published in 1995, we studied clinical cases where complicated UGI events occurred in the CLASS study. Of the 44 patients with clinically significant UGI events reported in detail on the FDA website, 19 patients out of 44 (43.2%) were admitted to hospital (in one case the patient "had a prolonged emergency room stay and intravenous hydration" – it was assumed that such a patient would be hospitalised in the UK). Five (26.3%) of the 19 hospitalised patients in CLASS had surgery, two of them for perforations. There were no UGI-related deaths in CLASS. Of the 44 case reports on the FDA website, nine (20.5%) patients had blood transfusions.

Surgery

Maetzel and colleagues quote a baseline rate for surgery of 8.5% (95% CI 4.8 to 12.2%) for hospitalised patients. We have not identified any better estimates for this parameter and have accepted this baseline figure and a range of 3.3–35.7% quoted by Maetzel and colleagues.[305]

Mortality

In the VIGOR study, 53 complicated PUBs were reported and four deaths (7.5%), directly due to UGI events, occurred: one in the naproxen group and three for rofecoxib. In MUCOSA, one patient of 67 with definite UGI complications died. Combining data on deaths from MUCOSA, VIGOR and CLASS indicates that 3.0% of people with a complicated UGI died (assuming 39 events in CLASS). This figure is close to that used by Maetzel and colleagues,[305] who quote a figure of 4.3% from data recorded before 1986.[309]

Results for the simpler AGM

Base-case results for the average patient

The model was initially run for a cohort of standard patients with starting age 58 years. Comparisons against ibuprofen (without PPI) are shown in *Table 80* and against diclofenac (without PPI) alone in *Table 81*. The ICERs for the comparison against ibuprofen are plotted on the cost-effectiveness plane in *Figure 50*.

One might initially want to consider the extent to which the resulting variation in incremental costs, incremental effects and ICERs between the COX-2 drugs is plausible and reasonable. It should be immediately obvious that the results are both plausible and reasonable. The incremental cost estimates are closely in line with the variation in the price of the drugs. For example, the highest price COX-2 is high-dose celecoxib, and this has the highest incremental cost, and the lowest price COX-2 is etodolac (generic), and this has the lowest incremental cost. Similarly, the COX-2s with prices between these two ends of the price scale have incremental cost estimates that are broadly in line with their prices. On the estimates of incremental effects, although the picture is less immediately obvious, the ordering of the COX-2s is as one would have predicted on the basis of the input parameter values. For the sake of exposition, one might crudely group the COX-2s on the basis of their incremental effectiveness results into two groups: 'higher' incremental effectiveness group (etoricoxib, valdecoxib and meloxicam) and 'lower' incremental effectiveness group (lumiracoxib,

TABLE 80 *Results comparing single COX-2 selective NSAIDs against ibuprofen*[a]

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALY)
Ibuprofen	520.06		3.19150		
Celecoxib (LD)	1,455.04	934.98	3.20100	0.00950	98,400
Celecoxib (HD)	2,564.55	2,044.49	3.20100	0.00950	215,000
Etodolac (branded)	1,142.49	622.43	3.20193	0.01043	59,700
Etodolac (generic)	786.20	266.14	3.20193	0.01043	25,500
Etoricoxib	1,526.05	1,005.99	3.21924	0.02774	36,300
Lumiracoxib	1,226.73	706.67	3.19737	0.00587	120,000
Meloxicam (LD)	805.73	285.67	3.21425	0.02275	12,600
Meloxicam (HD)	1,006.41	486.35	3.21425	0.02275	21,400
Rofecoxib	1,559.58	1,039.52	3.19805	0.00655	159,000
Valdecoxib	1,485.55	965.49	3.21439	0.02289	42,200

HD, high dose; LD, low dose.
[a] All incremental analysis is compared with ibuprofen.

TABLE 81 *Results comparing single COX-2 selective NSAIDs against diclofenac*[a]

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALY)
Diclofenac	530.72		3.18749		
Celecoxib (LD)	1,455.04	924.32	3.20100	0.01351	68,400
Celecoxib (HD)	2,564.55	2,033.83	3.20100	0.01351	151,000
Etodolac (branded)	1,142.49	611.77	3.20193	0.01444	42,400
Etodolac (generic)	786.20	255.48	3.20193	0.01444	17,700
Etoricoxib	1,526.05	995.33	3.21924	0.03175	31,300
Lumiracoxib	1,226.73	696.01	3.19737	0.00988	70,400
Meloxicam (LD)	805.73	275.01	3.21425	0.02676	10,300
Meloxicam (HD)	1,006.41	475.69	3.21425	0.02676	17,800
Rofecoxib	1,559.58	1,028.86	3.19805	0.01056	97,400
Valdecoxib	1,485.55	954.83	3.21439	0.0269	35,500

[a] All incremental analysis is compared with diclofenac.

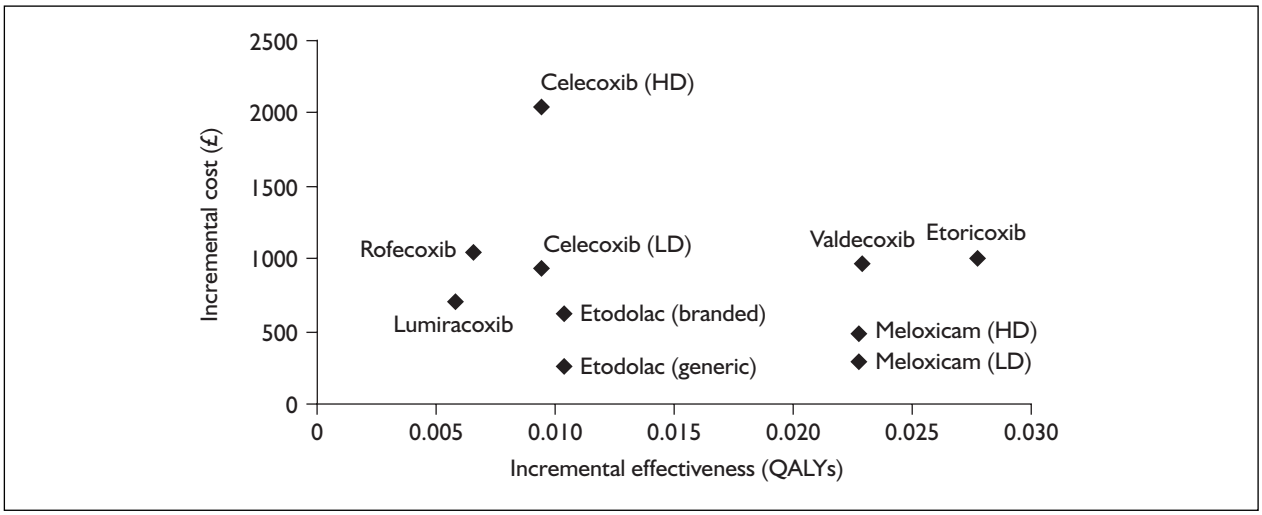


FIGURE 50 *ICERs plotted on the cost-effectiveness plane for single COX-2 selective NSAIDs against ibuprofen*

rofecoxib, celecoxib and etodolac). This grouping makes sense when one considers the RR of any GI event inputs into the model. These RRs were no higher than 0.71 for the 'higher' incremental effectiveness group and no lower than 0.84 for the 'lower' incremental effectiveness group. If we are satisfied that the estimates of incremental effectiveness and incremental cost are plausible and reasonable, then it has to follow that the ICERs are also.

Note that the effectiveness estimates (and hence the QALY scores) used in this analysis relate solely to the side-effect profiles of the drugs – no differences in drug efficacy are considered.

For both ibuprofen and diclofenac as comparators, all of the COX-2 products are associated with higher costs (i.e. positive incremental costs) and small increases in effectiveness (i.e. positive incremental effectiveness), measured in terms of QALYs. The magnitudes of the incremental costs and the incremental effects, and therefore the ICERs, vary considerably across all COX-2 drugs.

In order to explore the sensitivity of our results to variation in the comparator, we also compared COX-2 selective NSAIDs against non-selective NSAIDs with PPI. The results are shown in *Tables 82* and *83*. In most cases, non-selective NSAID plus PPI dominates the COX-2 selective NSAIDs (i.e. the COX-2 is associated with both a higher cost and poorer effectiveness). This is because in this model the RR of GI events for adding PPI to a non-selective NSAID is lower (more favourable) than the RR for COX-2 selective NSAIDs compared with non-selective NSAIDs. In a few cases, the COX-2 selective NSAID is cheaper than the non-selective NSAID plus PPI, but less effective. In this case, we have printed the ICER in *italics*: a low ICER favours non-selective NSAID plus PPI.

Base-case results for high-risk patients

We also ran this model for patients with previous history of GI events. In this case, given that it would be considered poor medical practice to prescribe a non-selective NSAID without a PPI for such high-risk patients, the comparison made is COX-2 selective NSAID alone against non-selective NSAID plus PPI. The results are shown in *Tables 84* and *85*.

The results show a very similar pattern to those reported in *Tables 82* and *83*, with the COX-2 drugs again looking generally unattractive from a cost-effectiveness point of view.

Sensitivity analysis results for the simpler AGM

We conducted a number of univariate sensitivity analyses where the sensitivity of the results of the simpler AGM is explored. The parameters varied are the GI risk of PPIs, the RRs of GI events, the RR of MI and the utility weight associated with arthritis. The sensitivity analyses for each of these sets of parameters are described in the following four sections. For the sake of brevity, the main body of the report gives the sensitivity analysis results only for the comparison of diclofenac – the sensitivity analysis results for the comparator of ibuprofen are given in Appendix 11.

TABLE 82 *Results comparing single COX-2 selective NSAIDs against ibuprofen plus PPI*[a]

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALY)[b]
Ibuprofen + PPI	950.38		3.22032		
Celecoxib (LD)	1,455.04	504.66	3.20100	–0.01932	D
Celecoxib (HD)	2,564.55	1,614.17	3.20100	–0.01932	D
Etodolac (branded)	1,142.49	192.11	3.20193	–0.01839	D
Etodolac (generic)	786.20	–164.18	3.20193	–0.01839	*8,930*
Etoricoxib	1,526.05	575.67	3.21924	–0.00108	D
Lumiracoxib	1,226.73	276.35	3.19737	–0.02295	D
Meloxicam (LD)	805.73	–144.65	3.21425	–0.00607	*23,800*
Meloxicam (HD)	1,006.41	56.03	3.21425	–0.00607	D
Rofecoxib	1,559.58	609.20	3.19805	–0.02227	D
Valdecoxib	1,485.55	535.17	3.21439	–0.00593	D

[a] All incremental analysis is compared with ibuprofen plus PPI.
[b] ICER in *italics* means that both incremental values are negative. D means that COX-2 selective NSAID is dominated by ibuprofen plus PPI.

TABLE 83 *Results comparing single COX-2 selective NSAIDs against diclofenac plus PPI*[a]

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALY)[b]
Diclofenac + PPI	970.56		3.21803		
Celecoxib (LD)	1,455.04	484.48	3.20100	–0.01703	D
Celecoxib (HD)	2,564.55	1,593.99	3.20100	–0.01703	D
Etodolac (branded)	1,142.49	171.93	3.20193	–0.0161	D
Etodolac (generic)	786.20	–184.36	3.20193	–0.0161	*11,500*
Etoricoxib	1,526.05	555.49	3.21924	0.00121	459,000
Lumiracoxib	1,226.73	256.17	3.19737	–0.02066	D
Meloxicam (LD)	805.73	–164.83	3.21425	–0.00378	*43,600*
Meloxicam (HD)	1,006.41	35.85	3.21425	–0.00378	D
Rofecoxib	1,559.58	589.02	3.19805	–0.01998	D
Valdecoxib	1,485.55	514.99	3.21439	–0.00364	D

[a] All incremental analysis is compared with diclofenac plus PPI.
[b] ICER in *italics* means that both incremental values are negative. D means that COX-2 selective NSAID is dominated by diclofenac plus PPI.

TABLE 84 *Results comparing single COX-2 selective NSAIDs against ibuprofen plus PPI for patients with previous history of GI events*[a]

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALY)[b]
Ibuprofen + PPI	980.56		3.21380		
Celecoxib (LD)	1,455.79	475.23	3.19393	–0.01987	D
Celecoxib (HD)	2,540.73	1,560.17	3.19393	–0.01987	D
Etodolac (branded)	1,139.97	159.41	3.19699	–0.01681	D
Etodolac (generic)	790.24	–190.32	3.19699	–0.01681	*11,300*
Etoricoxib	1,507.68	527.12	3.21378	–0.00002	D
Lumiracoxib	1,231.77	251.21	3.19202	–0.02178	D
Meloxicam (LD)	829.34	–151.22	3.20658	–0.00722	*20,900*
Meloxicam (HD)	1,025.94	45.38	3.20658	–0.00722	D
Rofecoxib	1,544.88	564.32	3.19246	–0.02134	D
Valdecoxib	1,482.54	501.98	3.20968	–0.00412	D

[a] All incremental analysis is compared with ibuprofen plus PPI.
[b] ICER in *italics* means that both incremental values are negative. D means that COX-2 selective NSAID is dominated by ibuprofen plus PPI.

Varying GI risk associated with PPIs

In our base-case analysis, we assumed that adding a PPI to a non-selective NSAID reduced the risk of a GI event (for all three categories: any GI event, PUB and POB) to an RR of 0.40 (see *Table 78*). Hooper and colleagues reported that PPIs were associated with an RR of 0.46, or better, for GI symptoms, endoscopic ulcers and serious GI events including complicated events.[310] In sensitivity analysis this RR was increased to 0.6; this value was chosen as it was similar to the RR of celecoxib for PUBs and was felt to be clinically plausible. We did not feel that a sensitivity analysis that allowed for an RR of 1.0 for PPIs, i.e. that PPIs had no benefit on GI events, was plausible. The results of the analyses following this change are reported in *Tables 86–88*, which can be compared with the base-case analyses reported in *Tables 81*, *83* and *85*.

Unsurprisingly, the results for the comparison of the single COX-2 selective NSAID against diclofenac alone are not very different from the base-case analysis. However, the results appear much more sensitive to the RR of adding PPI for the scenarios where the comparator includes the use of a PPI. Both *Tables 87* and *88* show positive incremental effects for etoricoxib, meloxicam (for both low and high dose) and valdecoxib. In fact, in considering both patients with and without a

TABLE 85 *Results comparing single COX-2 selective NSAIDs against diclofenac plus PPI for patients with previous history of GI events*[a]

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALY)[b]
Diclofenac + PPI	982.26		3.21537		
Celecoxib (LD)	1,455.79	473.53	3.19393	–0.02144	D
Celecoxib (HD)	2,540.73	1,558.47	3.19393	–0.02144	D
Etodolac (branded)	1,139.97	157.71	3.19699	–0.01838	D
Etodolac (generic)	790.24	–192.02	3.19699	–0.01838	*10,400*
Etoricoxib	1,507.68	525.42	3.21378	–0.00159	D
Lumiracoxib	1,231.77	249.51	3.19202	–0.02335	D
Meloxicam (LD)	829.34	–152.92	3.20658	–0.00879	*17,400*
Meloxicam (HD)	1,025.94	43.68	3.20658	–0.00879	D
Rofecoxib	1,544.88	562.62	3.19246	–0.02291	D
Valdecoxib	1,482.54	500.28	3.20968	–0.00569	D

[a] All incremental analysis is compared with diclofenac plus PPI.
[b] ICER in *italics* means that both incremental values are negative. D means that COX-2 selective NSAID is dominated by diclofenac plus PPI.

TABLE 86 *Single COX-2 selective NSAIDs against diclofenac (QALYs) (RR adding PPI: 0.6)*[a]

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALY)
Diclofenac	535.26		3.18168		
Celecoxib (LD)	1,458.77	923.51	3.19668	0.015	61,600
Celecoxib (HD)	2,567.52	2,032.26	3.19668	0.015	135,000
Etodolac (branded)	1,145.68	610.42	3.19768	0.016	38,200
Etodolac (generic)	789.57	254.31	3.19768	0.016	15,900
Etoricoxib	1,527.33	992.07	3.21735	0.03567	27,800
Lumiracoxib	1,230.66	695.40	3.19265	0.01097	63,400
Meloxicam (LD)	809.24	273.98	3.21090	0.02922	9,380
Meloxicam (HD)	1,009.77	474.51	3.21090	0.02922	16,200
Rofecoxib	1,562.90	1,027.64	3.19380	0.01212	84,800
Valdecoxib	1,487.80	952.54	3.21082	0.02914	32,700

[a] All incremental analysis is compared with diclofenac.

TABLE 87 *Single COX-2 selective NSAIDs against diclofenac plus PPI (RR adding PPI: 0.6)*[a]

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALY)[b]
Diclofenac + PPI	983.05		3.20181		
Celecoxib (LD)	1,458.77	475.72	3.19668	–0.00513	D
Celecoxib (HD)	2,567.52	1,584.47	3.19668	–0.00513	D
Etodolac (branded)	1,145.68	162.63	3.19768	–0.00413	D
Etodolac (generic)	789.57	–193.48	3.19768	–0.00413	*46,800*
Etoricoxib	1,527.33	544.28	3.21735	0.01554	35,000
Lumiracoxib	1,230.66	247.61	3.19265	–0.00916	D
Meloxicam (LD)	809.24	–173.81	3.21090	0.00909	[c]
Meloxicam (HD)	1,009.77	26.72	3.21090	0.00909	2,940
Rofecoxib	1,562.90	579.85	3.19380	–0.00801	D
Valdecoxib	1,487.80	504.75	3.21082	0.00901	56,000

[a] All incremental analysis is compared with diclofenac plus PPI.
[b] ICER in *italics* means that both incremental values are negative. D means that COX-2 selective NSAID is dominated by diclofenac plus PPI.
[c] Meloxicam (LD) dominates diclofenac plus PPI.

TABLE 88 *Single COX-2 selective NSAIDs against diclofenac plus PPI for patients with previous history of GI events (RR adding PPI: 0.6)*[a]

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALY)[b]
Diclofenac + PPI	1,000.30		3.19802		
Celecoxib (LD)	1,461.30	461.00	3.18933	–0.00869	D
Celecoxib (HD)	2,544.53	1,544.23	3.18933	–0.00869	D
Etodolac (branded)	1,144.42	144.12	3.19255	–0.00547	D
Etodolac (generic)	795.13	–205.17	3.19255	–0.00547	*37,500*
Etoricoxib	1,509.37	509.07	3.21175	0.01373	37,100
Lumiracoxib	1,237.48	237.18	3.18706	–0.01096	D
Meloxicam (LD)	834.98	–165.32	3.20291	0.00489	[c]
Meloxicam (HD)	1,031.26	30.96	3.20291	0.00489	6,330
Rofecoxib	1,549.58	549.28	3.18798	–0.01004	D
Valdecoxib	1,485.29	484.99	3.20592	0.0079	61,400

[a] All incremental analysis is compared with diclofenac plus PPI.
[b] ICER in *italics* means that both incremental values are negative. D means that COX-2 selective NSAID is dominated by diclofenac plus PPI.
[c] Meloxicam (LD) dominates diclofenac plus PPI.

TABLE 89 *Single COX-2 selective NSAIDs against diclofenac – results with relative risk for all types of GI event at the lower confidence limits (favouring COX-2 selective NSAIDs)*[a]

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALY)
Diclofenac	530.03		3.18763		
Celecoxib (LD)	1,451.06	921.03	3.20499	0.01736	53,100
Celecoxib (HD)	2,565.24	2,035.21	3.20499	0.01736	117,000
Etodolac (branded)	1,134.91	604.88	3.21070	0.02307	26,200
Etodolac (generic)	776.53	246.50	3.21070	0.02307	10,700
Etoricoxib	1,434.31	904.28	3.23421	0.04658	19,400
Lumiracoxib	1,222.85	692.82	3.20035	0.01272	54,500
Meloxicam (LD)	773.75	243.72	3.22006	0.03243	7,520
Meloxicam (HD)	975.69	445.66	3.22006	0.03243	13,700
Rofecoxib	1,474.12	944.09	3.21732	0.02969	31,800
Valdecoxib	1,460.35	930.32	3.22090	0.03327	28,000

[a] All incremental analysis is compared with diclofenac.

previous history of GI events, the low-dose meloxicam strategy now dominates diclofenac plus a PPI, that is, meloxicam (low dose) has both a negative incremental cost and a positive incremental effect.

Varying relative risks of GI events

For this analysis, we set the RRs of GI events to the lower and upper 95% CIs shown in *Table 78*. For each COX-2 selective NSAID, we set the risks of any GI event, clinical GI event and complicated GI event simultaneously to low values and then to high values. To maintain our assumption that risks for 'No NSAID' were equivalent to the lowest COX-2, we changed the risks for 'No NSAID' in line with the other changes. Hence the costs and effects for the comparator strategy alter, even though this is a sensitivity analysis about RRs of COX-2 selective NSAIDs compared with diclofenac or ibuprofen. The results for analyses of average patients for all of the COX-2 drugs, compared with diclofenac, are given in *Tables 89* and *90*. The results for the comparison with ibuprofen are given in Appendix 11. This sensitivity analysis has not been repeated for high-risk patients.

In general terms, the results are reasonably sensitive to variations in the value of the RR of GI events.

TABLE 90 *Single COX-2 selective NSAIDs against diclofenac – results with relative risk for all types of GI event at the upper confidence limits (favouring non-selective NSAIDs)*[a]

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALY)[b]
Diclofenac	531.42		3.18731		
Celecoxib (LD)	1,460.01	928.59	3.19598	0.00867	107,000
Celecoxib (HD)	2,561.98	2,030.56	3.19598	0.00867	234,000
Etodolac (branded)	1,154.47	623.05	3.18770	0.00039	1,600,000
Etodolac (generic)	804.80	273.38	3.18770	0.00039	701,000
Etoricoxib	1,586.25	1,054.83	3.18021	–0.00710	D
Lumiracoxib	1,231.61	700.19	3.19375	0.00644	109,000
Meloxicam (LD)	833.98	302.56	3.20503	0.01772	17,100
Meloxicam (HD)	1,032.06	500.64	3.20503	0.01772	28,300
Rofecoxib	1,580.67	1,049.25	3.15949	–0.02782	D
Valdecoxib	1,524.50	993.08	3.20073	0.01342	74,000

[a] All incremental analysis is compared with diclofenac.
[b] D means that COX-2 selective NSAID is dominated by diclofenac.

TABLE 91 *Single COX-2 selective NSAIDs against diclofenac – results with relative risk for MI at the lower confidence limits (favouring COX-2 selective NSAIDs)*[a]

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALY)
Diclofenac	530.72		3.18749		
Celecoxib (LD)	1,437.38	906.66	3.20360	0.01611	56,300
Celecoxib (HD)	2,547.11	2,016.39	3.20360	0.01611	125,000
Etodolac (branded)	1,124.73	594.01	3.20454	0.01705	34,800
Etodolac (generic)	768.37	237.65	3.20454	0.01705	13,900
Etoricoxib	1,490.59	959.87	3.22447	0.03698	26,000
Lumiracoxib	1,206.97	676.25	3.20027	0.01278	52,900
Meloxicam (LD)	798.23	267.51	3.21535	0.02786	9,600
Meloxicam (HD)	998.93	468.21	3.21535	0.02786	16,800
Rofecoxib	1,523.64	992.92	3.20335	0.01586	62,600
Valdecoxib	1,481.14	950.42	3.21504	0.02755	34,500

[a] All incremental analysis is compared with diclofenac.

Varying risk of MI

For each COX-2 selective NSAID separately, we varied the RR of MI across its 95% CIs shown in *Table 78*. For the analysis of the standard patient and the comparison with diclofenac, the results for all drugs are reported in full in *Table 91* for the lower limits and in *Table 92* for the upper limits. The results relating to the comparison with ibuprofen are reported in Appendix 11. In the absence of data, we assumed that the risks for etodolac were the same as those for celecoxib. Here, we also used the 95% CIs for celecoxib. This gives reasonable coverage of the range of values for COX-2 selective NSAIDs. This sensitivity analysis has again not been repeated for high-risk patients.

In general terms, the results are sensitive to variation in the value of the risk of MI events.

As a separate analysis, in order to explore the importance of the MI RR estimates, we extended our sensitivity analysis to consider the scenario of an MI RR of 1.0 for all COX-2 selective NSAIDs. This assumes that there is no MI risk associated with any of the COX-2s. This extra analysis was only conducted for the average patient scenario, and the results for the comparison with diclofenac are reported in *Table 93*.

Utility weight associated with arthritis

The utility weights used in our analyses are those applied by Maetzel and colleagues[305] in their

TABLE 92 *Single COX-2 selective NSAIDs against diclofenac – results with relative risk for MI at the upper confidence limits (favouring non-selective NSAIDs)*[a]

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALY)[b]
Diclofenac	530.72		3.18749		
Celecoxib (LD)	1,485.64	954.92	3.19649	0.009	106,000
Celecoxib (HD)	2,594.77	2,064.05	3.19590	0.00841	245,000
Etodolac (branded)	1,173.26	642.54	3.19748	0.00999	64,300
Etodolac (generic)	817.09	286.37	3.19748	0.00999	28,700
Etoricoxib	2,250.25	1,719.53	3.11143	–0.07606	D
Lumiracoxib	1,265.26	734.54	3.19171	0.00422	174,000
Meloxicam (LD)	982.53	451.81	3.18618	–0.00131	D
Meloxicam (HD)	1,182.82	652.10	3.18618	–0.00131	D
Rofecoxib	1,634.61	1,103.89	3.18571	–0.00178	D
Valdecoxib	1,503.00	972.28	3.21182	0.02433	40,000

[a] All incremental analysis is compared with diclofenac.
[b] D means that COX-2 selective NSAID is dominated by diclofenac.

TABLE 93 *Single COX-2 selective NSAIDs against diclofenac – results with relative risk for MI = 1.0*[a]

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALY)
Diclofenac	530.72		3.18749		
Celecoxib (LD)	1,437.12	906.40	3.20363	0.01614	56,200
Celecoxib (HD)	2,546.86	2,016.14	3.20363	0.01614	125,000
Etodolac (branded)	1,124.47	593.75	3.20458	0.01709	34,700
Etodolac (generic)	768.11	237.39	3.20458	0.01709	13,900
Etoricoxib	1,512.54	981.82	3.22123	0.03374	29,100
Lumiracoxib	1,210.12	679.40	3.19981	0.01232	55,100
Meloxicam (LD)	821.52	290.80	3.21194	0.02445	11,900
Meloxicam (HD)	1,022.17	491.45	3.21194	0.02445	20,100
Rofecoxib	1,515.11	984.39	3.20460	0.01711	57,500
Valdecoxib	1,503.14	972.42	3.21180	0.02431	40,000

[a] All incremental analysis is compared with diclofenac.

running of the model. The utility weight associated with the 'arthritis' state in the model is somewhat lower than that reported by others. Therefore, we conducted a further one-way sensitivity analysis to explore the sensitivity of the results to setting the utility weight on the state 'arthritis' to 0.82 (as reported in the Beaver Dam survey by Fryback and colleagues[311]). The results for average patient group and the diclofenac comparison are reported in *Table 94*.

The full AGM

Additional methods for the full AGM

In the full version of the model, a simulated patient initially starts in the model on one NSAID (either a non-selective or a COX-2 selective NSAID). If this is acceptable, then they continue on that NSAID at least until the end of the first 3-month cycle. However, if the NSAID is unacceptable (for whatever reason), they will switch early (i.e. within the first 3 months) to a different NSAID. Patients then enter a recurring process (i.e. the Markov model proper) in which they are at risk of GI and MI events. From this point on, the process of the Markov model and the data used to populate the model are exactly as described above for the simpler AGM. Separate Markov states are used for patients on different NSAIDs.

Even in the full AGM there is no provision for switching NSAIDs after the initial cycle (for simplicity of modelling). The purpose of the

TABLE 94 *Single COX-2 selective NSAIDs against diclofenac – results with utility for 'arthritis' state = 0.82*[a]

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALY)
Diclofenac	530.72		3.76756		
Celecoxib (LD)	1,455.04	924.32	3.79292	0.02536	36,400
Celecoxib (HD)	2,564.55	2,033.83	3.79292	0.02536	80,200
Etodolac (branded)	1,142.49	611.77	3.79361	0.02605	23,500
Etodolac (generic)	786.20	255.48	3.79361	0.02605	9,810
Etoricoxib	1,526.05	995.33	3.82303	0.05547	17,900
Lumiracoxib	1,226.73	696.01	3.78593	0.01837	37,900
Meloxicam (LD)	805.73	275.01	3.81322	0.04566	6,020
Meloxicam (HD)	1,006.41	475.69	3.81322	0.04566	10,400
Rofecoxib	1,559.58	1,028.86	3.78933	0.02177	47,300
Valdecoxib	1,485.55	954.83	3.81203	0.04447	21,500

[a] All incremental analysis is compared with diclofenac.

TABLE 95 *Strategies compared in the AGM*

Strategy	First-line treatment (N1)	Second-line treatment (N2)
No COX-2	Ibuprofen	Diclofenac
COX-2 second	Ibuprofen	COX-2 selective NSAID
COX-2 first	COX-2 selective NSAID	Ibuprofen

model is still to permit assessment of each COX-2 selective NSAID individually, not to compare non-selective NSAIDs with each other. Accordingly, a fixed pattern of non-selective NSAIDs is used as the basis for comparison, and only one COX-2 selective NSAID is considered in the model at any one time. Ibuprofen and diclofenac are the only two non-selective NSAIDs available for use in the model. These were selected on the basis of current patterns of NSAID use in England and Wales. Three possible general strategies of NSAID use are compared (shown in *Table 95*).

Therefore, for the strategy described as 'No COX-2' this always refers to initial treatment with ibuprofen and, if within the first 3 months ibuprofen is judged not to be acceptable for whatever reason, a switch to diclofenac may happen. Similarly, the strategy defined as 'COX-2 second' always indicates that patients initially receive ibuprofen but may switch to a COX-2 selective NSAID within the first 3 months if ibuprofen is not acceptable.

Initial model cycle (i.e. the first 3 months)

The basic structure for the initial sequences for patients with no special risk factors is shown in *Figure 51*. The probabilities on the branches in this initial cycle of the model are calculated from data given by Langman and colleagues, who describe NSAID switching patterns in primary care in the UK.[76] Although the patterns described by Langman and colleagues are not specifically those of patients with OA and RA, we believe that they are sufficiently representative of people with these conditions in the community. Details of the calculations are given in Appendix 9.

For the purpose of costing, switching from N1 to N2 (or dropping N1) is assumed to take place on average after 30 days, and dropping N2 after a further 30 days. If PPI is added to an existing NSAID, it is assumed to be added on average halfway through the remaining part of the cycle.

When modelling a patient population with a previous history of UGI events (i.e. one of the high-risk subgroups), the tree is simplified in that it is assumed that such patients would never be given a non-selective NSAID without a PPI. The follow-up to serious GI events in this initial treatment phase is the same as that for later Markov cycles, described below.

Transition probabilities and rates

The transition probabilities for the initial cycle are given in *Table 96* (and see Appendix 9 for further

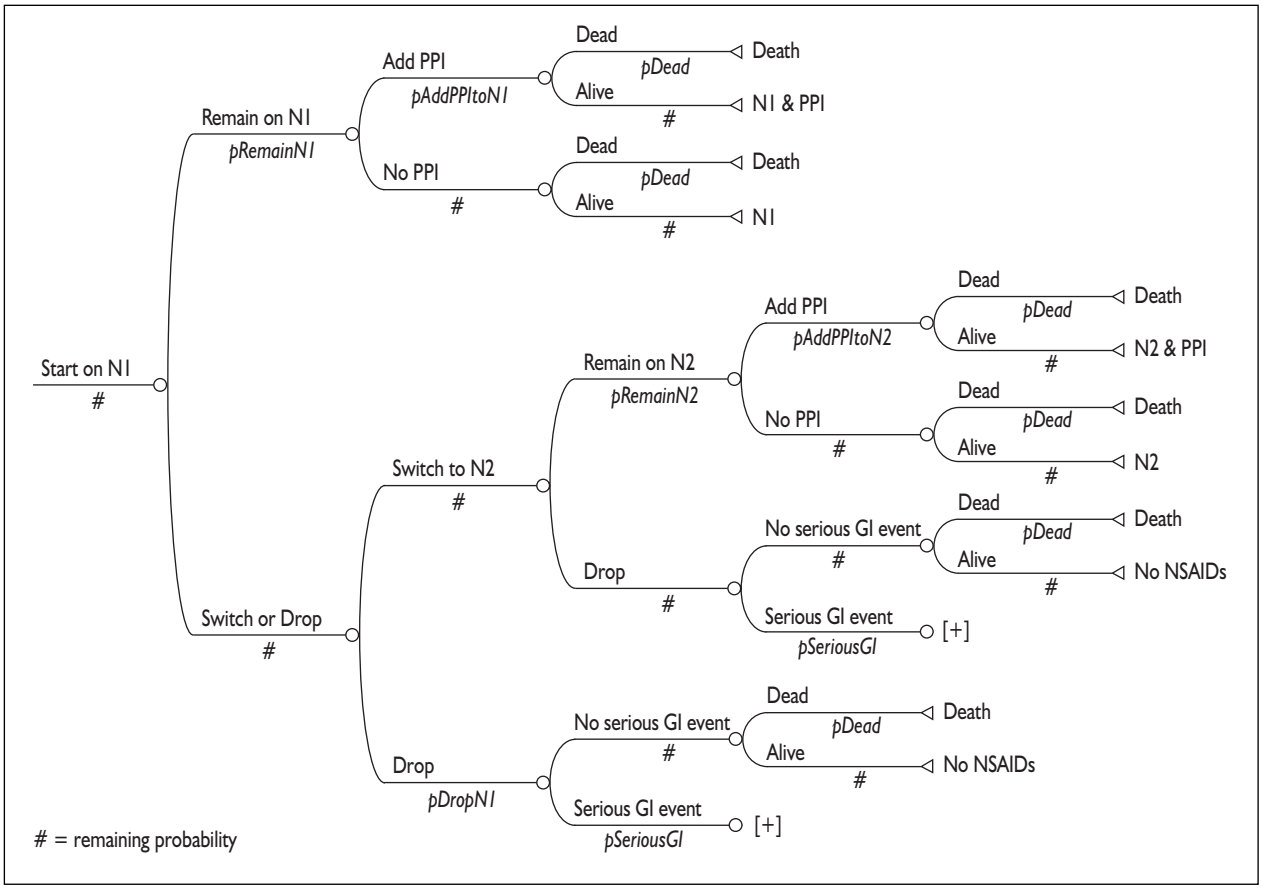


FIGURE 51 *The initial cycle*

details). The probability of switching to a different NSAID is deduced since the probabilities for four outcomes must add to 1. Note that actual probabilities are given for ibuprofen and diclofenac, but probabilities for COX-2 selective NSAIDs are given relative to ibuprofen.

Results for the full AGM

Results for the average patient

The full model was initially run for a cohort of average patients with starting age 58 years. The results are given in *Table 97*. As before, separate results for low and high dose are given for celecoxib and meloxicam.

These results are broadly consistent with those reported in *Tables 80* and *81* for the analyses using the simpler AGM. If we look first at the results relating to celecoxib, they indicate that its use second line (after initially trying ibuprofen) is dominated by the 'No COX-2' strategy (i.e. ibuprofen followed by diclofenac, if required) – it is associated with both a higher cost and a poorer level of effectiveness. The use of celecoxib first line is more promising in that the incremental effect is positive (albeit very small) but the cost increase is considerable, giving ICERs in excess of £130,000 per QALY gained. The COX-2 drugs that have ICERs relating to first-line use that are below £50,000 per QALY are etoricoxib, meloxicam and valdecoxib. A strategy of second-line use of COX-2 drugs looks very unattractive from a cost-effectiveness point of view for all of the drugs considered here.

Results for high-risk patients

The most important high-risk group consists of patients with previous GI history. For these patients, the comparison is between COX-2 selective NSAIDs (taken originally without PPI) and non-selective NSAIDs taken with PPI. The results are shown in *Table 98*.

Once again, these results are broadly consistent with those reported in *Tables 84* and *85* for the analyses using the simpler AGM. If we look first at the results relating to low-dose celecoxib, they indicate that its use second line (after initially trying ibuprofen) is associated with a lower cost but also reduced effectiveness compared with the

TABLE 96 *Data for initial cycle*

Drug	Probability or RR[a]	Source and comment
Probability of taking no further NSAIDs in the first 3 months after prescription		
Ibuprofen	0.315	Langman *et al.*[76]
Diclofenac	0.265	Langman *et al.*[76]
Celecoxib	RR 1	Assumed same as ibuprofen
Etodolac	RR 1	Assumed same as ibuprofen
Etoricoxib	RR 1.072	Hunt *et al.*,[253] 12-week trial
Meloxicam	RR 1	Assumed same as ibuprofen
Rofecoxib	RR 0.757	Range of RR 0.55–1.041. Mean value for rofecoxib doses 12.5–25 mg
Valdecoxib	RR 1	Assumed same as ibuprofen
Lumiracoxib	RR 1	Assumed same as ibuprofen
Probability of remaining on the same drug (alone)		
Ibuprofen	0.514	Langman *et al.*[76]
Diclofenac	0.603	Langman *et al.*[76]
Celecoxib	RR 1	Assumed same as ibuprofen
Etodolac	RR 1	Assumed same as ibuprofen
Etoricoxib	RR 0.992	Hunt *et al.*,[253] 12-week trial
Meloxicam	RR 1	Assumed same as ibuprofen
Rofecoxib	RR 1.034	Mean value for rofecoxib doses 12.5–25 mg
Valdecoxib	RR 1	Assumed same as ibuprofen
Lumiracoxib	RR 1	Assumed same as ibuprofen
Probability of adding PPI to given NSAID		
Ibuprofen	0.026	Langman *et al.*[76]
Diclofenac	0.036	Langman *et al.*[76]
Celecoxib	RR 1	Assumed same as ibuprofen
Etodolac	RR 1	Assumed same as ibuprofen
Etoricoxib	RR 1	Assumed same as ibuprofen
Meloxicam	RR 1	Assumed same as ibuprofen
Rofecoxib	RR 1	Assumed same as ibuprofen
Valdecoxib	RR 1	Assumed same as ibuprofen
Lumiracoxib	RR 1	Assumed same as ibuprofen

[a] In all cases, RR refers to comparison with ibuprofen.

'No COX-2' strategy (i.e. ibuprofen followed by diclofenac, if required). This gives an ICER of –£4050 for the move **from** the strategy of celecoxib second line **to** the strategy of no COX-2. It is clearly not cost-effective to use celecoxib either first or second line according to these results. All strategies relating to the use of COX-2 drugs (both first- and second-line use) look very unattractive from a cost-effectiveness point of view for all of the drugs considered here.

Comparison of Assessment Group Model and company models results

This section discusses the differences in the results of the economic analyses using the AGM and those based on the company models. For the purposes of comparability, the AGM results referred to here come from the 'simpler' AGM, i.e. the model without the initial cycle. The comparison does not include etodolac or lumiracoxib as no company model was submitted for either. The discussion considers separately the results for 'average-risk' and 'high-risk' patients.

'Average'-risk patients

For comparability, this section discusses the AGM results for COX-2 selective NSAIDs compared with non-selective NSAIDs alone (not combined with a PPI) in average-risk patients (*Table 99*). The results for meloxicam and etoricoxib using the company models and the AGM-based analysis results are very similar (*Table 99*).

For valdecoxib, comparability of the AGM and company results is complicated by the fact that the AGM ICER uses the QALY as the measure of effect whereas the company ICER uses life-years gained. Nevertheless, given that the additional years of life with COX-2s will be at a utility of less than 1, the company and AGM ICER results are not very different. Given their similarity and that they are all around or below £30,000 per QALY,

TABLE 97 *Base-case results*

Drug	Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALY)
Celecoxib (LD)	No COX-2	441.13		3.20434		
	COX-2 second	511.15	70.02	3.20398	–0.00036	(Dominated)
	COX-2 first[a]	951.33	510.20	3.20824	0.00390	131,000
Celecoxib (HD)	No COX-2	441.13		3.20434		
	COX-2 second	597.94	156.82	3.20398	–0.00036	(Dominated)
	COX-2 first[a]	1,561.22	1,120.10	3.20824	0.00390	287,000
Etodolac (branded)	No COX-2	441.13		3.20434		
	COX-2 second	486.19	45.07	3.20418	–0.00016	(Dominated)
	COX-2 first[a]	778.97	337.84	3.20890	0.00456	74,100
Etodolac (generic)	No COX-2	441.13		3.20434		
	COX-2 second	458.33	17.20	3.20418	–0.00016	(Dominated)
	COX-2 first[a]	583.19	142.06	3.20890	0.00456	31,200
Etoricoxib	No COX-2	441.13		3.20434		
	COX-2 second	516.12	75.00	3.20547	0.00113	66,600
	COX-2 first	988.41	472.29	3.21794	0.01247	37,900
	Excluding the option 'COX-2 second' (by extended dominance):					
	No COX-2	441.13		3.20434		
	COX-2 first	988.41	547.29	3.21794	0.01360	40,200
Lumiracoxib	No COX-2	441.13		3.20434		
	COX-2 second	492.97	51.84	3.2038	–0.00054	(Dominated)
	COX-2 first[a]	825.24	384.11	3.20652	0.00218	176,000
Meloxicam (LD)	No COX-2	441.13		3.20434		
	COX-2 second	460.71	19.58	3.20493	0.00059	33,100
	COX-2 first	597.21	136.50	3.21488	0.00995	13,700
	Excluding the option 'COX-2 second' (by extended dominance):					
	No COX-2	441.13		3.20434		
	COX-2 first	597.21	156.08	3.21488	0.01054	14,800
Meloxicam (HD)	No COX-2	441.13		3.20434		
	COX-2 second	476.41	35.28	3.20493	0.00059	59,600
	COX-2 first	707.54	231.13	3.21488	0.00995	23,200
	Excluding the option 'COX-2 second' (by extended dominance):					
	No COX-2	441.13		3.20434		
	COX-2 first	707.54	266.41	3.21488	0.01054	25,300
Rofecoxib	No COX-2	441.13		3.20434		
	COX-2 second	521.86	80.74	3.20381	–0.00053	(Dominated)
	COX-2 first[a]	1,034.90	593.77	3.20584	0.00150	395,000
Valdecoxib	No COX-2	441.13		3.20434		
	COX-2 second	513.10	71.97	3.20512	0.00078	92,400
	COX-2 first	969.43	456.33	3.21519	0.01007	45,300
	Excluding the option 'COX-2 second' (by extended dominance):					
	No COX-2	441.13		3.20434		
	COX-2 first	969.43	528.30	3.21519	0.01085	48,700

[a] ICER for 'COX-2 first' relative to 'No COX-2'.

the results for etoricoxib, valdecoxib and meloxicam will not be discussed further in this section. However, there are notable differences in the company and AGM ICERs for celecoxib and rofecoxib, the AGM ICERs being considerably less attractive than those of the companies. These differences are not explained by the company use of life-years gained and the AGM use of QALYs as the effectiveness measure. The reasons for theses differences are explored below.

TABLE 98 *Results for patients with previous GI history*

Drug	Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALY)
Celecoxib (LD)	COX-2 second	733.47		3.21115		
	No COX-2	754.11	20.63	3.21625	0.00509	4,050
	COX-2 first	991.48	237.37	3.20660	–0.00965	(Dominated)
Celecoxib (HD)	No COX-2	754.11		3.21625		
	COX-2 second	789.00	34.89	3.21115	–0.00509	(Dominated)
	COX-2 first	1,589.69	835.59	3.20660	–0.00965	(Dominated)
Etodolac (branded)	COX-2 second	714.64		3.21188		
	No COX-2	754.11	39.47	3.21625	0.00437	9,040
	COX-2 first	817.19	63.08	3.20831	–0.00793	(Dominated)
Etodolac (generic)	COX-2 first	624.53		3.20831		
	COX-2 second	696.62	72.09	3.21188	0.00357	20,200
	No COX-2	754.11	57.49	3.21625	0.00437	13,200
	Excluding the option 'COX-2 second' (by extended dominance):					
	COX-2 first	624.53		3.20831		
	No COX-2	754.11	129.58	3.21625	0.00793	16,300
Etoricoxib	COX-2 second	713.91		3.21405		
	No COX-2	754.11	40.20	3.21625	0.00220	18,300
	COX-2 first	1,015.03	260.92	3.21695	0.00071	368,000
Lumiracoxib	COX-2 second	721.09		3.21114		
	No COX-2	754.11	33.02	3.21625	0.00511	6,460
	COX-2 first	867.21	113.10	3.20572	–0.01053	(Dominated)
Meloxicam (LD)	COX-2 first	648.23		3.21295		
	COX-2 second	697.41	49.18	3.21271	–0.00025	(Dominated)
	No COX-2[a]	754.11	105.88	3.21625	0.00329	32,100
Meloxicam (HD)	COX-2 second	707.03		3.21271		
	No COX-2	754.11	47.07	3.21625	0.00354	13,300
	COX-2 first	756.62	2.52	3.21295	–0.00329	(Dominated)
Rofecoxib	COX-2 second	740.39		3.21109		
	No COX-2	754.11	13.71	3.21625	0.00516	2,660
	COX-2 first	1,080.51	326.41	3.20546	–0.01078	(Dominated)
Valdecoxib	COX-2 second	728.36		3.21355		
	No COX-2	754.11	25.75	3.21625	0.00269	9,570
	COX-2 first	1,007.30	253.19	3.21473	–0.00152	(Dominated)

[a] ICER for 'No COX-2' relative to 'COX-2 first'.

In the case of celecoxib, an important contribution to the difference in celecoxib ICERs is that the company (Pfizer) model (ACCES) does not explicitly take into account a difference in MI risk between COX-2 and non-selective NSAIDs, whereas the Birmingham AGM model does take into account this difference (this is not so much of an issue for the valdecoxib analysis, which is also based on this model, as the Birmingham meta-analysis shows an RR for MI of <1.00) (*Table 100*). The AGM sensitivity analysis indicates that the ICERs for all COX-2s are sensitive to variations in the relative MI risk. Furthermore, it can be seen from *Table 101* that the relative estimates for GI adverse events, POBs and PUBs used in the company model greatly favour celecoxib. The company submission states the source of the GI events as the SUCCESS trial whereas the AGM estimates are based on a meta-analysis of all potentially includable trials, including SUCCESS. Although the costs of celecoxib used by the company model and AGM appear similar, the non-selective NSAIDs costs used by the company are considerably higher (*Table 102*). This difference in non-selective NSAID cost would again favour the company model ICER for celecoxib.

In the case of rofecoxib, the company (Merck Sharp and Dohme) and AGM models used for rofecoxib appear relatively similar in structure.

TABLE 99 *Comparison of company models and assessment group model (AGM) (with no initial switching cycle) results for 'average'-risk patients*

	Incremental cost (£)	Incremental effectiveness	ICER (£)[a]	Comments
Rofecoxib				
MSD	+171	+0.0154	11,104	QALYs and 1-year time horizon
AGM	+1029	+0.01056	97,400	
Etoricoxib				
MSD	+178	+0.0084	22,143	QALYs and 1-year time horizon
AGM	+995	+0.03175	31,300	
Meloxicam				
BI	+118	+0.0139	8,543	QALYs and 5-year time horizon
AGM	+275/476	+0.02676	10,300/17,800	
Celecoxib				
Pfizer	+81	+0.00576	16,063	Life-years gained and 1-year time horizon
AGM	+924/2,033	+0.01351	68,400/151,000	
Valdecoxib				
Pfizer	+75	+0.00393	19,083	Life-years gained and 1-year time horizon
AGM	+954	+0.0269	35,500	

BI, Boehringer Ingelheim; MSD, Merck Sharp and Dohme.
[a] All ICER estimates reported for each model are those most in favour of COX-2s. Company ICER estimates are slightly different to those reported in company submissions and represent rounding errors. BI meloxicam results not reported in this form by the company and derived from run of the BI model by the assessment team.

TABLE 100 *Comparison of 'structure' of company models and AGM*

	Model name			
	ACCES	**MSD**	**Maetzel**	**AGM**
COX-2s	Celecoxib, valdecoxib	Rofecoxib, etoricoxib	Meloxicam	All COX-2s
Company	Pfizer	MSD	BI	Assessment group
Efficacy	Assumed equivalent between COX-2 and NSAIDs	Assumed equivalent between COX-2 and NSAIDs	Assumed equivalent between COX-2 and NSAIDs	Assumed equivalent between COX-2 and NSAIDs
GI parameters used	GI AEs POBs PUBs GI withdrawals	PUBs Lower GI events[a]	Any GI event[b] PUBs POBs	Any GI event[b] PUBs POBs
MI included?	No	Yes	Yes	Yes
Time horizon	1 year	1 year	5 years	5 years
Source of parameter values	Celecoxib – SUCCESS Valdecoxib – meta-analysis	Meta-analysis	SELECT or MELISSA	Meta-analysis

BI, Boehringer Ingelheim; MSD, Merck Sharp and Dohme.
[a] Set to RR 1.00 in base-case analysis.
[b] PUBs plus dyspepsia.

Both include GI adverse events, major GI and MI events, and, as with the AGM model, it is stated in the company submission that these estimates are sourced from a meta-analysis of trials. The GI parameter values used by the company appear to fall within the 95% CIs of the AGM values.

However, the RR of MI for rofecoxib in the company base-case model is set to a value of 1.00, in contrast to an RR of MI in the AGM of 2.92 (95% CI 1.29 to 6.60). Although the costs of rofecoxib used by the company model and AGM appear similar, the non-selective NSAIDs costs

TABLE 101 *Comparison of clinical effectiveness parameter values used by company models and AGM (with 95% CIs in parentheses)*

	Celecoxib		Valdecoxib		Rofecoxib		Etoricoxib		Meloxicam	
Parameter	**Pfizer[a]**	**AGM**	**Pfizer[a]**	**AGM**	**MSD[a]**	**AGM**	**MSD[a]**	**AGM**	**BI**	**AGM**
GI AE	0.76 (GI discomfort)	0.84 (0.78 to 0.89)	0.65 (GI discomfort)	0.71 (0.62 to 0.82)	0.87/0.90	0.84 (0.45 to 1.60)	0.80	0.48 (0.24 to 0.96)	Not included separately	0.66 (0.58 to 0.75)
PUB	0.23 (ulcer)	0.55 (0.40 to 0.76)	0.12 (ulcer)	0.20 (0.03 to 1.46)	0.26/0.37	0.43 (0.32 to 0.57)	0.53	0.23 (0.05 to 1.08)	0.139/0.371	0.53 (0.29 to 0.97)
POB	0.17 (serious GI event)	0.57 (0.35 to 0.95)	0.38 (serious GI event)	0.43 (0.19 to 0.97)	Not included	0.40 (0.23 to 0.70)	Not included	0.46 (0.07 to 3.10)	0.208	0.56 (0.27 to 1.15)
MI	Not included	1.77 (1.00 to 3.11)	Not included	0.25 (0.06 to 1.00)	1.00	2.92 (1.36 to 6.28)	1.00	1.58 (0.06 to 38.66)	0.139/0.149	0.33 (0.01 to 8.03)

BI, Boehringer Ingelheim; MSD, Merck Sharp and Dohme.
[a] The parameter descriptions for the company model are the nearest match to those of the AGM.

TABLE 102 *Daily drug costs included in company models and AGM*

	BI	MSD	Pfizer	AGM
Non-selective NSAID		0.28[a]	0.23 (generic) 0.44 (branded)	
Ibuprofen				0.11
Diclofenac	0.3343			0.13
Piroxicam	0.1193			
COX-2				
Celecoxib			0.75 (OA) 0.90 (RA)	0.718 (LD) 1.436 (HD)
Etodolac			0.52	0.29 (generic) 0.52 (branded)
Etoricoxib		0.82	0.82 (OA) 0.85 (RA)	0.82
Meloxicam	0.3333 (OA) 0.4633 (RA)		0.38	0.33 (LD) 0.46 (HD)
Rofecoxib		0.80	0.85 (OA) 0.89 (RA)	0.77
Valdecoxib			0.77	0.77
PPI		0.71[a]		
Omeprazole				0.46
Pantoprazole	0.8446			
NSAID + PPI			0.93	
Analgesics				0.05
Acetaminophen (paracetamol)	0.3760			

BI, Boehringer Ingelheim; MSD, Merck Sharp and Dohme.
[a] The average daily cost within a drug class (NSAID, PPI, H_2-antagonist) was obtained using data from the MediPlus database and taking the sum of individual products weighted by market share.

used by the company are considerably higher. This difference in non-selective NSAID cost would again favour the company model QALY ICER for rofecoxib.

In conclusion, not surprisingly, the cost-effectiveness results for COX-2s are dependent on model structure, effectiveness and cost parameter values. The company model and AGM both show that etoricoxib, valdecoxib and meloxicam for 'average' patients have an ICER around or below £30,000 relative to a non-selective agent. However, based on a more appropriate model structure (which includes MI events) and utilisation of parameters values based on available trial evidence, the Birmingham AGM model ICERs for celecoxib and rofecoxib are substantially less attractive than those of the company.

'High risk'-patients

The Boehringer Ingelheim and Pfizer reports present results for 'high-risk' patients, comparing COX-2 selective NSAID with non-selective NSAID alone. The Merck Sharp and Dohme report gives an ICER for a COX-2 selective NSAID compared with a non-selective NSAID combined with a PPI in average-risk patients. However, unlike the report of the AGM-based analyses, none of the company submissions gives explicit results for the comparison of a COX-2 selective NSAID with a non-selective combined with a PPI in high-risk patients. Therefore, no direct comparison of the cost-effectiveness results for the AGM and company models for high-risk patients is possible.

Summary

- The Assessment Group has undertaken a new modelling exercise that used the Markov model developed originally by Maetzel and colleagues[305] as a starting point.
- The model has been designed to run in two different forms: the 'full AGM', which includes an initial drug switching cycle, and the 'simpler AGM', where there is no initial cycle and no opportunity for the patient to switch NSAID.
- The main data sources for clinical parameters are the meta-analysis results from our systematic review. Where necessary, we have used other sources.

- Using the simpler AGM, with ibuprofen or diclofenac alone as the comparator, all of the COX-2 products are associated with higher costs (i.e. positive incremental costs) and small increases in effectiveness (i.e. positive incremental effectiveness), measured in terms of QALYs. The magnitude of the incremental costs and the incremental effects, and therefore the ICERs, vary considerably across all COX-2 selective NSAIDs.
- When the simpler AGM was run using ibuprofen or diclofenac combined with PPI as the comparator, the results change substantially, with the COX-2 drugs looking generally unattractive from a cost-effectiveness point of view. This applies both to 'average-risk' patients and to 'high-risk' patients defined in terms of previous GI events. The full model produced results broadly in line with the simpler model.
- Differences in the results of the AGM compared with company models and the publication by Maetzel and colleagues on their model reflect the wide variability in the choice of clinical and cost parameters. The parameter values used in the AGM model are based on a comprehensive meta-analysis of all known trial data and the unbiased selection of drug prices based on current NHS tariffs.

Chapter 6

Implications for other parties

RA and OA are common chronic conditions that have a substantial negative impact on the quality of life of sufferers. In addition to healthcare costs, arthritis is associated with considerable indirect costs incurred by patients and carers as the result of forgone paid work and forgone leisure time. Although the difference in pain relief between non-selective NSAIDs and COX-2 selective NSAIDs is likely to be small, differences in GI tolerability of NSAIDs and serious GI events, if realised, would have important quality of life implications for patients.

Chapter 7

Factors relevant to the NHS

An important implication of switching from non-selective NSAIDs to COX-2 selective NSAIDs for the management of individuals with OA and RA is drug cost and increased budget impact. Healthcare professionals need to be able to identify clearly the precise role of COX-2 selective NSAIDs in OA and RA to maximise health. Current NICE guidance recommends the use of COX-2 selective drugs in **high-risk** individuals (i.e. age ⩾65 years; previous history of GI events; patients taking concomitant anticoagulants or corticosteroids) with OA and RA. Individuals not at high risk are recommended to remain on non-selective NSAIDs.

The poor adherence to current guidelines in audits of routine practice, described in the introduction of this report, highlights the potential limitations of these guidelines. Clinicians prescribing drugs often make judgements about risks and benefits and choose drugs based on personal knowledge of individual patients and their preferences, professional experience and nuances of medical history. These factors cannot be incorporated readily into guidelines.

Chapter 8
Discussion

Main results

The purpose of this report was to assess the effectiveness and cost-effectiveness of COX-2 selective NSAIDs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for the management of patients with OA and RA.

Clinical effectiveness

Our review, which supports data in other reviews, showed that COX-2 selective NSAIDs are generally similar to non-selective NSAIDs for the symptomatic relief of RA and OA. Meloxicam appears to be less effective for pain than non-selective NSAIDs, particularly piroxicam, although this finding is very likely a result of inappropriate dose comparisons in trials.

Celecoxib, rofecoxib and lumiracoxib significantly reduced the risk of both PUBs and POBs compared with non-selective NSAIDs. The reduction in risk was also shown for other COX-2 selective NSAIDs, although differences failed to reach statistical significance. However, given the low number of events reported, the estimates of RRs are highly uncertain. Indeed, the RR across the COX-2 selective NSAIDs appear similar, for example, for PUBs: meloxicam RR 0.53 (95% CI 0.29 to 0.97); etodolac RR 0.32 (95% CI 0.15 to 0.71); celecoxib RR 0.55 (95% CI 0.40 to 0.76); rofecoxib RR 0.43 (95% CI 0.32 to 0.57); etoricoxib RR 0.23 (95% CI 0.05 to 1.08); valdecoxib RR 0.20 (95% CI 0.03 to 1.46); and lumiracoxib RR 0.47 (95% CI 0.37 to 0.61). Nevertheless, these comparisons should be interpreted with caution as they are based on differing amounts of evidence, concerns about appropriate doses of COX-2 selective NSAIDs, especially meloxicam, and are indirect comparisons. There are many potential confounding differences in the patient populations included, such as the use of concomitant therapies, choice and dosage of comparator NSAIDs and methods of assessing outcomes. The remarkable heterogeneity of non-selective NSAIDs in their ability to cause serious UGI events in observational studies also raises concerns about comparisons based on meta-analyses of single COX-2 selective NSAID versus a basket of non-selective NSAIDs.[45]

A proportion of patients at high risk were included in some trials, but many studies excluded higher risk patients, for example those on low-dose aspirin. This limits the generalisability of this trial evidence. Certain individuals such as those with a previous peptic ulcer have a higher risk of further bleeding, regardless of NSAID use. A small number of trials have included subgroup analyses comparing high-risk with 'average-risk' patients. For example, the GI protective effect of celecoxib appears to be independent of age ($\leq$65 versus >65 years), *H. pylori* status, low-dose aspirin use and steroid use. However, analyses are based on relatively small numbers of patients. A direct comparison of celecoxib with diclofenac combined with omeprazole in patients with a recent GI bleed did not show any significant differences, although the wisdom of giving any NSAIDs to some patients in this category is questionable.

We have shown that patients on a number of the COX-2 selective NSAIDs (celecoxib, rofecoxib, etoricoxib and lumiracoxib) appear to be at increased risk of an MI event compared with those on non-selective NSAIDs, especially naproxen, supporting other data indicating a cardioprotective effect of non-selective NSAIDs compared with placebo, presumably through inhibition of platelet activity.[308,312] Since this report was written, rofecoxib has been globally withdrawn on the basis of raised adverse CV events.

Cost-effectiveness

Review of cost-effectiveness literature

A systematic review of the cost-effectiveness literature on COX-2 selective NSAIDs has been undertaken. The results of published economic evaluations are highly variable. Virtually all analyses made use of a decision analytic model. Published models vary in some important aspects (e.g. whether switching of therapy is considered, time frame, nature of events considered) making direct comparisons difficult. Studies that explicitly considered CV events were generally less favourable to COX-2 selective NSAIDs. Economic analyses that modelled costs and benefits over a relatively short period (usually between 6 and 12 months) tended to favour COX-2 selective NSAIDs, but analyses allowing a longer time horizon, for example between 5 years and a

patient's lifetime, found ICERs that were considerably higher. Where restricted use of COX-2s was considered as part of the analysis, for example to high-risk patients, cost-effectiveness was more favourable.

Review of industry submissions

Industry submissions including a formal economic evaluation were received from three companies: Pfizer (celecoxib and valdecoxib), Merck Sharp and Dohme (rofecoxib and etoricoxib) and Boehringer Ingelheim (meloxicam). All three used a decision modelling approach, although the models vary in some important aspects, hence direct comparisons are, again, difficult. All analyses compared COX-2 selective NSAIDs with a non-selective NSAID strategy (in some cases with co-therapy). The results, if taken at face value, support the widespread use of celecoxib, rofecoxib, meloxicam, etoricoxib and valdecoxib. None of the analyses report direct comparisons of different COX-2 selective NSAIDs but all found, consistently, in sensitivity analyses, that cost-effectiveness was more favourable when drug use was restricted to 'high-risk' patients and when the COX-2 selective NSAIDs had a large beneficial effect on UGI events.

Assessment Group Model

Our own model was an extension of the model developed by Maetzel and colleagues.[305] We added an initial cycle allowing for early switching of drugs, in order to reflect more accurately the patterns of NSAID use in primary care. Subsequent cycles largely follow the original Maetzel model structure. Initial cycle probabilities are mainly based on Langman and colleagues,[76] who reported on patterns of NSAID use in a large cohort of primary care patients. For the main Markov cycles we used the results from our own systematic review, where possible.

Our model shows, that in comparison with non-selective NSAIDs, the various COX-2 selective NSAIDs considered in this report are associated with a wide range of costs per QALY gained in arthritis patients. Cost per QALY differed for each COX-2 selective agent, whether the drug was to be used for an 'average-risk' patient or a 'high-risk' patient (one with a previous GI ulcer or bleed), the choice of non-selective NSAID comparator and whether the non-selective NSAID was used in combination with a PPI.

These cost-effectiveness results appear plausible, given the costs and the effects of COX-2 selective NSAIDs. For example, the highest price COX-2 selective NSAID is high-dose celecoxib and this has the highest incremental cost, and the lowest price COX-2 selective NSAIDs is etodolac (generic) and this has the lowest incremental cost. Similarly, the COX-2 selective NSAIDs with prices between these two ends of the price scale have incremental cost estimates that are broadly in line with their prices. On the estimates of incremental effects, although the picture is less immediately obvious, the ordering of the COX-2 selective NSAIDs is as one would have predicted on the basis of the input clinical parameter values from meta-analyses. For the sake of exposition, COX-2 selective NSAIDs can be crudely divided on the basis of their incremental effectiveness results into two groups: 'higher' incremental effectiveness group (etoricoxib, valdecoxib and meloxicam) and 'lower' incremental effectiveness group (lumiracoxib, rofecoxib, celecoxib and etodolac). This grouping makes sense when considering the RR of any GI event inputs into the model. These RRs were no higher than 0.71 for the 'higher' incremental effectiveness group and no lower than 0.84 for the 'lower' incremental effectiveness group. Given that the estimates of incremental effectiveness and incremental cost are plausible and reasonable, then it follows that the ICERs are as well.

Assumptions, limitations and uncertainties

A key strength of our report was its comprehensiveness – this report has identified more trials than many previous systematic reviews – and direct integration of the results of the systematic review into the assessment group economic model. In addition, we were able to include a number of direct comparisons between COX-2 selective NSAIDs published recently. The latter, particularly for rofecoxib, celecoxib and lumiracoxib, show similar efficacy between agents but direct comparisons with adequate power, using comparable doses, and of sufficient duration are needed to clearly understand safety issues.

Some other limitations in the evidence were identified:

1. Outcomes examined by trials are relatively broad and sometimes poorly defined, particularly for older studies, increasing the potential for bias in the reporting and analysis of data. For example, in most trials, the PUB category did not provide specific data about the frequency of perforations, gastric outlet

obstructions or GI bleeds associated with haemodynamic instability or hospitalisation because of these adverse events.
2. Many studies did not report adverse events adequately or, perhaps worse, mentioned several events in an *ad hoc* manner, so that, when collated, events may not have reflected their actual occurrence or allowed meaningful comparisons between drugs used.
3. There was a lack of consistency in the reporting of the principle GI safety events of POBs and PUBs. This was due to both different operational definitions of these events across different studies and also the differential access to outcomes details, for example whether a full trial report was available. This reporting bias appeared to vary across COX-2 NSAIDs. Therefore, considerable caution needs to be applied in directly comparing the pooled POBs and PUBs between drugs.
4. The non-selective NSAID preferred in many studies, naproxen, reflects preferences in the USA, where naproxen is used widely. In England and Wales, diclofenac and ibuprofen predominate. In some studies, the choice and dose of non-selective NSAID comparator, and limited details of the population studied (for example, aspirin use and prior GI history), make it difficult to generalise this evidence base to routine clinical practice.
5. Age restrictions and other exclusion criteria also limit generalisability, supporting the case for more pragmatic studies. A variety of observational data clearly show the limitations of NSAIDs in clinical practice. Trials reported here invariably included individuals who were established and accepting of NSAIDs and indeed required a **flare** of symptoms on NSAID withdrawal before inclusion. This biases towards not only inflated figures on drug retention with chronic therapy, but also a greater likelihood of response to any therapy on the basis of spontaneous improvement of symptoms after a flare (regression to the mean).

Potential limitations of our review:

1. According to the assessment criteria used, the majority of included trials were judged to be of 'good' to 'excellent' quality, that is, with appropriate randomisation and concealment, double blinding and low loss to follow-up. However, despite selective inclusion criteria, there was often considerable attrition in many trials because of adverse events and lack of efficacy. This attrition varied for different drugs, so, for example, in the CLASS study 47 and 41% of patients completed the trial at 52 weeks in the celecoxib and non-selective NSAID (diclofenac and ibuprofen) arms, respectively. As a result, there is less patient 'exposure' to non-selective NSAID than celecoxib in the initially randomised groups. By implication, this would favour NSAID patients for GI safety outcomes. This is overcome, however, by presenting data that allow for differing durations of drug exposure.
2. The quality and amount of evidence for newer COX-2 selective drugs were generally far greater than for older drugs, particularly in terms of long-term GI and CV safety data. This, and the heterogeneity of outcome data for selective and non-selective NSAIDs (indicated by observational studies), raise a question about, conceptually, considering NSAIDs simply as two separate classes of agents.
3. For accuracy, we relied on full study reports for data. However, trial reports from drug sponsors were not available universally. For example, most celecoxib trials study reports were available, but in contrast no industry study reports were available for etodolac and meloxicam. This may have led to unforeseen biases.

There are a number of potential limitations of the cost-effectiveness analysis undertaken in this report, including issues of model structure and model parameters:

1. The majority of models developed for arthritis specifically exclude consideration of adverse events other than GI events and MI risk and therefore do not take into account differences in GI tolerance or efficacy between drugs. Nor do published models allow for differences between agents in other adverse events such as skin rashes or hepatitis. As an adaptation of the Maetzel model, the AGM is similar in this respect, but the initial ('switching') cycle added to our model allows drug switching and therefore does take into account, to some extent, drug changes, including withdrawal for lack of efficacy or adverse events.
2. The model only allows one clinical event possible in each cycle (i.e. an arthritis patient cannot undergo MI and a serious GI event within same Markov cycle).
3. Our model, in common with other published models, does not consider drug compliance and the tendency for many patients to use NSAIDs intermittently rather than continuously.
4. Relatively limited observational data were available to populate the initial (switching) cycle of the model.

5. Clinical GI events and MI risk for comparator NSAIDs used in the model were based on data from patients in CLASS not taking aspirin. In contrast, the model used RRs of clinical GI events and MI for the COX-2 selective agents were based on meta-analysis that includes all trial patients (i.e. both aspirin users and non-users). Nevertheless, evidence from our clinical review indicates that the effect of COX-2 on GI events and MI risk is maintained, regardless of aspirin status.
6. There is uncertainty around the GI protective RR associated with PPI plus non-selective NSAID compared with non-selective NSAID alone.
7. The utility values used are based on those reported by Maetzel and colleagues[305] using a sample of the general public and the standard gamble method. Although this is a recognised approach to the derivation of utility values, it has been pointed out that the method may underestimate the severity of short-term effects.[305]

Need for further research

Clinical evidence is still lacking for many areas related to the use of COX-2 selective NSAIDs for OA and RA patients. Further research addressing the following issues would be particularly valuable for clinical practice and policy decision-making:

1. Trials that assess the relative efficacy and costs of COX-2 selective NSAIDs versus combination of non-selective NSAIDs and gastroprotective agents (e.g. PPIs) in people at 'standard' risk and those at a higher risk.
2. Additional evidence of the safety of etodolac, meloxicam, etoricoxib and valdecoxib in terms of clinical GI events and serious CV events.
3. Trials that assess the relative costs, efficacy and safety effects:
   (a) of different COX-2 selective NSAIDs directly compared using equivalent doses which are used in standard clinical practice
   (b) of lower doses of non-selective NSAIDs, for example ibuprofen 1200 mg/day, which are routinely used in clinical practice
   (c) and include patients with differing CV and GI risks including those on aspirin and, particularly, older age groups likely to need NSAIDs
   (d) patients with differing types and severities of OA.
4. Further observational studies that describe patterns of drug use by informed patients with OA and RA including switching between agents.

Chapter 9
Conclusions

The COX-2 selective NSAIDs examined in this report (i.e. etodolac, meloxicam, celecoxib, rofecoxib, valdecoxib, etoricoxib and lumiracoxib) were found to be similar to non-selective NSAIDs for the symptomatic relief of RA and OA and provide superior GI tolerability (the majority of evidence is in patients with OA). Although COX-2 selective drugs offer protection against serious GI events (i.e. PUBs and POBs) compared to non-selective NSAIDs, the amount of evidence for this protective effect varied considerably across individual drugs. A number of the COX-2 selective NSAIDs appear to increase MI risk compared with non-selective NSAIDs, particularly naproxen (since this report was initially written, rofecoxib has been globally withdrawn because of its increased CV risk). In comparison with non-selective NSAIDs, COX-2 selective NSAIDs are more expensive.

Economic modelling shows a wide range of possible costs per QALY gained in patients with OA and RA. Costs per QALY also varied if individual drugs were used in 'average-risk' or 'high-risk' patients, and according to the choice of non-selective NSAID comparator and whether that NSAID was combined with a PPI.

Chapter 10

Postscript

Special note regarding contents presented in this report and the interpretation of the evidence

The contents of this Health Technology Assessment (HTA) report are based upon a technology assessment report that was compiled during a review of Technology Appraisal Guidance No. 27 carried out by NICE in 2004. The review of the guidance was temporarily suspended in February 2005 following the withdrawal of rofecoxib and pending the outcome of a review of the safety of COX-2 selective NSAIDs by EMEA. The EMEA review, released in June 2005, confirmed the increased CV risk of COX-2 selective NSAIDs and also raised important questions concerning the role of all NSAIDs within the pathway of care. As these issues are beyond the scope of the initial Technology Appraisal Guidance, NICE has subsequently decided not to proceed with the review of the guidance but instead will consider these issues in the forthcoming clinical guidelines for OA (publication expected in 2008) and RA (being proposed to the Department of Health).

HTA reports based on technology assessment reports are usually published towards the end of a technology appraisal. The publication of this HTA report was substantially delayed, however, because of the unusual circumstances surrounding the review of the technology appraisal for COX-2 selective NSAIDs. A decision was finally made by the National Coordinating Centre for Health Technology Assessment (NCCHTA) to publish the HTA monograph based on the technology assessment report that was completed in 2004, serving as an archive of the situation as it was when the work was conducted. Readers are therefore minded that evidence included in this report is based on searches of electronic databases up to November 2003 and industry submissions in February 2004 (which covers many of the trials subsequently published in 2004–5). New evidence that has emerged since should be considered alongside the evidence presented in this HTA report. A brief summary of significant events, current status (as in February 2007), and emerging evidence associated with COX-2 selective NSAIDs is provided in the next section. On occasion, new evidence and official documents may override statements previously made in this report. Where possible, a note has been inserted at the beginning of relevant sections to alert readers.

Current status of COX-2 selective NSAIDs and emerging evidence

Safety of COX-2 selective NSAIDs

Since the initial completion of this report, substantial evidence (largely from trials with indications other than OA and RA) concerning the safety of COX-2 selective NSAIDs has emerged. The new evidence, which is briefly summarised below, has profound implications on the licensing status and clinical use of these drugs.

On 30 September 2004, Merck announced a voluntary worldwide withdrawal of rofecoxib after the data from the Adenomatous Polyp Prevention on Vioxx (APPRPOVe) trial demonstrated an increased risk of serious CV events for rofecoxib 25 mg/day compared with placebo in individuals with a history of colorectal adenomas.[313] In December 2004, another Adenoma Prevention with Celecoxib (APC) trial that compared celecoxib 400–800 mg/day to placebo was halted prematurely following the recommendation of its data and safety monitoring board due to a dose-related increase in the risk of serious CV events for patients treated with celecoxib.[314] The safety of COX-2 selective NSAIDs was further questioned as an increased incidence of serious CV events was observed in patients treated with valdecoxib and parecoxib (intravenous prodrug of valdecoxib) compared with those treated with placebo in a short-term trial of postoperative pain after coronary artery bypass grafting.[315]

Triggered by the emerging evidence, both the FDA and EMEA conducted a thorough review of available data with regard to the safety of COX-2 selective NSAIDs and also non-selective NSAIDs in 2004–5. The FDA review, completed in April 2005, concluded:[316]

- The three approved COX-2 selective NSAIDs (i.e., celecoxib, rofecoxib and valdecoxib) are associated with an increased risk of serious adverse CV events compared with placebo. The available data do not permit a rank ordering of these drugs with regard to CV risk.
- Data from large long-term controlled clinical trials that have included a comparison of COX-2 selective and non-selective NSAIDs do not clearly demonstrate that the COX-2 selective agents confer a greater risk of serious adverse CV events than non-selective NSAIDs.
- Long-term placebo-controlled clinical trial data are not available to assess adequately the potential for the non-selective NSAIDs to increase the risk of serious adverse CV events.
- Pending the availability of additional long-term controlled clinical trial data, the available data are best interpreted as being consistent with a class effect of an increased risk of serious adverse CV events for COX-2 selective and non-selective NSAIDs.
- Short-term use of NSAIDs to relieve acute pain, particularly at low doses, does not appear to confer an increased risk of serious adverse CV events (with the exception of valdecoxib in hospitalised patients immediately postoperative from coronary artery bypass surgery).

The FDA review also concluded that valdecoxib is associated with an increased rate of serious and potentially life-threatening skin reactions compared with other COX-2 selective NSAIDs, and the overall benefit versus risk profile for valdecoxib is unfavourable for marketing. Pfizer has subsequently suspended sales of valdecoxib at the request of FDA and EMEA.[317]

The Committee for Medicinal Products for Human Use (CHMP) of the EMEA concluded its review of COX-2 selective NSAIDs (celecoxib, etoricoxib, lumiracoxib, parecoxib and valdecoxib) in June 2005.[318] It recommended the suspension of the marketing authorisation of valdecoxib and the following contraindications and precautions for the remaining COX-2 selective NSAIDs:

- Contraindications stating that COX-2 selective NSAIDs must not be used in patients with established ischaemic heart disease and/or cerebrovascular disease (stroke), and also in patients with peripheral arterial disease.
- Reinforced warnings to healthcare professionals to exercise caution when prescribing COX-2 selective NSAIDs to patients with risk factors for heart disease, such as hypertension, hyperlipidaemia (high cholesterol levels), diabetes and smoking.
- Given the association between CV risk and exposure to COX-2 selective NSAIDs, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment.
- Additional or strengthened warnings to healthcare professionals and patients that hypersensitivity reactions and rare, but serious and sometimes fatal skin reactions can occur with all COX-2 selective NSAIDs. In the majority of cases these occur in the first month of use, and prescribers are warned that patients with a history of drug allergies may be at greater risk.

The EMEA's safety review on non-selective NSAIDs (diclofenac, etodolac, ibuprofen, indomethacin, ketoprofen, meloxicam, nabumetone, naproxen, nimesulide and piroxicam) was completed in October 2005 and concluded that there are no new safety concerns regarding CV and GI safety and serious skin reactions with non-selective NSAIDs, but these drugs will be continuously monitored as for all medicinal products.[319]

Current licensing status and NICE guidance

As per February 2008, the withdrawal of rofecoxib and valdecoxib remains in effect. Lumiracoxib was launched in the UK in January 2006 but was withdrawn in December 2007 due to serious side-effects affecting the liver. Consequently, four (etodolac, meloxicam, celecoxib and etoricoxib) of the seven COX-2 selective NSAIDs are currently available for the treatment of OA and RA in the UK.

The EMEA safety review in 2005 resulted in some changes primarily related to cautions and contraindications in the summaries of product characteristics (SmPCs) of COX-2 selective NSAIDs. NICE concluded in January 2006 that its Guidance No. 27 issued in 2001 should not be withdrawn, but has issued a document detailing the interpretation of the guidance in view of these changes.[320] The key points of the document are:

- COX-2 selective NSAIDs should be used at the minimum effective dose for the shortest duration necessary.
- Prescribers should take note of the revised contraindications and warnings with regard to potentially life-threatening GI perforations, ulcers or bleeds associated with all NSAIDs, including COX-2 selective NSAIDs. Caution is

advised with treatment of patients most at risk of developing a GI complication with NSAIDs: the elderly, patients using any other NSAID or aspirin concomitantly or patients with a prior history of GI disease, such as ulceration and GI bleeding.
- A significant difference in GI safety between selective COX-2 selective NSAIDs + aspirin versus non-selective NSAIDs + aspirin has **not** been demonstrated in long-term clinical trials.
- As etodolac and meloxicam are regarded as non-selective NSAIDs in the EMEA review, these two drugs are now contraindicated in patients with a history of GI bleeding or perforation, related to previous NSAID therapy. In line with other non-selective NSAIDs, combination therapy with gastroprotective agents should be considered when prescribing etodolac and meloxicam for patients with a history of ulcer, those requiring concomitant low-dose aspirin, or other drugs likely to increase GI risk.
- The EMEA safety review has confirmed the concerns about the CV safety of COX-2 selective NSAIDs.

Emerging evidence and ongoing trials

Although the FDA and EMEA safety reviews generally supported that there is increased risk of serious CV events associated with COX-2 selective NSAIDs as a class, uncertainty remains with regard to whether and to what extent the risk differs between individual drugs, and whether such effect extends to the whole class of NSAIDs including non-selective NSAIDs.[321] Kearney and colleagues published a comprehensive meta-analysis of the incidence of serious vascular events in RCTs of COX-2 selective NSAIDs (celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) in 2006.[322] They found a 42% relative increase in the incidence of serious vascular events (rate ratio 1.42, 95% CI 1.13 to 1.78) for COX-2 selective NSAIDs compared with placebo, with little heterogeneity between individual drugs. COX-2 selective NSAIDs were also associated with an increased incidence of serious vascular events when compared with naproxen (rate ratio 1.57, 95% CI 1.21 to 2.03) but not other non-naproxen NSAIDs (rate ratio 0.88, 95% CI 0.69 to 1.12).

Another meta-analysis of 114 RCTs by Zhang and colleagues found significant heterogeneity between individual COX-2 selective NSAIDs with regard to the risk of adverse renal effects.[323] Compared with controls, rofecoxib was associated with an increased risk of composite renal events (RR 1.53, 95% CI 1.33 to 1.76) and arrhythmia (RR 2.90, 95% CI 1.07 to 7.88), whereas celecoxib was associated with a decreased risk of renal dysfunction (RR 0.61; 95% CI 0.40 to 0.94) and hypertension (RR 0.83, 95% CI 0.71 to 0.97). Other COX-2 selective NSAIDs were not significantly associated with risk.

As already highlighted earlier in this report, the amount of evidence from good-quality RCTs of sufficient sample size and duration varied substantially between individual COX-2 selective NSAIDs included in this report, with celecoxib, rofecoxib and lumiracoxib having accumulated the largest amount of trial evidence. The number of serious GI and CV events reported in etodolac, meloxicam, valecoxib and etoricoxib trials was still too small to allow the quantification of risk with sufficient precision. The results of three large etoricoxib trials have subsequently been published:[324–326] EDGE, $n = 7111$, etoricoxib 90 mg/day versus diclofenac 150 mg/day in OA; EDGE II, $n = 4086$, etoricoxib 90 mg/day versus diclofenac 150 mg/day in RA; MEDAL, $n = 23{,}504$, etoricoxib 60 or 90 mg/day versus diclofenac 150 mg/day in OA and RA. In addition, Pfizer has planned the largest celecoxib trial (PRECISION) in which 20,000 patients with OA or RA, with or at risk of developing CV disease will be enrolled to compare CV safety between celecoxib and ibuprofen/naproxen.[327] The results of these trials will help in expanding the existing evidence base.

Acknowledgements

The contents of this report remain the responsibility of the authors and Dr Rod Taylor is guarantor. The authors are grateful to the following individuals for their help and advice during the writing of this report: Dr Martin Connock, Dr Esther Albon, Ms Janine Dretzke, Ms Jayne Wilson, Dr Yaser Adi and Ms Josie Sandercock, for assisting with various aspects of data checking, data extraction and meta-analysis, Ms Wendy Clark, who undertook the review of previous systematic reviews and meta-analyses and data checking of trials for this report, Drs Khalid Khan and Arri Coomarasamy, who assisted with data extraction, Dr Andreas Maetzel, who made an electronic version of his model available, and Ms Rebecca Mason, for her administrative assistance throughout the project and preparation of this report.

We wish to acknowledge with thanks the three peer reviewers for their helpful comments on this report.

This project was funded by the NHS R&D HTA Programme (project number 03/34/01) and commissioned on behalf of NICE. The views and opinions expressed here are those of the authors and do not necessarily reflect those of the funders.

Contribution of authors

Yen-Fu Chen (Systematic Reviewer) coordinated the clinical evidence aspects of the review, applied the inclusion and exclusion criteria, extracted data, appraised studies, conducted meta-analysis, wrote the body of the report and edited the report. Paresh Jobanputra (Consultant Rheumatologist) wrote the introduction and background, carried out data extraction, assisted in the identification of non-trial data inputs to the model and edited the report. Pelham Barton (Lecturer in Mathematical Modelling) adapted the 'front end' to the Maetzel model, ran the assessment group model, wrote the model section and edited the report. Stirling Bryan (Professor of Health Economics) appraised the industry models, wrote the review of economic studies and edited the report. Anne Fry-Smith (Information Specialist) carried out the searches. Gwyn Harris (General Practitioner) provided advice on relevant clinical issues and commented on the drafts of the report. Rod Taylor (Reader in Public Health and Epidemiology) supervised the project, applied the inclusion and exclusion criteria, extracted data, appraised studies and conducted meta-analysis and drafted the discussion section of the report.

References

1. National Institute for Clinical Excellence. *Guidance on the use of cyclo-oxygenase (Cox) II selective inhibitors, celecoxib, rofecoxib, meloxicam, and etodolac for osteoarthritis and rheumatoid arthritis*. London: National Institute for Clinical Excellence. 2001. URL: http://www.nice.org.uk/docref.asp?d=18034. Accessed 17 June 2003.
2. National Institute for Health and Clinical Excellence. *The interpretation of the NICE Technology Appraisal No. 27: use of COX II inhibitors for osteoarthritis and rheumatoid arthritis in the context of license changes made in 2005*. London: National Institute for Health and Clinical Excellence. URL: http://www.nice.org.uk/page.aspx?o=289065. Accessed 29 August 2006.
3. Sheen CL, Dillon JF, Bateman DN, Simpson KJ, MacDonald TM. Paracetamol pack size restriction: the impact on paracetamol poisoning and the over-the-counter supply of paracetamol, aspirin and ibuprofen. *Pharmacoepidemiol Drug Saf* 2002; **11**:329–31.
4. Griffin MR. Epidemiology of nonsteroidal anti-inflammator drug-associated gastrointestinal injury. *Am J Med* 1998;**104**:23S–9S.
5. Prescription Pricing Authority. *Analgesics and NSAIDs prescribing. PACT centre pages*. URL: http://www.ppa.org.uk/news/pact-042002.htm. Accessed 31 January 2004.
6. Doherty M, Jones A, Cawston TE. Osteoarthritis. In Maddison P, Isenberg D, Woo P, Glass D, editors. *Oxford textbook of rheumatology*, 2nd edition. Oxford: Oxford University Press; 1998. pp. 1515–53.
7. Hadler NM. Knee pain is the malady – not osteoarthritis. *Ann Intern Med* 1992;**116**:598–9.
8. Penn H, Jobanputra P. Osteoarthritis: drug treatment in primary care. *Prescriber* 2002;13(9). URL: http://www.escriber.com/Prescriber/Features.asp?ID=432&GroupID=6&Action=View. Accessed 24 April 2004.
9. US Department of Health and Human Services, Food and Drug Administration. *Guidance for industry on clinical development programs for drugs, devices, and biological products intended for the treatment of osteoarthritis (OA)*. 1999. URL: http://www.fda.gov/cder/guidance/2199dft.doc. Accessed 7 May 2004.
10. Lo GH, LaValley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in the treatment of knee osteoarthritis: a meta-analysis. *JAMA* 2003; **290**:3115–21.
11. Jobanputra P, Nuki G. Nonsteroidal anti-inflammatory drugs in the treatment of osteoarthritis. *Curr Opin Rheumatol* 1994;**6**:433–9.
12. Scott D, Smith C, Lohmander S, Chard J. *Musculoskeletal disorders: osteoarthritis*. In: *Clinical evidence*, November 2002. London: BMJ Publishing Group. URL: http://www.clinicalevidence.com/ceweb/conditions/msd/1104/1104_Q1.jsp. Accessed 24 April 2004.
13. Symmons D, Turner G, Webb R, Asten P, Barrett E, Lunt M, *et al*. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. *Rheumatology* 2002; **41**:793–800.
14. Symmons DPM, Barrett EM, Bankhead CR, Scott DGI, Silman AJ. The incidence of rheumatoid arthritis in the United Kingdom: results from the Norfolk Arthritis Register. *Br J Rheumatol* 1994;**33**:735–9.
15. Harrison B, Symmons D. Early inflammatory polyarthritis: results from the Norfolk Arthritis Register with a review of the literature. II. Outcomes at three years. *Rheumatology* 2000; **39**:939–49.
16. Wolfe F, Zwillich S. The long-term outcome of rheumatoid arthritis. A 23-year prospective, longitudinal study of total joint replacement and its predictors in 1,600 patients with rheumatoid arthritis. *Arthritis Rheum* 1998;**41**:1072–82.
17. Jobanputra P, Barton P, Bryan S, Burls A. The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation. *Health Technol Assess* 2002;**6**(21).
18. Scott DL, Shipley M, Dawson A, Edwards S, Symmons DPM, Woolf AD. The clinical management of rheumatoid arthritis and osteoarthritis: strategies for improving clinical effectiveness. *Rheumatology* 1998;**37**:546–54.
19. Strand V, Cohen S, Crawford B, Smolen JS, for the leflunomide investigators, Scott DL. Patient-reported outcomes better discriminate active treatment from placebo in randomised controlled trials in rheumatoid arthritis. *Rheumatology* 2004; **43**:640–7.
20. Chandrasekharan NV, Dai H, Roos LT, Evanson NK, Tomsik J, Elton TS, *et al*. COX-3, a cyclooxygenase-1 variant inhibited by

acetaminophen and other analgesic/antipyretic drugs: cloning, structure and expression. *Proc Natl Acad Sci USA* 2002;**99**:13926–31.

21. Fitzgerald GA. The Coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001;**345**:433–42.
22. Wallace JL, McKnight W, Reuter BK, Vergnolle N. NSAID-induced gastric damage in rats: requirement for inhibition of both cyclooxygenase 1 and 2. *Gastroenterology* 2000;**119**:706–14.
23. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *BMJ* 2000;**321**:1183–7.
24. Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full *in vitro* analysis. *Proc Natl Acad Sci USA* 1999;**96**:7561–8.
25. MacDonald TM, Morant SV, Goldstein JL, Burke TA, Pettitt D. Channelling bias and the incidence of gastrointestinal haemorrhage in users of meloxicam, coxibs, and older, non-specific non-steroidal anti-inflammatory drugs. *Gut* 2003; **52**:1265–70.
26. Hawkey CJ. COX-2 inhibitors. *Lancet* 1999; **353**:307–14.
27. Hawkey CJ. NSAID toxicity: where are we and how do we go forward? *J Rheumatol* 2002;**29**:650–2.
28. National Institute for Clinical Excellence. *The appropriate use of proton pump inhibitors in the treatment of dyspepsia*. 2004. URL: http://www.nice.org.uk/pdf/ppi_hta_report.pdf. Accessed 1 May 2004.
29. Logan R, Delaney B. ABC of the upper gastrointestinal tract. Implications of dyspepsia for the NHS. *BMJ* 2001;**323**:675–7.
30. Lapane KL, Spooner JJ, Pettitt D. The effect of nonsteroidal anti-inflammatory drugs on the use of gastroprotective medication in people with arthritis. *Am J Managed Car*e 2001;**7**:402–8.
31. Ofman J, MacLean CH, Straus WL, Morton SC, Berger ML, Roth EA, *et al*. Meta-analysis of dyspepsia and nonsteroidal antiinflammatory drugs. *Arthritis Rheum* 2003;**49**:508–18.
32. Langman MJ, Jensen DM, Watson DJ, Harper SE, Zhao PL, Quan H, *et al*. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. *JAMA* 1999;**282**:1929–33.
33. Williams B, Luckas M, Ellingham JH, Dain A, Wick AC. Do young patients with dyspepsia need investigation? *Lancet* 1988;**ii**:1349–51.
34. Okamoto K, Iwakiri R, Mori M, Hara M, Odak K, Danjo A, *et al*. Clinical symptoms in endoscopic reflux esophagitis: evaluation in 8031 adult subjects. *Dig Dis Sci* 2003;**48**:2237–41.
35. Tramer MR, Moore RA, Reynolds DJM, McQuay HJ. Quantitative estimation of rare events which follow a biological progression: a new model applied to chronic NSAID use. *Pain* 2000; **85**:169–82.
36. Singh G, Ramey DR, Morfeld D, Shi H, Hatoum HT, Fries JF. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. *Arch Intern Med* 1996;**156**:1530–6.
37. Laine L, Harper S, Simon T, Bath R, Johanson J, Schwartz H, *et al*. A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. *Gastroenterology* 1999;**117**:776–83.
38. Olivero JJ, Graham DY. Gastric adaptation to nonsteroidal anti-inflammatory drugs in man. *Scand J Gastroenterol* 1992;**193**:53–8.
39. Laine L, Connors GL, Reicin A, Hawkey CJ, Burgos-Vargas R, Schnitzer TJ, *et al*. Serious lower gastrointestinal clinical events with nonselective NSAID or coxib use. *Gastroenterology* 2003; **124**:288–92.
40. Hernandez-Diaz S, Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. *Arch Intern Med* 2000;**160**:2093–9.
41. MacDonald TM, Morant SV, Robinson GC, Sheild MJ, McGilchrist MM, Murray FE. Association of upper gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with continued exposure: cohort study. *BMJ* 1997; **315**:1333–7.
42. Fries JF, Bruce B. Rates of serious gastrointestinal events from low dose use of acetylsalicylic acid, acetaminophen, and ibuprofen in patients with osteoarthritis and rheumatoid arthritis. *J Rheumatol* 2003;**30**:2226–33.
43. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1999; **340**:1888–99.
44. Laine L, Bombardier C, Hawkey CJ, Davis B, Shapiro D, Brett C, *et al*. Stratifying the risk of NSAID-related upper gastrointestinal clinical events: results of a double-blind outcomes study in patients with rheumatoid arthritis. *Gastroenterology* 2002;**123**:1006–12.
45. Garcia Roderiguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994;**343**:769–72.
46. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Concurrent use of nonsteroidal anti-inflammatory

drugs and oral anticoagulants places elderly persons at high risk for haemorrhagic peptic ulcer disease. *Arch Intern Med* 1993;**153**:1665–70.

47. Price-Forbes AN, Callaghan R, Allen ME, Rowe IF. A regional audit of the use of COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDS) in rheumatology clinics in the West Midlands, according to NICE guidelines. *Rheumatology* 2004; **43**:Abstract 157-ii78.

48. Gabriel SE, Jaakimainen L, Bombardier C. Risk for serious gastrointestinal complications related to the use of nonsteroidal anti-inflammatory drugs. *Ann Intern Med* 1991;**115**:787–96.

49. Department of Health and Human Services FaDAC. Arthritis Advisory Committee NDA 20-988/S009, Celebrex. 2001. URL: http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3677t1.rtf. Accessed 26 February 2004.

50. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, *et al*. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA* 2000;**284**:1247–55.

51. Rostom A, Dube C, Jolicoeur E, Boucher M, Joyce J. *Gastroduodenal ulcers associated with the use of non-steroidal anti-inflammatory drugs: a systematic review of preventive pharmacological interventions*. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA). 2004. Technology Overview No. 12. URL: http://www.ccohta.ca/publications/pdf/261_gastro_to_e.pdf. Accessed 7 May 2004.

52. Ng WF, Hall A, Steuer A. COX II selective inhibitors versus traditional NSAIDS: are we using them appropriately? *Rheumatology* 2004; **43**:Abstract 154-ii77.

53. Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. *BMJ* 2002;**325**:619.

54. Food and Drug Administration. Arthritis Advisory Committee, 7 February 2001. *Briefing information. NDA 20-998/S009 Celebrex (celecoxib). Searle*. 2001. URL: http://www fdagov/ohrms/dockets/ac/01/briefing/3677b1 htm. Accessed 11 March 2004.

55. Lai KC, Lam SK, Chu KM, Wong BCY, Hui WM, Hu WHC, *et al*. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N Engl J Med* 2002; **346**:2033–8.

56. Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, *et al*. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomised placebo controlled trial. *Ann Intern Med* 1995;**123**:241–9.

57. Graham DY, Agrawal N, Campbell DR, Haber MM, Collis C, Lukasik NL, *et al*. Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs. *Ann Intern Med* 2002;**136**:169–75.

58. Hawkey CJ, Karrasch JA, Szczepanski L, Walker DG, Barkun A, Swannell AJ, *et al*. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1998;**338**:727–34.

59. Chan FK, Hung LC, Suen BY, Wu JC, Lee KC, Leung VK, *et al*. Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. *N Engl J Med* 2002;**347**:2104–10.

60. Chan FKL, Leung WK. Peptic-ulcer disease. *Lancet* 2002;**360**:933–41.

61. Stack WA, Atherton JC, Hawkey GM, Logan RFA, Hawkey CJ. Interactions between *Helicobacter pylori* and other risk factors for peptic ulcer bleeding. *Aliment Pharmacol Ther* 2002;**16**:497–506.

62. Hawkey CJ. Personal review: *Helicobacter pylori*, NSAIDs and cognitive dissonance. *Aliment Pharmacol Ther* 1999;**13**:695–702.

63. Department of Health and Human Services, Food and Drug Administration. Medical Officer's Gastroenterology Advisory Committee briefing document. NDA 20, 998: Supplement #9. *Celecoxib: review of Celecoxib Long-Term Arthritis Safety Study (CLASS)*. 2000. URL: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_05_gi.doc. Accessed 6 March 2004.

64. Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, *et al*. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001;**345**:1809–17.

65. Baigent C, Patrono C. Selective cyclooxygenase 2 inhibitors, aspirin, and cardiovascular disease. A reappraisal. *Arthritis Rheum* 2003;**48**:12–20.

66. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, *et al*. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;**343**:1520–8.

67. Verma S, Szmitko PE. Coxibs and the endothelium. *J Am Coll Cardiol* 2003;**42**:1754–6.

68. Patel TN, Goldberg KC. Use of aspirin and ibuprofen compared with aspirin alone and the risk of myocardial infarction. *Arch Intern Med* 2004;**164**:852–6.

69. Curtis JP, Wang Y, Portnay EL, Masoudi FA, Havranek EP, Krumholz HM. Aspirin, ibuprofen, and mortality after myocardial infarction: retrospective cohort study. *BMJ* 2003;**327**:1322–3.

70. Dunn MJ. Are COX-2 selective inhibitors nephrotoxic? *Am J Kidney Dis* 2000;**35**:976–7.

71. European Agency for the Evaluation of Medicinal Products. *EMEA public statement on parecoxib sodium (Dynstat/Ryzor/Xapit) risk of serious hypersensitivity and skin reactions*. London: EMEA; 2004. Report no. EMEA/25175/01. URL: http://www.emea.eu.int/pdfs/human/press/pus/2517502en.pdf. Accessed 30 April 2004.

72. Woessner KM, Simon RA, Stevenson DD. The safety of celecoxib in patients with aspirin-sensitive asthma. *Arthritis and Rheum* 2002;**46**:2201–6.

73. Mahadevan V, Loftus EVJ, Tremain WJ, Sandborn WJ. Safety of selective cyclooxygenase-2 inhibitors in inflammatory bowel disease. *Am J Gastroenterol* 2002;**97**:910–4.

74. American College of Rheumatology Subcommittee on Osteoarthritis. Recommendations for the medical management of osteoarthritis of the hip and knee. *Arthritis Rheum* 2004;**43**:1905–15.

75. Felson DT. The verdict favors nonsteroidal anti-inflammatory drugs for treatment of osteoarthritis and a plea for more evidence on other treatments. *Arthritis Rheum* 2001;**44**:1477–80.

76. Langman M, Kahler ST, Kong SX, Zhang Q, Finch E, Bentkover JD, *et al*. Drug switching patterns among patients taking non-steroidal anti-inflammatory drugs: a retrospective cohort study of a general practitioners database in the United Kingdom. *Pharmacoepidemiol Drug Saf* 2001; **10**:517–24.

77. Patino FG, Allison J, Olivieri J, Mudano A, Juarez L, Person S, *et al*. The effects of physician speciality and patient comorbidities on the use and discontinuation of Coxibs. *Arthritis Rheum* 2003;**49**:293–9.

78. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis. *Arthritis Rheum* 2002;**46**:328–46.

79. Bardell E, Gordon M-M, Porter D. COX-2 inhibitors – implementation of the NICE guidelines. *Rheumatology* 2002;**41**:590–2.

80. White WB, Faich G, Borer JS, Makuch RW. Cardiovascular thrombotic events in arthritis trials of the cyclooxygenase-2 inhibitor celecoxib. *Am J Cardiol* 2003;**92**:411–18.

81. Moskowitz RW, Sunshine A, Brugger A, Lefkowith JB, Zhao WW, Geis GS. American pain society pain questionnaire and other pain measures in the assessment of osteoarthritis pain: a pooled analysis of three celecoxib pivotal studies. *Am J Ther* 2003;**10**:12–20.

82. Gertz BJ, Krupa D, Bolognese JA, Sperling RS, Reicin A. A comparison of adverse renovascular experiences among osteoarthritis patients treated with rofecoxib and comparator non-selective non-steroidal anti-inflammatory agents. *Curr Med Res Opin* 2002;**18**:82–91.

83. Patterson R, Bello AE, Lefkowith J. Immunologic tolerability profile of celecoxib. *Clin Ther* 1999; **21**:2065–79.

84. Reicin AS, Shapiro D, Sperling RS, Barr E, Yu Q. Comparison of cardiovascular thrombotic events in patients with osteoarthritis treated with rofecoxib versus nonselective nonsteroidal anti-inflammatory drugs (ibuprofen, diclofenac, and nabumetone). *Am J Cardiol* 2002;**89**:204–9.

85. Watson DJ, Harper SE, Zhao PL, Bolognese JA, Simon TJ. Gastrointestinal medications and procedures in osteoarthritis patients treated with rofecoxib compared with nonselective NSAIDs. Medgenmed [Computer File]. *Medscape Gen Med* 2001;**3**:6.

86. Detora LM, Krupa D, Bolognese J, Sperling RS, Ehrich EW. Rofecoxib shows consistent efficacy in osteoarthritis clinical trials, regardless of specific patient demographic and disease factors. *J Rheumatol* 2001;**28**:2494–503.

87. Konstam MA, Weir MR, Reicin A, Shapiro D, Sperling RS, Barr E, *et al*. Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib. *Circulation* 2001;**104**:2280–8.

88. Hawkey CJ, Laine L, Harper SE, Quan HU, Bolognese JA, Mortensen E, *et al*. Influence of risk factors on endoscopic and clinical ulcers in patients taking rofecoxib or ibuprofen in two randomized controlled trials. *Aliment Pharma Ther* 2001;**15**:1593–601.

89. Lisse J, Espinoza L, Zhao SZ, Dedhiya SD, Osterhaus JT. Functional status and health-related quality of life of elderly osteoarthritic patients treated with celecoxib. *J Gerontol A Biol Sci Med Sci* 2001;**56**:M167–75.

90. Hawkey CJ, Jackson L, Harper SE, Simon TJ, Mortensen E, Lines CR. Review article: the gastrointestinal safety profile of rofecoxib, a highly selective inhibitor of cyclooxygenase-2, in humans. *Aliment Pharmacol Ther* 2001;**15**:1–9.

91. Whelton A, Maurath CJ, Verburg KM, Geis GS. Renal safety and tolerability of celecoxib, a novel cyclooxygenase-2 inhibitor. [published erratum appears in *Am J Ther* 2000;**7**:341]. *Am J Ther* 2000;**7**:159–75.

92. Maddrey WC, Maurath CJ, Verburg KM, Geis GS. The hepatic safety and tolerability of the novel cyclooxygenase-2 inhibitor celecoxib. [published erratum appears in *Am J Ther* 2000;**7**:341]. *Am J Ther* 2000;**7**:153–8.

93. Watson DJ, Harper SE, Zhao PL, Quan H, Bolognese JA, Simon TJ. Gastrointestinal tolerability of the selective cyclooxygenase-2 (COX-2) inhibitor rofecoxib compared with

nonselective COX-1 and COX-2 inhibitors in osteoarthritis. *Arch Intern Med* 2000;**160**:2998–3003.

94. Bensen WG, Zhao SZ, Burke TA, Zabinski RA, Makuch RW, Maurath CJ, *et al*. Upper gastrointestinal tolerability of celecoxib, a COX-2 specific inhibitor, compared to naproxen and placebo. *J Rheumatol* 2000;**27**:1876–83.

95. Goldstein JL, Silverstein FE, Agrawal NM, Hubbard RC, Kaiser J, Maurath CJ, *et al*. Reduced risk of upper gastrointestinal ulcer complications with celecoxib, a novel COX-2 inhibitor. *Am J Gastroenterol* 2000;**95**:1681–90.

96. Distel M, Mueller C, Bluhmki E, Fries J. Safety of meloxicam: a global analysis of clinical trials. *Br J Rheumatol* 1996;**35**(Suppl 1):68-77.

97. Bacon PA. Safety profile of etodolac in the elderly population. *Eur J Rheumatol Inflamm* 1994;**14**:19–22.

98. Bacon P. Worldwide experience with etodolac (Lodine) 300 mg b.i.d. in the treatment of osteoarthritis. *Rheumatol Int* 1993;**13**(2 Suppl): S7–12.

99. Porzio F. Meta-analysis of two double-blind comparative studies with the sustained-release form of etodolac in rheumatoid arthritis. *Rheumatol Int* 1993;**13**(2 Suppl):S25–30.

100. Porzio F. Meta-analysis of three double-blind comparative trials with sustained-release etodolac in the treatment of osteoarthritis of the knee. *Rheumatol Int* 1993;**13**(2 Suppl):S19–24.

101. Brater DC. Evaluation of etodolac in subjects with renal impairment. *Eur J Rheumatol Inflamm* 1990; **10**:44–55.

102. Karbowski A. A global safety evaluation of etodolac. *Clin Rheumatol* 1989;**8**(Suppl 1):73–9.

103. Shand DG, Epstein C, Kinberg-Calhoun J, Mullane JF, Sanda M. The effect of etodolac administration on renal function in patients with arthritis. *J Clin Pharmacol* 1986;**26**:269–74.

104. Distel M, Mueller C, Bluhmki E. Global analysis of gastrointestinal safety of a new NSAID, meloxicam. *Inflammopharmacology* 1996;**4**:71–81.

105. Schattenkirchner M. An updated safety profile of etodolac in several thousand patients. *Eur J Rheumatol Inflamm* 1990;**10**:56–65.

106. Mullane JF, Salem S. Double-blind evaluation of the effect of etodolac and placebo on uric acid levels. *Curr Ther Res Clin Exp* 1988;**43**:552–7.

107. Sanda M, Zuchero D, Shand D. Etodolac: safety profile in 992 patients. *Adv Ther* 1985;**2**:1–10.

108. Ryder S, Salom I, Jacob G. Etodolac (Ultradol(TM)): The safety profile of a new structurally novel nonsteroidal anti-inflammatory drug. *Curr Ther Res Clin Exp* 1983;**33**:948–65.

109. Degner F, Bluhmki E. Global analysis of safety experience with meloxicam in randomised double-blind clinical trials performed in Scandinavian countries in rheumatoid arthritis and osteoarthritis [abstract P83]. *Scand J Rheumatol Suppl* 1996; **106**(Suppl):60.

110. Singh G, Triadafilopoulos G. Meloxicam has a low risk of serious gastrointestinal complications: pooled analysis of 27,039 patients [abstract SAT0085 EULAR 2001]. *Ann Rheum Dis* 2001; **60**(Suppl 1):235.

111. Sanda M, Jacob G, Shand D. A safety profile of etodolac in arthritics: clinical experience based on 600 patient-years. *Today's Ther Trends* 2004;**3**:1–15.

112. Garner S, Fidan D, Frankish R, Judd M, Shea B, Towheed T, *et al*. Celecoxib for rheumatoid arthritis. *Cochrane Database Syst Rev* 2002;CD003831.

113. Kaplan-Machlis B, Klostermeyer BS. The cyclooxygenase-2 inhibitors: safety and effectiveness [published erratum appears in *Ann Pharmacother* 1999 Dec;33(12):1376]. *Ann Pharmacother* 1999; **33**:979–88.

114. Schnitzer TJ. Osteoarthritis management: the role of cyclooxygenase-2-selective inhibitors. *Clin Ther* 2001;**23**:313–26.

115. Vasoo S, Ng SC. New cyclooxygenase inhibitors. *Ann Acad Med Singapore* 2001;**30**:164–9.

116. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 2001;**286**:954–9.

117. Weaver AL. Rofecoxib: clinical pharmacology and clinical experience. *Clin Ther* 2001;**23**:1323–38.

118. Garner S, Fidan D, Frankish R, Judd M, Towheed T, Wells G, *et al*. Rofecoxib for rheumatoid arthritis. *Cochrane Database Syst Rev* 2002; Issue 3: CD003685.

119. Chavez ML, DeKorte CJ. Valdecoxib: a review. *Clin Ther* 2003;**25**:817–51.

120. Schoenfeld P, Palmer RH, McCarthy DM. Gastrointestinal safety profile of meloxicam: a meta-analysis and systematic review of randomized controlled trials. *Am J Med* 1999;**107**:48S–54S.

121. Ashcroft DM, Chapman SR, Clark WK, Millson DS. Upper gastroduodenal ulceration in arthritis patients treated with celecoxib. *Ann Pharmacother* 2001;**35**:829–34.

122. de Vries C. *Cox-II inhibitors versus non-steroidal anti-inflammatory drugs in rheumatoid and osteoarthritis patients: gastrointestinal effects*. STEER: Succinct and Timely Evaluated Evidence Reviews 2(8). Southampton: Wessex Institute for Health Research and Development, University of Southampton; 2002.

123. Emery P, Kong SX, Ehrich EW, Watson DJ, Towheed TE. Dose–effect relationships of nonsteroidal anti-inflammatory drugs: a literature review. *Clin Ther* 2002;**24**:1225–91.

124. Watson MC, Brookes ST, Kirwan JR, Faulkner A. Non-aspirin, non-steroidal anti-inflammatory drugs for osteoarthritis of the knee. *Cochrane Database of Syst Rev* 2000;CD000142.

125. Rostom A, Dubé C, Jolicoeur E, Boucher M, Joyce J. *Gastro-duodenal ulcers associated with the use of non-steroidal anti-inflammatory drugs: a systematic review of preventive pharmacological interventions*. Technology Report No. 38 commissioned by CCOHTA. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2003.

126. Luong BT, Chong BS, Lowder DM. Treatment options for rheumatoid arthritis: celecoxib, leflunomide, etanercept, and infliximab. *Ann Pharmacother* 2000;**34**:743–60.

127. Hogue JH, Mersfelder TL. Pathophysiology and first-line treatment of osteoarthritis. *Ann Pharmacother* 2002;**36**:679–86.

128. Towheed TE, Hochberg MC. A systematic review of randomized controlled trials of pharmacological therapy in osteoarthritis of the knee, with an emphasis on trial methodology. *Semin Arthritis Rheum* 1997;**26**:755–70.

129. El Desoky ES. Pharmacotherapy of rheumatoid arthritis: an overview. *Curr Ther Res Clin Exp* 2001;**62**:92–112.

130. NICE appraisal team. *The clinical effectiveness and cost effectiveness of celecoxib, rofecoxib, meloxicam and etodolac (COX-II inhibitors) for rheumatoid arthritis and osteoarthritis*. London: National Institute for Clinical Excellence; 2000.

131. Gisbert JP, Pajares JM. Cyclooxygenase-2 and gastroduodenal lesions. Any relationship with *Helicobacter pylori*? A systematic review. *Med Clin* 2003;**120**:550–8.

132. Hernandez-Cruz B, Ariza-Ariza R, Navarro SF. Efficiency, toxicity and economic evaluation of the classical non-steroidal anti-inflammatory drugs versus the COX 2 selective inhibitors in the treatment of rheumatoid arthritis: a critical appraisal. *Semin Fund Esp Reumatol* 2002;**3**:124–37.

133. Egger M, Davey-Smith G, Phillips AN. Meta-analysis: principles and procedures. *BMJ* 1997;**315**:1533–7.

134. Der Simonian R, Laird N. Meta-analysis in clinical trials. *Controll Clin Trials* 1986;**7**:177–88.

135. Cutler J. Variance imputation for overviews of clinical trials with continuous response. *J Clin Epidemiol* 1992;**45**:769–73.

136. Bacon PA. An overview of the efficacy of etodolac in arthritic disorders. *Eur J Rheumatol Inflamm* 1990;**10**:22–34.

137. Platt PN. Recent clinical experience with etodolac in the treatment of osteoarthritis of the knee. *Clin Rheumatol* 1989;**8**(Suppl 1):54–62.

138. Williams PI, Hosie J, Scott DL. Etodolac therapy for osteoarthritis: a double-blind, placebo-controlled trial. *Curr Med Res Opin* 1989;**11**:463–70.

139. Freitas GG. A double-blind comparison of etodolac and piroxicam in the treatment of osteoarthritis. *Curr Med Res Opin* 1990;**12**:255–62.

140. Brasseur JP, Faeman F, Franchimont P. Double-blind parallel comparison of etodolac and diclofenac S.R. in patients with osteoarthritis of the knee. *Acta Ther* 1991;**17**:345–54.

141. Karbowski A. Double-blind, parallel comparison of etodolac and indomethacin in patients with osteoarthritis of the knee. *Curr Med Res Opin* 1991;**12**:309–17.

142. Palferman TG, Struthers GR, Williams PI. Double-blind, parallel comparison of etodolac and naproxen in patients with osteoarthritis of the knee. *Acta Ther* 1991;**17**:19–34.

143. Astorga Paulsen G, Baigun S, Galvao de Figueiredo J, Gomes de Freitas G. Efficacy and tolerability comparison of etodolac and piroxicam in the treatment of patients with osteoarthritis of the knee. *Curr Med Res Opin* 1991;**12**:401–12.

144. Pena M, Lizarazo H. Double-blind comparison of etodolac and naproxen in patients with osteoarthritis. *Acta Ther* 1991;**17**:5–18.

145. Perpignano G, Bogliolo A, Demelia L. Evaluation of the efficacy and gastro-intestinal safety of etodolac vs naproxen in patients with osteoarthritis. *Reumatismo* 1991;**43**:25–31.

146. Dick WC, Bulstra S, Schardijn GH, Feenstra RM. Safety and efficacy of etodolac compared with piroxicam in patients with degenerative joint disease of the knee. *Clin Ther* 1992;**14**:517–26.

147. Grisanti AM, Vaz AA, Samara AM. Comparison of etodolac and diclofenac in osteoarthritis of the knee. *Clin Ther* 1992;**14**:791–800.

148. Waterworth RF, Petrie JP. Double-blind comparative study of etodolac and piroxicam in patients with osteoarthritis of the knee. *Adv Ther* 1992;**9**:240–9.

149. Burssens A, Hohmeister R, Klein G. Double-blind comparison of etodolac SR tablets and tenoxicam capsules in the treatment of osteoarthritis of the knee. *Acta Ther* 1993;**19**:35–48.

150. Eisenkolb T, Cawley MID, Dean S, Wagenhauser F. Double-blind, parallel-group evaluation of the safety and efficacy of etodolac compared with diclofenac in patients with osteoarthritis of the knee. *Acta Ther* 1993;**19**:137–50.

151. Chikanza IC, Clarke B, Hopkins R, MacFarlane DG, Bird H, Grahame R. A comparative study of the efficacy and toxicity of etodolac and naproxen in the treatment of osteoarthritis. *Br J Clin Pract* 1994;**48**:67–9.

152. Lucker PW, Pawlowski C, Friedrich I, Faiella F, Magni E. Double-blind, randomised, multi-centre clinical study evaluating the efficacy and tolerability of nimesulide in comparison with etodolac in patients suffering from osteoarthritis of the knee. *Eur J Rheumatol Inflamm* 1994;**14**:29–38.

153. Perpignano G, Bogliolo A, Puccetti L. Double-blind comparison of the efficacy and safety of etodolac SR 600 mg u.i.d. and of tenoxicam 20 mg u.i.d. in elderly patients with osteoarthritis of the hip and of the knee. *Int J Clin Pharmacol Res* 1994;**14**:203–16.

154. Dore R, Ballard I, Constantine G, McDonald P. Efficacy and safety of etodolac and naproxen in patients with osteoarthritis of the knee: a double-blind, placebo-controlled study. *Clin Ther* 1995; **17**:656–66.

155. Schnitzer TJ, Ballard IM, Constantine G, McDonald P. Double-blind, placebo-controlled comparison of the safety and efficacy of orally administered etodolac and nabumetone in patients with active osteoarthritis of the knee. *Clin Ther* 1995;**17**:602–12.

156. Jennings MB, Alfieri DM. A controlled comparison of etodolac and naproxen in osteoarthritis of the foot. *Lower Extremity* 1997;**4**:43–8.

157. Rogind H, Bliddal H, Klokker D, Jensen F. Comparison of etodolac and piroxicam in patients with osteoarthritis of the hip or knee: a prospective, randomised, double-blind, controlled multicentre study. *Clin Drug Invest* 1997;**13**:66–75.

158. Schnitzer TJ, Constantine G. Etodolac (Lodine) in the treatment of osteoarthritis: recent studies. *J Rheumatol Suppl* 1997;**24**(Suppl 47):23–31.

159. Taha AS, McLaughlin S, Sturrock RD, Russell RI. Evaluation of the efficacy and comparative effects on gastric and duodenal mucosa of etodolac and naproxen in patients with rheumatoid arthritis using endoscopy. *Br J Rheumatol* 1989;**28**:329–32.

160. Russell RI. Endoscopic evaluation of etodolac and naproxen, and their relative effects on gastric and duodenal prostaglandins. *Rheumatol Int* 1990; **10**(Suppl):17–21.

161. Kivitz AJ, Greenwald MW, Cohen SB, Polis AB, Najarian DK, Dixon ME, *et al*. Efficacy and safety of rofecoxib 12.5 mg versus nabumetone 1,000 mg in patients with osteoarthritis of the knee: a randomized controlled trial. *J Am Geriatr Soc* 2004;**52**:666–74.

162. Taha AS, McLaughlin S, Holland PJ, Kelly RW, Sturrock RD, Russell RI. Effect on gastric and duodenal mucosal prostaglandins of repeated intake of therapeutic doses of naproxen and etodolac in rheumatoid arthritis. *Ann Rheum Dis* 1990;**49**:354–8.

163. Lightfoot R. Comparison of the efficacy and safety of etodolac and piroxicam in patients with rheumatoid arthritis. Etodolac Study 326 Rheumatoid Arthritis Investigators Group. *J Rheumatol* 1997;**24**(Suppl 47):10–16.

164. Neustadt DH. Double blind evaluation of the long-term effects of etodolac versus ibuprofen in patients with rheumatoid arthritis. *J Rheumatol* 1997;**24**(Suppl 47):17–22.

165. Linden B, Distel M, Bluhmki E. A double-blind study to compare the efficacy and safety of meloxicam 15 mg with piroxicam 20 mg in patients with osteoarthritis of the hip. *Br J Rheumatol* 1996;**35**(Suppl 1):35–8.

166. Goei The HS, Lund B, Distel MR, Bluhmki E. A double-blind, randomized trial to compare meloxicam 15 mg with diclofenac 100 mg in the treatment of osteoarthritis of the knee. *Osteoarthritis Cartilage* 1997;**5**:283–8.

167. Furst DE, Kolba KS, Fleischmann R, Silverfield J, Greenwald M, Roth S, *et al*. Dose response and safety study of meloxicam up to 22.5 mg daily in rheumatoid arthritis: a 12 week multicenter, double blind, dose response study versus placebo and diclofenac. *J Rheumatol* 2002;**29**:436–46.

168. Carrabba M, Paresce E, Angelini M, Galanti A, Marini MG, Cigarini P. A comparison of the local tolerability, safety and efficacy of meloxicam and piroxicam suppositories in patients with osteoarthritis: a single-blind, randomized, multicentre study [published erratum appears in *Curr Med Res Opin* 1996;**13**:427–8]. *Curr Med Res Opin* 1995;**13**:343–55.

169. Carrabba M, Paresce E, Angelini M, Galanti A, Marini MG, Cigarini P, *et al*. Corrigendum: a comparison of the local tolerability, safety and efficacy of meloxicam and piroxicam suppositories in patients with osteoarthritis: a single-blind, randomized, multicentre study [*Journal of Current Research and Opinion* (1995) **13** 6 (343–355)]. *Curr Med Res Opin* 1995;**13**:427–8.

170. Hosie J, Distel M, Bluhmki E. Meloxicam in osteoarthritis: a 6-month, double-blind comparison with diclofenac sodium. *Br J Rheumatol* 1996;**35**(Suppl 1):39–43.

171. Hosie J, Distel M, Bluhmki E. Efficacy and tolerability of meloxicam versus piroxicam in patients with osteoarthritis of the hip or knee. A six-month double-blind study. *Clin Drug Invest* 1997;**13**:175–84.

172. Dequeker J, Hawkey C, Kahan A, Steinbruck K, Alegre C, Baumelou E, *et al*. Improvement in gastrointestinal tolerability of the selective cyclooxygenase (COX)-2 inhibitor, meloxicam, compared with piroxicam: results of the Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies (SELECT) trial in osteoarthritis. *Br J Rheumatol* 1998;**37**:946–51.

173. Hawkey C, Kahan A, Steinbruck K, Alegre C, Baumelou E, Begaud B, *et al*. Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. International MELISSA Study Group. Meloxicam Large-scale International Study Safety Assessment [published erratum appears in *Br J Rheumatol* 1998 Oct;**37**:1142]. *Br J Rheumatol* 1998;**37**:937–45.

174. Lund B, Distel M, Bluhmki E. A double-blind, randomized, placebo-controlled study of efficacy and tolerance of meloxicam treatment in patients with osteoarthritis of the knee. *Scand J Rheumatol* 1998;**27**:32–7.

175. Lund B, Distel M, Bluhmki E. A double-blind placebo controlled study of three different doses of meloxicam in patients with osteoarthritis (OA) of the knee. *Scand J Rheumatol* 1994;Suppl 98:117.

176. Yocum D, Fleischmann R, Dalgin P, Caldwell J, Hall D, Roszko P. Safety and efficacy of meloxicam in the treatment of osteoarthritis: a 12-week, double-blind, multiple-dose, placebo-controlled trial. The Meloxicam Osteoarthritis Investigators. *Arch Intern Med* 2000;**160**:2947–54.

177. Yocum DE, Fleischmann R, Dalgin P, Caldwell J, Hall D, Roszko P, *et al*. Efficacy and safety of meloxicam in the treatment of osteoarthritis: results of a phase III double-blind, placebo controlled trial. *Z Rheumatol* 2001;**60**:38.

178. Yocum DE, Hall DB, Roszko PJ. Efficacy and safety of meloxicam in the treatment of osteoarthritis (OA): results of a phase III double-blind, placebo controlled trial [abstract 459]. *Arthritis Rheumatism* 1999;**42**(Suppl):S147.

179. Chang DM, Young TH, Hsu CT, Kuo SY, Hsieh TC. Endoscopic comparison of the gastroduodenal safety and the effects on arachidonic acid products between meloxicam and piroxicam in the treatment of osteoarthritis. *Clin Rheumatol* 2001; **20**:104–13.

180. Valat JP, Accardo S, Reginster JY, Wouters M, Hettich M, Lieu PL, *et al*. A comparison of the efficacy and tolerability of meloxicam and diclofenac in the treatment of patients with osteoarthritis of the lumbar spine. *Inflamm Res* 2001;**50**(Suppl 1):S30–4.

181. Xu JH, Li XP, Zhang YC, Ding CH, Shuai ZW, Xu SQ, *et al*. Meloxicam vs nabumetone in treating osteoarthritis: a double-blind, control study. *Chin J New Drugs Clin Remedies* 2002;**21**:213–5.

182. Wojtulewski JA, Schattenkirchner M, Barcelo P, Le L, X, Bevis PJ, Bluhmki E, *et al*. A six-month double-blind trial to compare the efficacy and safety of meloxicam 7.5 mg daily and naproxen 750 mg daily in patients with rheumatoid arthritis. *Br J Rheumatol* 1996;**35**(Suppl 1):22–8.

183. Schattenkirchner M, Bluhmki E, Distel M. Randomised double-blind clinical test over 6 months for the comparison of meloxicam 7.5 mg with naproxen 750 mg by rheumatoid arthritis [abstract P139] [in German]. *Z Rheumatol* 1996; **55** Suppl 1:112.

184. Lemmel EM, Bolten W, Burgos-Vargas R, Platt P, Nissila M, Sahlberg D, *et al*. Efficacy and safety of meloxicam in patients with rheumatoid arthritis. *J Rheumatol* 1997;**24**:282–90.

185. Bolten W, Lemmel EM, Distel M, Bluhmki E, Hanft G, Degner FL. Treatment of rheumatoid arthritis (RA) with meloxicam: controlled double-blind clinical test with placebo [abstract P136] [in German]. *Z Rheumatol* 1996;**55** Suppl 1:112.

186. Furst DE, Hall DB, Roszko J, Leonard JP. Efficacy, safety and dose response of meloxicam up to 22.5 mg in the treatment of rheumatoid arthritis (RA): results of a phase III double-blind, placebo controlled trial. *Z Rheumatol* 2001;**60**:38.

187. Xu J-H, Ding C-H, Xu S-Y, Zhang Y-C, Li X-P, Sun G-H, *et al*. A double-blind, randomized controlled clinical study of meloxicam and nabumetone in the treatment of rheumatoid arthritis. *Chin Pharm J* 2002;**37**:310–12.

188. Gao SM, Sun GH, Xu JH, Xu SQ, Shuai ZW, Wang F, *et al*. A double-blind, controlled clinical study of meloxicam and nabumetone in the treatment of rheumatoid arthritis. *Acta Univ Med Anhui* 2001;**36**:290–2.

189. Center for Drug Evaluation and Research. Application Number 20-998/S-009. Statistical Review(s). 2001. URL: http://www.fda.gov/cder/foi/nda/2002/20-998S009_Celebrex_stratr.pdf. Accessed 6 March 2004.

190. Simon LS, Lanza FL, Lipsky PE, Hubbard RC, Talwalker S, Schwartz BD, *et al*. Preliminary study of the safety and efficacy of SC-58635, a novel cyclooxygenase 2 inhibitor: efficacy and safety in two placebo-controlled trials in osteoarthritis and rheumatoid arthritis, and studies of gastrointestinal and platelet effects. *Arthritis Rheum* 1998;**41**:1591–602.

191. Bensen WG, Fiechtner JJ, McMillen JI, Zhao WW, Yu SS, Woods EM, *et al*. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. *Mayo Clin Proc* 1999;**74**:1095–105.

192. Zhao SZ, McMillen JI, Markenson JA, Dedhiya SD, Zhao WW, Osterhaus JT, *et al*. Evaluation of the functional status aspects of health-related quality of life of patients with osteoarthritis treated with celecoxib. *Pharmacotherapy* 1999;**19**:1269–78.

193. Lanier WL, Scheife RT, Bensen WG, Zhao SZ. Erratum: Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial [*Mayo Clinic Proceedings* (November 1999) **74** (1095–1105)]. *Mayo Clin Proc* 2000;**75**:1340–1.

194. Williams GW, Ettlinger RE, Ruderman EM, Hubbard RC, Lonien ME, Yu SS, *et al*. Treatment of osteoarthritis with a once-daily dosing regimen of celecoxib: a randomized, controlled trial. *J Clin Rheumatol* 2000;**6**:65–74.

195. Goldstein J, Eisen G, Bensen W, Agrawal N, Singh G, Pavelka K, *et al*. SUCCESS in osteoarthritis (OA) trial: celecoxib significantly reduces the risk of upper gastrointestinal (UGI) hospitalizations compared to diclofenac and naproxen in 13,274 randomized patients with OA [abstract SAT0097]. Annual European Congress of Rheumatology, EULAR 2001, Prague.

196. Kivitz AJ, Moskowitz RW, Woods E, Hubbard RC, Verburg KM, Lefkowith JB, *et al*. Comparative efficacy and safety of celecoxib and naproxen in the treatment of osteoarthritis of the hip. *J of Int Med Res* 2001;**29**:467–79.

197. McKenna F, Weaver A, Fiechtner JJ, Bello AE, Fort JG. COX-2 specific inhibitors in the management of osteoarthritis of the knee: A placebo-controlled, randomized, double-blind study. *J Clin Rheumatol* 2001;**7**(3 Suppl):151–9.

198. McKenna F, Borenstein D, Wendt H, Wallemark C, Lefkowith JB, Geis GS. Celecoxib versus diclofenac in the management of osteoarthritis of the knee. *Scand J Rheumatol* 2001;**30**:11–18.

199. McKenna F, Arguelles L, Burke T, Lefkowith J, Geis GS. Upper gastrointestinal tolerability of celecoxib compared with diclofenac in the treatment of osteoarthritis and rheumatoid arthritis. *Clin Exp Rheumatol* 2002;**20**:35–43.

200. Williams GW, Hubbard RC, Yu SS, Zhao W, Geis GS. Comparison of once-daily and twice-daily administration of celecoxib for the treatment of osteoarthritis of the knee. *Clin Ther* 2001; **23**:213–27.

201. Suarez-Otero R, Robles-San Roman M, Jaimes-Hernandez J, Oropeza-De La Madrid E, Medina-Penaloza RM, Rosas-Ramos R, *et al*. Efficacy and safety of diclofenac–cholestyramine and celecoxib in osteoarthritis. *Proc West Pharmacol Soc* 2002; **45**:26–8.

202. Gibofsky A, Williams GW, McKenna F, Fort JG. Comparing the efficacy of cyclooxygenase 2-specific inhibitors in treating osteoarthritis: appropriate trial design considerations and results of a randomized, placebo-controlled trial. *Arthritis Rheum* 2003;**48**:3102–11.

203. Hawel R, Klein G, Singer F, Mayrhofer F, Kahler ST. Comparison of the efficacy and tolerability of dexibuprofen and celecoxib in the treatment of osteoarthritis of the hip. *Int J Clin Pharmacol Ther* 2003;**41**:153–64.

204. Pincus T, Koch G, Lei H, Mangal B, Sokka T, Moskowitz R, *et al*. Patient preference for placebo, acetaminophen (paracetamol) or celecoxib efficacy studies (PACES): two randomized, double blind, placebo controlled, crossover clinical trials in patients with knee or hip osteoarthritis. *Ann Rheum Dis* 2004;**63**:931–9.

205. Pincus T, Fort JF, Mangal B, Koch G, Wolfe F, Moskowitz R, *et al*. Patient preference for placebo, acetaminophen (paracetamol), or celecoxib effectiveness study (PACE-1): a double-blind, randomized, cross-over clinical trial in patients with osteoarthritis of the hip or knee [abstract OP0028]. Annual European Congress of Rheumatology, EULAR 2003, Lisbon.

206. Sowers J, White W, Pitt B, Whelton A, Simon L, Van Ingen H, *et al*. Rofecoxib, but not celecoxib, at doses providing equal OA efficacy, increases mean 24-hr systolic blood pressure in treated hypertensive patients with osteoarthritis and type 2 diabetes mellitus [abstract FRI0279]. (Abstract) Annual European Congress of Rheumatology, EULAR 2003, Lisbon.

207. Hawkey C, PUCCINI Group. Reduced cumulative incidence of gastroduodenal ulcers with two doses of a new coxib, COX189, compared with standard therapeutic doses of ibuprofen in osteoarthritis patients [abstract]. Digestive Disease Week (DDW), 19–22 May 2002, San Francisco.

208. Fleischmann R, Sheldon E, Maldonado Cocco J, Yu S, Dutta D, Usiskin K. A prospective randomized 13-week study evaluating the efficacy of lumiracoxib in patients with osteoarthritis of the knee [abstract FRI0233]. Annual European Congress of Rheumatology, EULAR 2003.

209. Novartis. Lumiracoxib Study 0109. 2004 submission (commercial-in-confidence). 2004.

210. Tannenbaum H, Berenbaum F, Reginster J-Y, Zacher J, Robinson J, Poor G, *et al*. Lumiracoxib is effective in the treatment of osteoarthritis of the knee: a 13-week, randomized, double-blind study versus placebo and celecoxib. *Ann Rheum Dis* 2004;**63**:1419–26.

211. Emery P, Zeidler H, Kvien TK, Guslandi M, Naudin R, Stead H, *et al*. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. *Lancet* 1999;**354**:2106–11.

212. Simon LS, Weaver AL, Graham DY, Kivitz AJ, Lipsky PE, Hubbard RC, *et al*. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA* 1999;**282**:1921–8.

213. Zhao SZ, Fiechtner JI, Tindall EA, Dedhiya SD, Zhao WW, Osterhaus JT, *et al*. Evaluation of health-related quality of life of rheumatoid arthritis patients treated with celecoxib. *Arthritis Care Res* 2000;**13**:112–21.

214. Kivitz AJ, Nayiager S, Schimansky T, Gimona A, Thurston HJ, Hawkey C. Reduced incidence of gastroduodenal ulcers associated with lumiracoxib compared with ibuprofen in patients with

rheumatoid arthritis. *Aliment Pharmacol Ther* 2004; **19**:1189–98.

215. Witter J. *Celebrex capsules (celecoxib) NDA 20-998/ S-009 Medical Officer Review*. Food & Drug Administration; 2000. URL: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_03_med.pdf. Accessed 17 March 2004.
216. White WB, Faich G, Whelton A, Maurath C, Ridge NJ, Verburg KM, *et al*. Comparison of thromboembolic events in patients treated with celecoxib, a cyclooxygenase-2 specific inhibitor, versus ibuprofen or diclofenac. *Am J Cardiol* 2002;**89**:425–30.
217. Juni P, Rutjes AW, Dieppe PA. Are selective COX 2 inhibitors superior to traditional non steroidal anti-inflammatory drugs? *BMJ* 2002;**324**:1287–8.
218. Budenholzer BR. Are selective COX 2 inhibitors superior to traditional NSAIDs? Rofecoxib did not provide unequivocal benefit over traditional NSAIDs. [letter]. *BMJ* 2002;**325**:161.
219. Goldstein JL, Eisen GM, Burke TA, Pena BM, Lefkowith J, Geis GS. Dyspepsia tolerability from the patients' perspective: a comparison of celecoxib with diclofenac. *Aliment Pharmacol Ther* 2002;**16**:819–27.
220. Goldstein JL, Correa P, Zhao WW, Burr AM, Hubbard RC, Verburg KM, *et al*. Reduced incidence of gastroduodenal ulcers with celecoxib, a novel cyclooxygenase-2 inhibitor, compared to naproxen in patients with arthritis. *Am J Gastroenterol* 2001;**96**:1019–27.
221. Pfizer and Searle. Celecoxib Study 021. 2001 submission (commercial-in-confidence). 2001.
222. Novartis. Lumiracoxib Study 0114. 2004 submission (commercial-in-confidence). 2004.
223. Pfizer. Celecoxib Study 216. 2004 submission (commercial-in-confidence). 2004.
224. Pfizer. Celecoxib Study 096 (SUCCESS-1). 2004 submission (commercial-in-confidence). 2004.
225. Pfizer. Celecoxib Study 211. 2004 submission (commercial-in-confidence). 2004.
226. Pfizer and Searle. Celecoxib Study 071. 2001 submission (commercial-in-confidence). 2001.
227. Pfizer and Searle. Celecoxib Study 023. 2001 submission (commercial-in-confidence). 2001.
228. Niccoli L, Bellino S, Cantini F. Renal tolerability of three commonly employed non-steroidal anti-inflammatory drugs in elderly patients with osteoarthritis. *Clin Exp Rheumatol* 2002;**20**:201–7.
229. Ehrich EW, Schnitzer TJ, McIlwain H, Levy R, Wolfe F, Weisman M, *et al*. Effect of specific COX-2 inhibition in osteoarthritis of the knee: a 6 week double blind, placebo controlled pilot study of rofecoxib. *J Rheumatol* 1999;**26**:2438–47.
230. Cannon GW, Caldwell JR, Holt P, McLean B, Seidenberg B, Bolognese J, *et al*. Rofecoxib, a specific inhibitor of cyclooxygenase 2, with clinical efficacy comparable with that of diclofenac sodium: results of a one-year, randomized, clinical trial in patients with osteoarthritis of the knee and hip. *Arthritis Rheum* 2000;**43**:978–87.
231. Cannon GW, Krupa DA, Sperling R, Reicin A, Van Adelsberg J. Two-year efficacy of rofecoxib and diclofenac in treatment of knee and hip osteoarthritis (OA) [abstract FRI0228 and poster]. Annual European Congress of Rheumatology, EULAR 2003, Lisbon.
232. Day R, Morrison B, Luza A, Castaneda O, Strusberg A, Nahir M, *et al*. A randomized trial of the efficacy and tolerability of the COX-2 inhibitor rofecoxib vs ibuprofen in patients with osteoarthritis. *Arch Intern Med* 2000;**160**:1781–7.
233. Bolognese JA, Ehrich EW, Schnitzer TJ. Precision of composite measures of osteoarthritis efficacy in comparison to that of individual endpoints. *J Rheumatol* 2001;**28**:2700–4.
234. Hawkey C, Laine L, Simon T, Beaulieu A, Maldonado-Cocco J, Acevedo E, *et al*. Comparison of the effect of rofecoxib (a cyclooxygenase 2 inhibitor), ibuprofen, and placebo on the gastroduodenal mucosa of patients with osteoarthritis: a randomized, double-blind, placebo-controlled trial. The Rofecoxib Osteoarthritis Endoscopy Multinational Study Group. *Arthritis Rheum* 2000;**43**:370–7.
235. Saag K, van der HD, Fisher C, Samara A, DeTora L, Bolognese J, *et al*. Rofecoxib, a new cyclooxygenase 2 inhibitor, shows sustained efficacy, comparable with other nonsteroidal anti-inflammatory drugs: a 6-week and a 1-year trial in patients with osteoarthritis. *Arch Family Med* 2000;**9**:1124–34.
236. Acevedo E, Castaneda O, Ugaz M, Beaulieu AD, Pons-Estel B, Caeiro F, *et al*. Tolerability profiles of rofecoxib (Vioxx) and Arthrotec. A comparison of six weeks treatment in patients with osteoarthritis. *Scand J Rheumatol* 2001;**30**:19–24.
237. Ehrich EW, Bolognese JA, Watson DJ, Kong SX. Effect of rofecoxib therapy on measures of health-related quality of life in patients with osteoarthritis. *Am J Managed Care* 2001;**7**:609–16.
238. Ehrich E, Schnitzer T, Kivitz A, Weaver A, Wolfe F, Morrison B, *et al*. MK-966, a highly selective COX-2 inhibitor, was effective in the treatment of osteoarthritis (OA) of the knee and hip in a 6-week placebo controlled study [abstract 330]. *Arthritis Rheum* 1997;**40**(Suppl 9):S85.
239. Ehrich E, Bolognese J, Watson DJ, Kong SX, Stem S, Mease P, *et al*. The effect of MK-0966 (VIOXX™), a COX-2 specific inhibitor, on health-related quality-of-life in osteoarthritis patients [abstract 197]. *Rheumatol Eur* 1998;**27**(Suppl 2):119.

240. Ehrich E, Bolognese J, Kong S, Watson DJ, Zeng Q, Seidenberg B. Improvements in SF-36 mental health domains with treatment of OA: a result of decreased pain and disability or independent mechanisms? [abstract 1134]. *Arthritis Rheum* 1998;**41**(Suppl 9):S221.

241. Ehrich E, Schnitzer T, Weaver A, Brabham AM, Schiff M, Ko A, *et al*. Treatment with MK-966 (VIOXX™), a specific COX-2 inhibitor, resulted in clinical improvement in osteoarthritis (OA) of the knee and hip, that was sustained over six months [abstract 198]. *Rheumatol Eur* 1998;**27**(Suppl 2):119.

242. Truitt KE, Sperling RS, Ettinger WH Jr, Greenwald M, DeTora L, Zeng Q, *et al*. A multicenter, randomized, controlled trial to evaluate the safety profile, tolerability, and efficacy of rofecoxib in advanced elderly patients with osteoarthritis. *Aging Clin Exp Res* 2001;**13**:112–21.

243. Myllykangas-Luosujärvi R, Lu HS, Chen SL, Choon D, Amante C, Chow CT, *et al*. Comparison of low-dose rofecoxib versus 1000 mg naproxen in patients with osteoarthritis. Results of two randomized treatment trials of six weeks duration. *Scand J Rheumatol* 2002;**31**:337–44.

244. Lisse JR, Perlman M, Johansson G, Shoemaker JR, Schechtman J, Skalky CS, *et al*. Gastrointestinal tolerability and effectiveness of rofecoxib versus naproxen in the treatment of osteoarthritis: a randomized, controlled trial. *Ann Intern Med* 2003;**139**:539–46.

245. Moskowitz RW, Jones JB, Cawkwell G. Valdecoxib 10 mg demonstrates a rapid onset of action following a single dose in patients with OA of the knee in a flare state [abstract FRI0277]. Annual European Congress of Rheumatology, EULAR 2003, Lisbon.

246. Schnitzer TJ, Truitt K, Fleischmann R, Dalgin P, Block J, Zeng Q, *et al*. The safety profile, tolerability, and effective dose range of rofecoxib in the treatment of rheumatoid arthritis. Phase II Rofecoxib Rheumatoid Arthritis Study Group. *Clin Ther* 1999;**21**:1688–702.

247. Geusens PP, Truitt K, Sfikakis P, Zhao PL, DeTora L, Shingo S, *et al*. A placebo and active comparator-controlled trial of rofecoxib for the treatment of rheumatoid arthritis. *Scand J Rheumatol* 2002;**31**:230–8.

248. Hawkey CJ, Laine L, Simon T, Quan H, Shingo S, Evans J, *et al*. Incidence of gastroduodenal ulcers in patients with rheumatoid arthritis after 12 weeks of rofecoxib, naproxen, or placebo: a multicentre, randomised, double blind study [published erratum appears in *Gut* 2003;**52**:1800]. *Gut* 2003;**52**:820–6.

249. Pfizer. Celecoxib Study 002. 2004 submission (commercial-in-confidence). 2004.

250. Gottesdiener K, Schnitzer T, Fisher C, Bockow B, Markenson J, Ko A, *et al*. Results of a randomized, dose-ranging trial of etoricoxib in patients with osteoarthritis [published erratum appears in *Rheumatology* 2003;**42**:814]. *Rheumatology* 2002; **41**:1052–61.

251. Gottesdiener K, Schnitzer T, Fisher C, Bockow B, Markenson J, Ko A, *et al*. Erratum: results of a randomized, dose-ranging trial of etoricoxib in patients with osteoarthritis [*Rheumatology* (2002) vol. 41 (1052-1061)]. *Rheumatology* 2003;**42**:814.

252. Leung AT, Malmstrom K, Gallacher AE, Sarembock B, Poor G, Beaulieu A, *et al*. Efficacy and tolerability profile of etoricoxib in patients with osteoarthritis: a randomized, double-blind, placebo and active-comparator controlled 12-week efficacy trial. *Curr Med Res Opin* 2002;**18**:49–58.

253. Hunt RH, Harper S, Watson DJ, Yu C, Quan H, Lee M, *et al*. The gastrointestinal safety of the COX-2 selective inhibitor etoricoxib assessed by both endoscopy and analysis of upper gastrointestinal events. *Am J Gastroenterol* 2003; **98**:1725–33.

254. Zacher J, Feldman D, Gerli R, Scott D, Hou S-M, Uebelhart D, *et al*. A comparison of the therapeutic efficacy and tolerability of etoricoxib and diclofenac in patients with osteoarthritis [published erratum appears in *Curr Med Res Opin* 2004;**20**:1689]. *Curr Med Res Opin* 2003; **19**:725–36.

255. Collantes E, Curtis SP, Lee KW, Casas N, McCarthy T, Melian A, *et al*. A multinational randomized, controlled, clinical trial of etoricoxib in the treatment of rheumatoid arthritis [ISRCTN25142273]. *BMC Family Pract* 2002;**3**:10.

256. Matsumoto AK, Melian A, Mandel DR, McIlwain HH, Borenstein D, Zhao PL, *et al*. A randomized, controlled, clinical trial of etoricoxib in the treatment of rheumatoid arthritis. *J Rheumatol* 2002;**29**:1623–30.

257. Hunt RH, Harper S, Callegari P, Yu C, Quan H, Evans J, *et al*. Complementary studies of the gastrointestinal safety of the cyclo-oxygenase-2-selective inhibitor etoricoxib. *Aliment Pharmacol Ther* 2003;**17**:201–10.

258. Fiechtner JJ, Sikes D, Recker D. A double-blind, placebo-controlled dose ranging study to evaluate the efficacy of valdecoxib, a novel COX-2 specific inhibitor, in treating the signs and symptoms of osteoarthritis of the knee [abstract OP0048]. Annual European Congress of Rheumatology, EULAR 2001, Prague.

259. Kivitz A, Eisen G, Zhao WW, Bevirt T, Recker DP. Randomized placebo-controlled trial comparing efficacy and safety of valdecoxib with naproxen in patients with osteoarthritis. *J Family Pract* 2002; **51**:530–7.

260. Makarowski W, Zhao WW, Bevirt T, Recker DP. Efficacy and safety of the COX-2 specific inhibitor valdecoxib in the management of osteoarthritis of the hip: a randomized, double-blind, placebo-controlled comparison with naproxen. *Osteoarthritis Cartilage* 2002;**10**:290–6.

261. Sikes DH, Agrawal NM, Zhao WW, Kent JD, Recker DP, Verburg KM. Incidence of gastroduodenal ulcers associated with valdecoxib compared with that of ibuprofen and diclofenac in patients with osteoarthritis. *Eur J Gastroenterol Hepatol* 2002;**14**:1101–11.

262. Pfizer. Valdecoxib Study 063. 2004 submission (commercial-in-confidence). 2004.

263. Pfizer. Valdecoxib Study 047. 2004 submission (commercial-in-confidence). 2004.

264. Bensen W, Weaver A, Espinoza L, Zhao WW, Riley W, Paperiello B, *et al*. Efficacy and safety of valdecoxib in treating the signs and symptoms of rheumatoid arthritis: a randomized, controlled comparison with placebo and naproxen. *Rheumatology* 2002;**41**:1008–16.

265. Pavelka K, Recker DP, Verburg KM. Valdecoxib is as effective as diclofenac in the management of rheumatoid arthritis with a lower incidence of gastroduodenal ulcers: results of a 26-week trial. *Rheumatology* 2003;**42**:1207–15.

266. Pfizer. Valdecoxib Study 016. 2004 submission (commercial-in-confidence). 2004.

267. Pfizer. Valdecoxib Study 061. 2004 submission (commercial-in-confidence). 2004.

268. Pfizer. Valdecoxib Study 015. 2004 submission (commercial-in-confidence). 2004.

269. Flandermeyer A, Rosenberger S. Integrated clinical and statistical report for a multicenter, double-blind, parallel group study comparing the incidence of gastroduodenal ulcer associated with SC-58635 200 mg bid with that of naproxen 500 mg bid taken for 12 weeks in patients with osteoarthritis or rheumatoid arthritis. (Study 62 – unpublished). 1998.

270. Schnitzer TJ, Geusens P, Hasler P, Patel SK, Poor G, Senftleber I, *et al*. Efficacy and safety of COX189 in osteoarthritis: a multi-national study [abstract 1616]. *Arthritis Rheum* 2000;**43**(Suppl 9): S336.

271. Benevolenskaya L, Tüzün S, Hagin E, Moore A, Gimona A. Lumiracoxib is effective in relieving symptoms of knee or hip osteoarthritis after 4 weeks of treatment: results from a randomized, placebo-controlled trial [abstract FRI0246]. Annual European Congress of Rheumatology, EULAR 2003, Lisbon.

272. Grifka J, Zacher J, Brown J, Seriolo B, Lee A, Moore A, *et al*. Lumiracoxib is effective and well tolerated in patients with osteoarthritis of the hand: results from a randomized, placebo-controlled trial [abstract FRI0222]. Annual European Congress of Rheumatology, EULAR 2003, Lisbon.

273. Farkouh ME, Kirshner H, Harrington RA, Ruland S, Verheugt FW, Schnitzer TJ, *et al*. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. *Lancet* 2004;**364**:675–84.

274. Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehrsam E, *et al*. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet* 2004;**364**:665–74.

275. Hawkey CJ, Farkouh M, Gitton X, Ehrsam E, Huels J, Richardson P. Therapeutic arthritis research and gastrointestinal event trial of lumiracoxib – study design and patient demographics. *Aliment Pharmacol Ther* 2004; **20**:51–63.

276. Geusens P, Alten R, Rovensky J, Sloan V, Krammer G, Kralidis G, *et al*. Efficacy, safety and tolerability of lumiracoxib in patients with rheumatoid arthritis: results of a randomized double-blind study [abstract]. Annual Meeting of the American College of Rheumatology (ACR) 2003, 24–28 October, Orlando, FL.

277. Scott G, Rordorf C, Milosavljev S, Chase W, Fleischmann R, Kivitz A. Multiple-dose lumiracoxib shows rapid absorption and cyclooxygenase-2 (COX-2) selectivity without accumulation in patients with rheumatoid arthritis [poster P-197] [abstract]. 6th Congress of the European Association of Clinical Pharmacology and Therapeutics (EAPCT), 24–28 June 2003, Istanbul.

278. Novartis. Lumiracoxib Study A2335. 2004 submission (commercial-in-confidence). 2004.

279. Novartis. Lumiracoxib Study 0105. 2004 submission (commercial-in-confidence). 2004.

280. Novartis. Lumiracoxib Study 0128. 2004 submission (commercial-in-confidence). 2004.

281. Novartis. Lumiracoxib Study 2312. 2004 submission (commercial-in-confidence). 2004.

282. Whelton A, Fort JG, Puma JA, Normandin D, Bello AE, Verburg KM, *et al*. Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. [published appears in *Am J Ther* 2001;**8**:220]. *Am J Ther* 2001;**8**:85–95.

283. Whelton A, Fort JG, Puma JA, Normandin D, Bello AE, Verburg KM. Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized,

controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. *Am J Managed Care* 2002;**8**(15 Suppl):S371–82.

284. Whelton A, White WB, Bello AE, Puma JA, Fort JG, SUCCESS-VII Investigators. Effects of celecoxib and rofecoxib on blood pressure and edema in patients > or =65 years of age with systemic hypertension and osteoarthritis. *Am J Cardiol* 2002;**90**:959–63.

285. Geba GP, Weaver AL, Polis AB, Dixon ME, Schnitzer TJ, VACT Group. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: a randomized trial [published erratum appears in *JAMA* 2002;**287**:989]. *JAMA* 2002; **287**:64–71.

286. Pfizer. Valdecoxib Study 143. 2004 submission (commercial-in-confidence). 2004.

287. Hawkey CC, Svoboda P, Fiedorowicz-Fabrycy IF, Nasonov EL, Pikhlak EG, Cousin M, *et al*. Gastroduodenal safety and tolerability of lumiracoxib compared with ibuprofen and celecoxib in patients with osteoarthritis. *J Rheumatol* 2004;**31**:1804–10.

288. Novartis. Lumiracoxib Study 2307. 2004 submission (commercial-in-confidence). 2004.

289. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the *BMJ*. 1996;**313**:275–83.

290. Marshall JK, Pellissier JM, Attard CL, Kong SX, Marentette MA. Incremental cost-effectiveness analysis comparing rofecoxib with nonselective NSAIDs in osteoarthritis: Ontario Ministry of Health perspective. *Pharmacoeconomics* 2001; **19**:1039–49.

291. Pellissier JM, Straus WL, Watson DJ, Kong SX, Harper SE. Economic evaluation of rofecoxib versus nonselective nonsteroidal anti-inflammatory drugs for the treatment of osteoarthritis. *Clin Ther* 2001;**23**:1061–79.

292. Moore RA, Phillips CJ, Pellissier JM, Kong SX. Health economic comparisons of rofecoxib versus conventional nonsteroidal antiinflammatory drugs for osteoarthritis in the United Kingdom. *J Med Econ* 2001;**4**:1–17.

293. Zabinski RA, Burke TA, Johnson J, Lavoie F, Fitzsimon C, Tretiak R, *et al*. An economic model for determining the costs and consequences of using various treatment alternatives for the management of arthritis in Canada. *Pharmacoeconomics* 2001;**19**(Suppl 1):49–58.

294. Haglund U, Svarvar P. The Swedish ACCES model: predicting the health economic impact of celecoxib in patients with osteoarthritis or rheumatoid arthritis. *Rheumatology* 2000; **39**(Suppl 2):51–6.

295. Chancellor JV, Hunsche E, de Cruz E, Sarasin FP. Economic evaluation of celecoxib, a new cyclo-oxygenase 2 specific inhibitor, in Switzerland. *Pharmacoeconomics* 2001;**19**(Suppl 1):59–75.

296. Svarvar P, Aly A. Use of the ACCES model to predict the health economic impact of celecoxib in patients with osteoarthritis or rheumatoid arthritis in Norway. *Rheumatology* 2000;**39**(Suppl 2):43–50.

297. El-Serag HB, Graham DY, Richardson P, Inadomi JM. Prevention of complicated ulcer disease among chronic users of nonsteroidal anti-inflammatory drugs: the use of a nomogram in cost-effectiveness analysis. *Arch Intern Med* 2002; **162**:2105–10.

298. Spiegel BM, Targownik L, Dulai GS, Gralnek IM. The cost-effectiveness of cyclooxygenase-2 selective inhibitors in the management of chronic arthritis. *Ann Int Med* 2003;**138**:795–806.

299. Maetzel A, Krahn M, Naglie G. The cost effectiveness of rofecoxib and celecoxib in patients with osteoarthritis or rheumatoid arthritis. *Arthritis Rheum* 2003;**49**:283–92.

300. Rafter N, Milne R, Jackson R. *Listing rofecoxib and celecoxib in the Pharmaceutical Schedule*. Technology Assessment Report No. 55. Wellington, New Zealand: PHARMAC, Pharmaceutical Management Agency; 2003.

301. Kamath CC, Kremers HM, Vanness DJ, O'Fallon WM, Cabanela RL, Gabriel SE. The cost-effectiveness of acetaminophen, NSAIDs, and selective COX-2 inhibitors in the treatment of symptomatic knee osteoarthritis. *Value Health* 2003;**6**:144–57.

302. Bae SC, Corzillius M, Kuntz KM, Liang MH. Cost-effectiveness of low dose corticosteroids versus non-steroidal anti-inflammatory drugs and COX-2 specific inhibitors in the long-term treatment of rheumatoid arthritis. *Rheumatology* 2003;**42**:46–53.

303. Tavakoli M. Modelling therapeutic strategies in the treatment of osteoarthritis: an economic evaluation of meloxicam versus diclofenac and piroxicam. *Pharmacoeconomics* 2003;**21**:443–54.

304. Fendrick AM, Bandekar RR, Chernew ME, Scheiman JM. Role of initial NSAID choice and patient risk factors in the prevention of NSAID gastropathy: A decision analysis. *Arthritis Rheum* 2002;**47**:36–43.

305. Maetzel A, Krahn M, Naglie G. *The cost-effectiveness of celecoxib and rofecoxib in patients with osteoarthritis or rheumatoid arthritis*. Technology Report No 23. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2001.

306. Ekstrom P, Carling L, Wetterhus S, Wingren PE, Anker-Hansen O, Lundegardh G, *et al*. Prevention of peptic ulcer and dyspeptic symptoms with omeprazole in patients receiving continuous non-steroidal anti-inflammatory drug therapy. A Nordic multicentre study. *Scand J Gastroenterol* 1996;**31**:753–8.

307. Sanmuganathan PS, Ghahramani P, Jackson PR, Wallis EJ, Ramsay LE. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from a meta-analysis of randomised trials. *Heart* 2001;**85**:265–71.

308. Kimmel SE, Berlin JA, Reilly M, Jaskowiak J, Kishel L, Chittams J, *et al*. The effects of nonselective non-aspirin non-steroidal anti-inflammatory medications on the risk of nonfatal myocardial infarction and their interaction with aspirin. *J Am Coll Cardiol* 2004;**43**:985–90.

309. Katschinski B, Logan R, Davies J, Faulkner G, Pearson J, Langman M. Prognostic factors in upper gastrointestinal bleeding. *Dig Dis Sci* 1994; **39**:706–12.

310. Hooper L, Brown TJ, Elliott R, Payne K, Roberts C, Symmons D. The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs: systematic review. *BMJ* 2004;**329**:948–52.

311. Fryback DG, Dasbach EJ, Klein R, Klein BEK, Dorn N, Peterson K, *et al*. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. *Med Decis Making* 1993;**13**:89–102.

312. Curtis JP, Krumholz HM. The case for an adverse interaction between aspirin and non-steroidal anti-inflammatory drugs. *J Am Coll Cardiol* 2004; **43**:991–3.

313. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, *et al*. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005; **352**:1092–102.

314. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, *et al*. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;**352**:1071–80.

315. Nussmeier NA, Whelton AA, Brown MT, Langford RM, Hoeft A, Parlow JL, *et al*. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *N Engl J Med* 2005;**352**:1081–91.

316. Jenkins JK, Seligman PJ, Galson S. *Analysis and recommendations for Agency action regarding non-steroidal anti-inflammatory drugs and cardiovascular risk*. Food and Drug Administration. URL: http://www.fda.gov/cder/drug/infopage/cox2/NSAIDdecisionMemo.pdf. Accessed 20 April 2005.

317. Lenzer J. Pfizer is asked to suspend sales of painkiller. *BMJ* 2005;**330**:862-a.

318. European Medicines Agency. European Medicines Agency concludes action on COX-2 inhibitors. *European Medicines Agency*. URL: http://www.emea.eu.int/pdfs/human/press/pr/20776605en.pdf. Accessed 31 August 2006.

319. European Medicines Agency. *European Medicines Agency update on non-selective NSAIDs*. URL: http://www.emea.eu.int/pdfs/human/press/pr/29896405en.pdf. Accessed 31 August 2006.

320. National Institute for Health and Clinical Excellence. *The interpretation of the NICE Technology Appraisal No. 27: use of Cox II inhibitors for osteoarthritis and rheumatoid arthritis, in the context of license changes made in 2006*. London: National Institute for Health and Clinical Excellence. URL: http://www.nice.org.uk/page.aspx?o=289065. Accessed 24 August 2006.

321. Graham DJ. COX-2 inhibitors, other NSAIDs, and cardiovascular risk. *JAMA* 2006;**296**:1653–6.

322. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006;**332**:1302–8.

323. Zhang J, Ding EL, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmias events: meta-analysis of randomized trials. *JAMA* 2006;**296**:1619–32.

324. Cannon CP, Curtis SP, Bolognese JA, Laine L, MEDAL Steering Committee. Clinical trial design and patient demographics of the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) study program: cardiovascular outcomes with etoricoxib versus diclofenac in patients with osteoarthritis and rheumatoid arthritis. *Am Heart J* 2006;**152**:237–45.

325. Laine L, Curtis SP, Cryer B, Kaur A, Cannon CP. Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2007;**369**:465–73.

326. Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, *et al*. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2006;**368**:1771–81.

327. Pfizer. *PRECISION: Prospective randomized evaluation of celecoxib integrated safety vs ibuprofen or naproxen*. US National Institutes of Health (ClinicalTrials.gov). URL: http://www.clinicaltrials.gov/ct/gui/show/NCT00346216;jsessionid=9EEA34B53F397D4D47F460CD5373A9E1?order=43. Accessed 31 August 2006.

328. Oxman AD, Guyatt GH. Guidelines for reading literature reviews. *Can Med Assoc J* 1988; **138**:697–703.

329. Katz N. Coxibs: evolving role in pain management. *Semin Arthritis Rheum* 2002; **32**(3 Suppl 1):15–24.

330. Clemett D, Goa KL. Celecoxib: a review of its use in osteoarthritis, rheumatoid arthritis and acute pain [published erratum appears in *Drugs* 2001;**61**:498]. *Drugs* 2000;**59**:957–80.

331. Lipsky PE, Isakson PC. Outcome of specific COX-2 inhibition in rheumatoid arthritis. *J Rheumatol* 1997;**24**(Suppl 49):9–14.

332. Andelman SY. Etodolac, aspirin, and placebo in patients with degenerative joint disease: a twelve-week study. *Clin Ther* 1983;**5**:651–61.

333. Bianchi Porro G, Caruso I, Petrillo M, Montrone F, Ardizzone S. A double-blind gastroscopic evaluation of the effects of etodolac and naproxen on the gastrointestinal mucosa of rheumatic patients. *J Intern Med* 1991;**229**:5–8.

334. Bianchi Porro G, Petrillo M, Ardizzone S, Caruso I. Naproxene v etodolac: a controlled endoscopic study in patients with rheumatoid arthritis [abstract]. *Gut* 1988;**29**(Suppl 10):A1443.

335. Briancon D, Peterschmitt J, Laviec G. Double-blind parallel-group evaluation of the safety and efficacy of etodolac capsules compared with piroxicam capsules in patients with rheumatoid arthritis. *Acta Ther* 1991;**17**:35–47.

336. Ciompi ML, Puccetti L, Bazzichi L, Remorini E, Marotta G. Etodolac versus diclofenac: double-blind cross-over study in rheumatoid arthritis. *Int J Clin Pharmacol Res* 1989;**9**:217–22.

337. de Queiros MF. Double-blind comparison of etodolac and naproxen in the treatment of rheumatoid arthritis. *Clin Ther* 1991;**13**:38–46.

338. del Toro RA, Concepcion R. Twelve-week study of etodolac, aspirin, and placebo in patients with rheumatoid arthritis. *Clin Ther* 1983;**5**:436–44.

339. Delcambre B. Polyarthrite rhumatoide: efficacite, tolerance et benefice therapeutique compares de l'etodolac (600 mg/j) et de l'indometacine (100 mg/j) [in French]. *Rhumatologie* 1990; **42**:213–8.

340. Dick WC, Franchimont P, Veys E. Double-blind comparison of etodolac and piroxicam in the treatment of rheumatoid arthritis. *Clin Ther* 1993;**15**:148–59.

341. Edwards W. Etodolac, aspirin, and placebo in patients with rheumatoid arthritis: a 12-week study. *Clin Ther* 1983;**5**:495–503.

342. Fioravanti A, Vaccai D, Megale F, Dragonetti C, Iudice A, Marcolongo R. Single-blind, randomized, parallel-group study of etodolac and naproxen in patients with osteoarthritis. *Curr Ther Res Clin Exp* 1989;**46**:648–53.

343. Gordon GV, Polsky BG. Three-month trial of etodolac (Ultradol(TM)) compared with aspirin and placebo in patients with rheumatoid arthritis. *Curr Ther Res Clin Exp* 1983;**33**:89–99.

344. Jacob GB, Hart KK, Mullane JF. Placebo-controlled study of etodolac and aspirin in the treatment of rheumatoid arthritis. *Curr Ther Res Clin Exp* 1983;**33**:703–13.

345. Jacob G, Sanda M, Mullane J. Long-term evaluation of the efficacy and safety of etodolac in the treatment of rheumatoid arthritis. *Adv Ther* 1985;**2**:82–95.

346. Jacob G, Messina M, Caperton E. Safety and efficacy of etodolac, once or twice a day, in the treatment of active rheumatoid arthritis. *Curr Ther Res Clin Exp* 1985;**37**:1124–9.

347. Jacob G, Messina M, Kennedy J, Epstein C, Sanda M, Mullane J. Minimum effective dose of etodolac for the treatment of rheumatoid arthritis. *J Clin Pharmacol* 1986;**26**:195–202.

348. Jubb RW, Platt P, Price TR. Double-blind comparison of etodolac sustained-release tablets and piroxicam capsules in patients with rheumatoid arthritis: an interim report. *Curr Ther Res Clin Exp* 1992;**52**:769–79.

349. Khan FM, Williams PI. Double-blind comparison of etodolac SR and diclofenac SR in the treatment of patients with degenerative joint disease of the knee. *Curr Med Res Opin* 1992;**13**:1–12.

350. Liang TH, Hsu PN. Double-blind, randomised, comparative trial of etodolac SR versus diclofenac in the treatment of osteoarthritis of the knee. *Curr Med Res Opin* 2003;**19**:336–41.

351. Lonauer G, Tisscher JR, Lim HG, Bijlsma JW. Double-blind comparison of etodolac and diclofenac in patients with rheumatoid arthritis. *Curr Med Res Opin* 1993;**13**:70–7.

352. Porzio F, Schattenkirchner M. Double-blind comparison of etodolac sustained-release tablets and diclofenac sustained-release tablets in patients with rheumatoid arthritis. *Curr Ther Research, Clin Exp* 1993;**53**:144–53.

353. Sanda M, Collins SH, Mahady J. Three-month multicenter study of etodolac (Ultradol(TM)) in patients with osteoarthritis of the hip. *Curr Ther Res Clin Exp* 1983;**33**:782-92.

354. Schattenkirchner M. Double-blind comparison of etodolac and piroxicam in patients with rheumatoid arthritis. *Curr Med Res Opin* 1991; **12**:497–506.

355. Vetter G, Placchi M, Joubert L. Comparative efficacy of etodolac and placebo in rheumatoid arthritic patients. *Int J Clin Pharmacol Ther Toxicol* 1982;**20**:240–5.

356. Waltham-Weeks CD. Etodolac versus naproxen in rheumatoid arthritis: a double-blind crossover study. *Curr Med Res Opin* 1987;**10**:540–7.

357. Ghozlan PR, Bernhardt M, Velicitat P, Bluhmki E. Tolerability of multiple administration of intramuscular meloxicam: a comparison with intramuscular piroxicam in patients with rheumatoid arthritis or osteoarthritis. *Br J Rheumatol* 1996;**35**(Suppl 1):51–5.

358. Hettich M, Degner F, Sigmund R. The selective COX-2 inhibitor meloxicam improves patient outcome and quality of life [abstract]: European League Against Rheumatism, EULAR Congress, 1997, Vienna.

359. Hsu MY, Yang YHK, Yang CY, Chan KWA. Comparison of safety and efficacy between meloxicam and diclofenac in osteoarthritis patients [abstract]: International Congress on Clinical Pharmacy, 1997, Orlando, FL.

360. Huskisson EC, Ghozlan R, Kurthen R, Degner FL, Bluhmki E. A long-term study to evaluate the safety and efficacy of meloxicam therapy in patients with rheumatoid arthritis. *Br J Rheumatol* 1996;**35**(Suppl 1):29–34.

361. Lipscomb GR, Wallis N, Armstrong G, Rees WD. Gastrointestinal tolerability of meloxicam and piroxicam: a double-blind placebo-controlled study. *Br J Clin Pharmacol* 1998;**46**:133–7.

362. Prouse PJ, Bevis PJ, Bluhmki E, Distel M. Evaluation of the safety, tolerability, and efficacy of meloxicam tablets in patients with osteoarthritis. *Clin Ther* 1996;**18**:429–39.

363. Reginster JY, Distel M, Bluhmki E. A double-blind, three-week study to compare the efficacy and safety of meloxicam 7.5 mg and meloxicam 15 mg in patients with rheumatoid arthritis. *Br J Rheumatol* 1996;**35**(Suppl 1):17–21.

364. Geba GP, Polis AB, Najarian DK, Dixon ME, Storms WW, Weaver AL. Onset of efficacy and patient assessment of clinical response in osteoarthritis (OA): comparison of rofecoxib to nabumetone [abstract]. Annual Meeting of the American Geriatric Society, 9–13 May 2001, Chicago, IL.

365. Lanza FL, Rack MF, Simon TJ, Quan H, Bolognese JA, Hoover ME, *et al*. Specific inhibition of cyclooxygenase-2 with MK-0966 is associated with less gastroduodenal damage than either aspirin or ibuprofen. *Aliment Pharmacol Ther* 1999;**13**:761–7.

366. Saag K, Fisher C, McKay J, Ehrich E, Zhao P-L, Bolognese J, *et al*. MK-0966, a specific COX-2 inhibitor, has clinical efficacy comparable to ibuprofen in the treatment of knee and hip osteoarthritis (OA) in a 6-week controlled clinical trial [abstract 984]. *Arthritis Rheum* 1998; **41**(Suppl 9):S196.

367. Truitt KE, Lee M, DeTora LM, Anderson M, Zhao PL. Results of a pivotal (phase III) placebo and active comparator controlled efficacy trial of rofecoxib 12.5 and 25 mg in adult patients with rheumatoid arthritis (RA) [abstract 1897]. *Arthritis Rheum* 2001;**44**(Suppl):S369.

368. Rinder HM, Tracey JB, Souhrada M, Wang C, Gagnier RP, Wood CC. Effects of meloxicam on platelet function in healthy adults: a randomized, double-blind, placebo-controlled trial. *J Clin Pharmacol* 2002;**42**:881–6.

369. Combe B, Velicitat P, Garzon N, Bluhmki E. Comparison of intramuscular and oral meloxicam in rheumatoid arthritis patients. *Inflamm Res* 2001;**50**(Suppl 1):S10–16.

370. Mejjad O, Favre S, Dujardin F, Thomine J, Le Loët X, Weber J. Efficacy of etodolac on gait in hip osteoarthritis as assessed by Bessou's locometer: a randomized, crossover, double-blind study versus placebo. Groupe de Recherche sur le Handicap de L'Appareil Locomoteur. *Osteoarthritis Cartilage* 2000;**8**:230–5.

371. Bianchi M, Broggini M. A randomised, double-blind, clinical trial comparing the efficacy of nimesulide, celecoxib and rofecoxib in osteoarthritis of the knee. *Drugs* 2003;**63**(Suppl 1): 37–46.

372. Pawlotsky Y, Le Dantec P, Jacquelinet C, Lapicque F, Goasguen J, Perdriger A, *et al*. Influence of severity of chronic inflammatory joint disease on the pharmacokinetics of indomethacin and etodolac. *Rev Rhumatisme (English Edition)* 1996;**63**:179–87.

373. Reitblat T, Zamir D, Estis L, Priluk R, Drogenikov T, Viskoper JR. The different patterns of blood pressure elevation by rofecoxib and nabumetone. *J Hum Hyperten* 2002;**16**:431–4.

374. Gospodinoff A, Fiore L, Dardano B, Fiore D, Scapato P. [Open clinical study on the efficacy and tolerance of acemetacin in rheumatoid arthritis and osteoarthrosis] [in Italian]. *Clin Ter* 1989; **130**:109–13.

375. Llorente Melero MJ, Tenias Burillo JM, Zaragoza MA. Comparative incidence of upper gastrointestinal bleeding associated with individual non-steroidal anti-inflammatory drugs. *Rev Esp Enferm Dig* 2002;**94**:13–8.

376. Karaoglan B, Erten A, Ayhan F, Dumlu S, Oguz A, Erdem R. The effects of etodolac on the clinical course and gastric mucosal PGE of knee osteoarthritis. *Gazi Tip Dergisi* 1995;**6**:169–72.

377. Anderson KO, Bradley LA, Turner RA, Agudelo CA, Pisko EJ. Pain behavior of rheumatoid arthritis patients enrolled in experimental drug trials. *Arthritis Care Res* 1994;**7**:64–8.

378. Carrabba M, Galanti A, Paresce E, Angelini MRK, Torchiana E, Fichera G, *et al*. Gastrointestinal

effects of meloxicam versus piroxicam by means of gastroduodenoscopy in patients with rheumatoid arthritis [abstract]. *Scand J Rheumatol Suppl* 1996; **106**:55.

379. Layton D, Riley J, Wilton LV, Shakir SA. Safety profile of rofecoxib as used in general practice in England: results of a prescription-event monitoring study. *Br J Clin Pharmacol* 2003; **55**:166–74.

380. Tindall EA, Sharp JT, Burr A, Katz TK, Wallemark CB, Verburg K, *et al*. A 12-month, multicenter, prospective, open-label trial of radiographic analysis of disease progression in osteoarthritis of the knee or hip in patients receiving celecoxib. *Clin Ther* 2002;**24**:2051–63.

381. Bunyaratavej N, Keorochana S, Pithkul S. Safety and efficacy of meloxicam 7.5 mg in the treatment of osteoarthritis in Thai patients. *J Med Ass Thailand* 2001;**84**(Suppl 2):S542–6.

382. Tsvetkova ES, Alekseeva LI, Balabanova RM, Chichasova NV, Shostak NA, Shmidt EI. [Effectiveness and tolerance of celebrex in osteoarthrosis (data of a Russian study)] [in Russian]. *Ter Arkh* 2001;**73**:61–3.

383. Iakushin SS, Filonenko SP, Kosov IN, Sorokina OS. [The evaluation of the effectiveness and tolerance of movalis in patients with osteoarthrosis] [in Russian]. *Klin Med (Mosk)* 1999;**77**:47–9.

384. Bevis PJ, Bird HA, Lapham G. An open study to assess the safety and tolerability of meloxicam 15 mg in subjects with rheumatic disease and mild renal impairment. *Br J Rheumatol* 1996; **35** Suppl **1**:56–60.

385. Benhamou CL, Feldmann JL, Dropsy R. [Efficacy, tolerability and therapeutic benefit of etodolac (Lodine 200) in rheumatologic practice] [in French]. *Rev Med Interne* 1989;**10**:163–73.

386. Arboleya LR, de la Figuera E, Garcia MS, Aragon B. Experience of rofecoxib in patients with osteoarthritis previously treated with traditional non-steroidal anti-inflammatory drugs in Spain: results of phase 2 of the VICOXX study. *Curr Med Res Opin* 2003;**19**:288–97.

387. Schumacher HR Jr, Boice JA, Daikh DI, Mukhopadhyay S, Malmstrom K, Ng J, *et al*. Randomised double blind trial of etoricoxib and indometacin in treatment of acute gouty arthritis. *BMJ* 2002;**324**:1488–92.

388. Vidal L, Kneer W, Baturone M, Sigmund R. Meloxicam in acute episodes of soft-tissue rheumatism of the shoulder. *Inflamm Res* 2001; **50**(Suppl 1):S24–9.

389. Sigthorsson G, Crane R, Simon T, Hoover M, Quan H, Bolognese J, *et al*. COX-2 inhibition with rofecoxib does not increase intestinal permeability in healthy subjects: a double blind crossover study comparing rofecoxib with placebo and indomethacin. *Gut* 2000;**47**:527–32.

390. Hunt RH, Bowen B, Mortensen ER, Simon TJ, James C, Cagliola A, *et al*. A randomized trial measuring fecal blood loss after treatment with rofecoxib, ibuprofen, or placebo in healthy subjects. *Am J Med* 2000;**109**:201–6.

391. Leese PT, Recker DP, Kent JD. The COX-2 selective inhibitor, valdecoxib, does not impair platelet function in the elderly: Results of a randomized controlled trial. *J Clin Pharmacol* 2003;**43**:504–13.

392. Arnold JD, Salom IL, Berger AE. Comparison of gastrointestinal microbleeding associated with use of etodolac, ibuprofen, indomethacin, and naproxen in normal subjects. *Curr Ther Res Clin Exp* 1985;**37**:730–8.

393. Bolognese JA, Schnitzer TJ, Ehrich EW. Response relationship of VAS and Likert scales in osteoarthritis efficacy measurement. *Osteoarthritis Cartilage* 2003;**11**:499–507.

394. Knijff-Dutmer EA, Kalsbeek-Batenburg EM, Koerts J, van de Laar MA. Platelet function is inhibited by non-selective non-steroidal anti-inflammatory drugs but not by cyclo-oxygenase-2-selective inhibitors in patients with rheumatoid arthritis. *Rheumatology* 2002;**41**:458–61.

395. Ehrich EW, Davies GM, Watson DJ, Bolognese JA, Seidenberg BC, Bellamy N. Minimal perceptible clinical improvement with the Western Ontario and McMaster Universities osteoarthritis index questionnaire and global assessments in patients with osteoarthritis. *J Rheumatol* 2000;**27**:2635–41.

396. Rabeneck L, Wristers K, Goldstein JL, Eisen G, Dedhiya SD, Burke TA. Reliability, validity, and responsiveness of severity of dyspepsia assessment (SODA) in a randomized clinical trial of a COX-2-specific inhibitor and traditional NSAID therapy. *Am J Gastroenterol* 2002;**97**:32–9.

397. Schwartz JI, Agrawal NG, Wong PH, Bachmann KA, Porras AG, Miller JL, *et al*. Lack of pharmacokinetic interaction between rofecoxib and methotrexate in rheumatoid arthritis patients. *J Clin Pharmacol* 2001;**41**:1120–30.

398. Kosinski M, Zhao SZ, Dedhiya S, Osterhaus JT, Ware JE Jr. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. *Arthritis Rheum* 2000;**43**:1478–87.

399. Jallad NS, Sanda M, Salom IL, Perdomo CS, Garg DC, Mullane JF, *et al*. Gastrointestinal blood loss in arthritic patients receiving chronic dosing with etodolac and piroxicam. *Am J Med Sci* 1986; **292**:272–6.

400. Degner F. MELISSA and SELECT: double-blind clinical trials with meloxicam, diclofenac and

piroxicam in 15000 patients with osteoarthritis. *Scand J Rheumatol Suppl* 1996;**106**:60.

401. Towheed TE, Judd MJ, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* 2003;CD004257.
402. Tomita T, Ochi T, Sugano K, Uemura S, Makuch RW. Systematic review of NSAID-induced adverse reactions in patients with rheumatoid arthritis in Japan. *Mod Rheumatol* 2003;**13**:143–52.
403. Uemura S, Ochi T, Sugano K, Makuch RW. Systematic review for evaluation of tolerability of nonsteroidal antiinflammatory drugs in osteoarthritis patients in Japan. *J Orthop Sci* 2003; **8**:279–87.
404. Pham T. Comparative efficacy of antalgesics and non-steroidal anti-inflammatory drugs. *Presse Med* 2002;**31**:4S3–6.
405. Johnson DL, Hisel TM, Phillips BB, Guzman-Santos WM, Parent M. Effect of cyclooxygenase-2 inhibitors on blood pressure. *Ann Pharmacother* 2003;**37**:442–6.
406. Armstrong EP, Malone DC. The impact of nonsteroidal anti-inflammatory drugs on blood pressure, with an emphasis on newer agents. *Clin Ther* 2003;**25**:1–18.
407. Lexchin J. New drugs with novel therapeutic characteristics. Have they been subject to randomized controlled trials? *Can Family Physician* 2002;**48**:1487–92.
408. Fransen J, Stucki G. Current use of health status instruments in randomised controlled trials on patients with rheumatoid arthritis. *Dis Manage Health Outcomes* 1998;**3**:271–7.
409. Rochon PA, Gurwitz JH, Simms RW, Fortin PR, Felson DT, Minaker KL, *et al*. A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis. *Arch Intern Med* 1994;**154**:157–63.
410. Briancon D. International experience with etodolac therapy for rheumatoid arthritis: an interim report of comparative efficacy. *Clin Rheumatol* 1989;**8**(Suppl 1):63–72.
411. Hanft G, Turck D, Scheuerer S, Sigmund R. Meloxicam oral suspension: a treatment alternative to solid meloxicam formulations. *Inflamm Res* 2001;**50** Suppl 1:S35–7.
412. Dreiser RL. A comparison of the efficacy of etodolac SR (Lodine SR) and etodolac (Lodine) in patients with rheumatoid arthritis or osteoarthritis. *Rheumatol Int* 1993;**13**(2 Suppl):S13–18.
413. Dreiser RL. Etodolac 400 LP versus etodolac 200: comparative double blind study of etodolac 400 mg/daily (sustained release formulation) versus etodolac 200 mg twice daily (conventional formulation) in patients with osteoarthritis of the hip or the knee. *Rhumatologie* 1993;**45**:57–61.
414. Dreiser RL, Dropsy R. A double-blind, multicentric study of etodolac 300 mg twice daily verus 200 mg three times daily in patients with osteoarthritis of the knee. *Today's Ther Trends* 1992;**10**:87–100.
415. Degner FL, Huskisson EC, Narjes H, Bluhmki E. Randomised double-blind clinical test over 3 weeks to compare meloxicam 15 mg with piroxicam 20 mg by rheumatoid arthritis (RA) [abstract P140] [in German]. *Z Rheumatol* 1996; **55**(Suppl 1):113.
416. Huskisson EC, Narjes H, Bluhmki E. Efficacy and tolerance of meloxicam, a new NSAID, in daily oral doses of 15, 30 and 60 mg in comparison to 20 mg piroxicam in patients with rheumatoid arthritis. *Scand J Rheumatol* 1994;Suppl 98:115.
417. Towheed TE. Published meta-analyses of pharmacological therapies for osteoarthritis. *Osteoarthritis Cartilage* 2002;**10**:836–7.
418. Tukker JJ. Celecoxib versus diclofenac/omeprazole and the risk of bleeding ulcers. *Geneesmiddelenbulletin* 2003;**37**:43–4.
419. Meyerhoff J. Rofecoxib, 25 mg/d, was more effective than rofecoxib, 12.5 mg/d, celecoxib, or acetaminophen in osteoarthritis of the knee. *ACP J Club* 2002;**137**:26.
420. Laine L. Celecoxib was as effective as diclofenac plus omeprazole in reducing recurrent ulcer bleeding in arthritis. *ACP J Club* 2003;**139**:12.
421. Anonymous. Etoricoxib more effective than naproxen for rheumatoid arthritis. *Pharm J* 2002; **269**:273.
422. Silverfield JC, Kamin M, Wu SC, Rosenthal N, Study Group. Tramadol/acetaminophen combination tablets for the treatment of osteoarthritis flare pain: a multicenter, outpatient, randomized, double-blind, placebo-controlled, parallel-group, add-on study. *Clin Ther* 2002; **24**:282–97.
423. Roy V, Gupta U, Sharma S, Dhaon BK, Singh NP, Gulati P. Comparative efficacy and tolerability of nimesulide and piroxicam in osteoarthritis with specific reference to chondroprotection: a double blind randomised study. *J Indian Med Ass* 1999; **97**:442–5.
424. Prupas HM, Loose LD, Spindler JS, Dietz AJ Jr, Gum OB, Weisman MH, *et al*. Tenidap in patients with rheumatoid arthritis. A 4-week, placebo-controlled study. *Scand J Rheumatol* 1996; **25**:345–51.
425. Fioravanti A, Storri L, Di Martino S, Bisogno S, Oldani V, Scotti A, *et al*. A randomized, double-blind, multicenter trial of nimesulide-beta-cyclodextrin versus naproxen in patients with osteoarthritis. *Clin Ther* 2002;**24**:504–19.
426. Tarricone R, Martelli E, Parazzini F, Darba J, Le Pen C, Rovira J. Economic evaluation of

nimesulide versus diclofenac in the treatment of osteoarthritis in France, Italy and Spain. *Clin Drug Invest* 2001;**21**:453–64.

427. Spencer-Green G. Low dose etodolac in rheumatoid arthritis: a review of early studies. *J Rheum Suppl* 1997;**24**(Suppl 47):3–9.

428. Whelton A. COX-2-specific inhibitors and the kidney: effect on hypertension and oedema. *J Hypertens* 2002;**20**(Suppl 6):S31–5.

429. Cochrane DJ, Jarvis B, Keating GM. Etoricoxib. *Drugs* 2002;**62**:2637–51.

430. Pomp E. [A critical evaluation of side effect data on COX-2 inhibitors] [in Norwegian]. *Tidsskr Nor Laegeforen* 2002;**122**:476–80.

431. Schoenfeld P. An evidence-based approach to the gastrointestinal safety profile of COX-2-selective anti-inflammatories. *Gastroenterol Clin North Am* 2001;**30**:1027–44.

432. Gehling M, Niebergall H. [Non-opioid analgesics and co-analgesics in therapy of chronic pain] [in German]. *Z Arztl Fortbild Qualitatssich* 1998; **92**:41–6.

433. Wasielewski S. Celecoxib has fewer gastrointestinal side-effects than diclofenac. *Dtsch Apoth Ztg* 2000; **140**:41–3.

434. Oviedo JAW. Gastroprotection by coxibs: what do the Celecoxib Long-Term Arthritis Safety Study and the Vioxx Gastrointestinal Outcomes Research Trial tell us? *Rheum Dis Clin North Am* 2003; **29**:769–88.

435. Chenevard R, Hurlimann D, Bechir M, Enseleit F, Spieker L, Hermann M, *et al*. Selective COX-2 inhibition improves endothelial function in coronary artery disease. *Circulation* 2003;**107**:405–9.

436. White WB, Kent J, Taylor A, Verburg KM, Lefkowith JB, Whelton A. Effects of celecoxib on ambulatory blood pressure in hypertensive patients on ACE inhibitors. *Hypertension* 2002; **39**:929–34.

437. Patel BR. A comparative study of subsyde-CR versus meloxicam in rheumatic disorders. *J Indian Med Assoc* 2000;**98**:250–2.

438. Schnitzer TJ, Beier J, Geusens P, Hasler P, Patel SK, Senftleber I, *et al*. Efficacy and safety of four doses of lumiracoxib versus diclofenac in patients with knee or hip primary osteoarthritis: a phase II, four-week, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2004;**51**:549–57.

439. Pfizer. Celecoxib Study 209. 2004 submission (commercial-in-confidence). 2004.

440. Pfizer. Celecoxib Study 210. 2004 submission (commercial-in-confidence). 2004.

441. Novartis. Lumiracoxib Study 2316. 2004 submission (commercial-in-confidence). 2004.

442. Novartis. Lumiracoxib Study 2319. 2004 submission (commercial-in-confidence). 2004.

443. Novartis. Lumiracoxib Study 0111. 2004 submission (commercial-in-confidence). 2004.

444. Pfizer and Searle. Celecoxib Study 047. 2001 submission (commercial-in-confidence). 2001.

445. Pfizer. Celecoxib Study 105. 2004 submission (commercial-in-confidence). 2004.

446. Pfizer. Celecoxib Study 106. 2004 submission (commercial-in-confidence). 2004.

447. Pfizer. Celecoxib Study 107. 2004 submission (commercial-in-confidence). 2004.

448. Edwards JE, Moore RA, McQuay HJ. Valdecoxib in osteoarthritis and rheumatoid arthritis: systematic review and meta-analysis of information from clinical trial reports. Pfizer 2004 submission (commercial-in-confidence).

449. Rostom A, Dube C, Wells G, Tugwell P, Welch V, Jolicoeur E, *et al*. Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database Syst Rev* 2002; Issue 4. CD002296.

450. Symmons D. A comparison of the cost-effectiveness of four strategies for the prevention of non-steroidal anti-inflammatory drug (NSAID) induced gastrointestinal toxicity – a systematic review with economic modelling. National Research Register 2003; Issue 1, N0484112113.

451. Geba GP, Lisse JR, Perlman M, Polis AB, Dixon ME, Skalky CS, *et al*. Gastrointestinal tolerability in primary care patients treated with naproxen or rofecoxib for osteoarthritis (OA): the Advantage Trial [abstract]. European Congress of Rheumatology, EULAR 2001, Prague.

452. Daniels B, Krupa D, Ehrich E, Bolognese J, Seidenberg B. Clinical response of OA patients who use acetaminophen when randomized to rofecoxib or ibuprofen [abstract]. *Arthritis Rheum* 1999;**42**(Suppl 9):S143.

453. Daniels B, Seidenberg B. Cardiovascular safety profile of rofecoxib in controlled clinical trials [abstract]. *Arthritis Rheum* 1999;**42**(Suppl 9):S143.

454. Daniels B, Gertz B, Morrison B, Seidenberg B. Renal safety profile of rofecoxib, a specific inhibitor of COX-2, in controlled clinical trials [abstract]. *Arthritis Rheum* 1999;**42**(Suppl 9):S143.

455. Laurenzi M. Evaluation of onset of action of rofecoxib, naproxen and nabumetone in patients with osteoarthritis (OA) [abstract]. Annual European Congress of Rheumatology, EULAR 2000, Nice.

456. Agrawal N, Paperiello B, Zhao W, Kent JD, Recker D, Verburg KM. Supratherapeutic doses of valdecoxib have a reduced incidence of gastroduodenal ulcers compared with conventional therapeutic doses of naproxen in osteoarthritis

and rheumatoid arthritis patients [abstract]. *Arthritis Rheum* 2001;**44**(Suppl 9): S372.

457. Goldstein JL, Fakouhi KM, Zhao WW, Verburg KM, Kent JD, Recker DP, *et al*. Reduced incidence of gastroduodenal ulcers with valdecoxib compared to ibuprofen and diclofenac in patients with osteoarthritis: a multicentre trial [abstract]. *Gastroenterology* 2001;**120**(5 Suppl 1): A597.

458. Goldstein JL, Kent J, Shu V, Maurath C, Recker D, Verburg K. Valdecoxib is less ulcerogenic than conventional NSAIDs in osteoarthritis (OA) and rheumatoid arthritis (RA) in patients with high risk of peptic ulcer disease [abstract]. *Gastroenterology* 2002;**122**(Suppl 1): A344.

459. Goldstein JL, Stenson WF, Agrawal N, Eisen G, Omachi J, Kent JD, *et al*. Valdecoxib is associated with a significantly lower incidence of ulcer complications and symptomatic ulcers in arthritis patients compared to NSAID [abstract]. *Gastroenterology* 2002;**122**(Suppl 1): A469.

460. Richardson CE, Emery P. New cyclo-oxygenase and cytokine inhibitors. *Baillières Clin Rheumatol* 1995;**9**:731–58.

461. Mazur M. A double-blind comparison of movalis and diclofenac in the treatment of patients with early rheumatoid arthritis. *Rheumatol Eur* 1998; Suppl 2:115.

462. Groeneveld PW, Lieu TA, Fendrick MA, Hurley LB, Ackerson LM, Levin TR, *et al*. Quality of life measurement clarifies the cost-effectiveness of Helicobacter pylori eradication in peptic ulcer disease and uninvestigated dyspepsia. *Am J Gastroenterol* 2001;**96**:338–47.

463. Goldstein JL, Agrawal NM, Silverstein F, Kaiser J, Burr AM, Verburg KM, *et al*. Celecoxib is associated with a significantly lower incidence of clinically significant upper gastrointestinal events in osteoarthritis and rheumatoid arthritis patients compared to NSAIDs. *Gastroenterology* 1999; **116**:A174.

464. Schnitzer TJ, Kivitz AJ, Greenwald M, Fleischmann RM, Matzura-Wolfe D, Polis AB, et al. Rofecoxib provides superior relief of symptoms of osteoarthritis (OA) compared to celecoxib [abstract]. European League Against Rheumatism Congress, EULAR 2001, Prague.

465. Geba GP, Schnitzer TJ, Polis AB, Petruschke RA, Weaver AL. Patient global assessment and WOMAC response among osteoarthritis patients treated with rofecoxib, celecoxib or acetaminophen in the VACT-2 trial [abstract]. European League Against Rheumatism Congress, EULAR 2003, Lisbon.

466. Fisher C, Curtis S, Resnick H, Ripley P, Leung AT, Ko A, *et al*. Results of a one-year study of etoricoxib in patients with osteoarthritis of the knee or hip [abstract]. American College of Rheumatology 65th Annual Scientific Meeting, 11–15 November 2001, San Francisco, CA.

467. Curtis S, Maldonado-Cocco J, Losada B, Gallagher A, Ng Y, Ng J, *et al*. Characterization of the clinically effective dose range of MK-0663 (etoricoxib), a COX-2 selective inhibitor, in the treatment of rheumatoid arthritis [abstract]. American College of Rheumatology 64th Annual Scientific Meeting, 29 October – 2 November 2000, Philadelphia, PA.

This version of HTA monograph volume 12, number 11 does not include the 124 pages of appendices. This is to save download time from the HTA website.

The printed version of this monograph also excludes the appendices.

View/download the appendices (1.5 Mbytes).

Health Technology Assessment reports published to date

Volume 1, 1997

No. 1
Home parenteral nutrition: a systematic review.
By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

No. 2
Diagnosis, management and screening of early localised prostate cancer.
A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

No. 3
The diagnosis, management, treatment and costs of prostate cancer in England and Wales.
A review by Chamberlain J, Melia J, Moss S, Brown J.

No. 4
Screening for fragile X syndrome.
A review by Murray J, Cuckle H, Taylor G, Hewison J.

No. 5
A review of near patient testing in primary care.
By Hobbs FDR, Delaney BC, Fitzmaurice DA, Wilson S, Hyde CJ, Thorpe GH, *et al*.

No. 6
Systematic review of outpatient services for chronic pain control.
By McQuay HJ, Moore RA, Eccleston C, Morley S, de C Williams AC.

No. 7
Neonatal screening for inborn errors of metabolism: cost, yield and outcome.
A review by Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, *et al*.

No. 8
Preschool vision screening.
A review by Snowdon SK, Stewart-Brown SL.

No. 9
Implications of socio-cultural contexts for the ethics of clinical trials.
A review by Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL.

No. 10
A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment.
By Davis A, Bamford J, Wilson I, Ramkalawan T, Forshaw M, Wright S.

No. 11
Newborn screening for inborn errors of metabolism: a systematic review.
By Seymour CA, Thomason MJ, Chalmers RA, Addison GM, Bain MD, Cockburn F, *et al*.

No. 12
Routine preoperative testing: a systematic review of the evidence.
By Munro J, Booth A, Nicholl J.

No. 13
Systematic review of the effectiveness of laxatives in the elderly.
By Petticrew M, Watt I, Sheldon T.

No. 14
When and how to assess fast-changing technologies: a comparative study of medical applications of four generic technologies.
A review by Mowatt G, Bower DJ, Brebner JA, Cairns JA, Grant AM, McKee L.

Volume 2, 1998

No. 1
Antenatal screening for Down's syndrome.
A review by Wald NJ, Kennard A, Hackshaw A, McGuire A.

No. 2
Screening for ovarian cancer: a systematic review.
By Bell R, Petticrew M, Luengo S, Sheldon TA.

No. 3
Consensus development methods, and their use in clinical guideline development.
A review by Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CFB, Askham J, *et al*.

No. 4
A cost–utility analysis of interferon beta for multiple sclerosis.
By Parkin D, McNamee P, Jacoby A, Miller P, Thomas S, Bates D.

No. 5
Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews.
By MacLeod A, Grant A, Donaldson C, Khan I, Campbell M, Daly C, *et al*.

No. 6
Effectiveness of hip prostheses in primary total hip replacement: a critical review of evidence and an economic model.
By Faulkner A, Kennedy LG, Baxter K, Donovan J, Wilkinson M, Bevan G.

No. 7
Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials.
By Song F, Glenny AM.

No. 8
Bone marrow and peripheral blood stem cell transplantation for malignancy.
A review by Johnson PWM, Simnett SJ, Sweetenham JW, Morgan GJ, Stewart LA.

No. 9
Screening for speech and language delay: a systematic review of the literature.
By Law J, Boyle J, Harris F, Harkness A, Nye C.

No. 10
Resource allocation for chronic stable angina: a systematic review of effectiveness, costs and cost-effectiveness of alternative interventions.
By Sculpher MJ, Petticrew M, Kelland JL, Elliott RA, Holdright DR, Buxton MJ.

No. 11
Detection, adherence and control of hypertension for the prevention of stroke: a systematic review.
By Ebrahim S.

No. 12
Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review.
By McQuay HJ, Moore RA.

No. 13
Choosing between randomised and nonrandomised studies: a systematic review.
By Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C.

No. 14
Evaluating patient-based outcome measures for use in clinical trials.
A review by Fitzpatrick R, Davey C, Buxton MJ, Jones DR.

No. 15
Ethical issues in the design and conduct of randomised controlled trials.
A review by Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J.

No. 16
Qualitative research methods in health technology assessment: a review of the literature.
By Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P.

No. 17
The costs and benefits of paramedic skills in pre-hospital trauma care.
By Nicholl J, Hughes S, Dixon S, Turner J, Yates D.

No. 18
Systematic review of endoscopic ultrasound in gastro-oesophageal cancer.
By Harris KM, Kelly S, Berry E, Hutton J, Roderick P, Cullingworth J, *et al*.

No. 19
Systematic reviews of trials and other studies.
By Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F.

No. 20
Primary total hip replacement surgery: a systematic review of outcomes and modelling of cost-effectiveness associated with different prostheses.
A review by Fitzpatrick R, Shortall E, Sculpher M, Murray D, Morris R, Lodge M, *et al*.

Volume 3, 1999

No. 1
Informed decision making: an annotated bibliography and systematic review.
By Bekker H, Thornton JG, Airey CM, Connelly JB, Hewison J, Robinson MB, *et al*.

No. 2
Handling uncertainty when performing economic evaluation of healthcare interventions.
A review by Briggs AH, Gray AM.

No. 3
The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Thomas H.

No. 4
A randomised controlled trial of different approaches to universal antenatal HIV testing: uptake and acceptability. Annex: Antenatal HIV testing – assessment of a routine voluntary approach.
By Simpson WM, Johnstone FD, Boyd FM, Goldberg DJ, Hart GJ, Gormley SM, *et al*.

No. 5
Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review.
By Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ.

No. 6
Assessing the costs of healthcare technologies in clinical trials.
A review by Johnston K, Buxton MJ, Jones DR, Fitzpatrick R.

No. 7
Cooperatives and their primary care emergency centres: organisation and impact.
By Hallam L, Henthorne K.

No. 8
Screening for cystic fibrosis.
A review by Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J.

No. 9
A review of the use of health status measures in economic evaluation.
By Brazier J, Deverill M, Green C, Harper R, Booth A.

No. 10
Methods for the analysis of quality-of-life and survival data in health technology assessment.
A review by Billingham LJ, Abrams KR, Jones DR.

No. 11
Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis.
By Zeuner D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN.

No. 12
Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses.
A review by Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, *et al*.

No. 13
'Early warning systems' for identifying new healthcare technologies.
By Robert G, Stevens A, Gabbay J.

No. 14
A systematic review of the role of human papillomavirus testing within a cervical screening programme.
By Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, *et al*.

No. 15
Near patient testing in diabetes clinics: appraising the costs and outcomes.
By Grieve R, Beech R, Vincent J, Mazurkiewicz J.

No. 16
Positron emission tomography: establishing priorities for health technology assessment.
A review by Robert G, Milne R.

No. 17 (Pt 1)
The debridement of chronic wounds: a systematic review.
By Bradley M, Cullum N, Sheldon T.

No. 17 (Pt 2)
Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds.
By Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D.

No. 18
A systematic literature review of spiral and electron beam computed tomography: with particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease.
By Berry E, Kelly S, Hutton J, Harris KM, Roderick P, Boyce JC, *et al*.

No. 19
What role for statins? A review and economic model.
By Ebrahim S, Davey Smith G, McCabe C, Payne N, Pickin M, Sheldon TA, *et al*.

No. 20
Factors that limit the quality, number and progress of randomised controlled trials.
A review by Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, *et al*.

No. 21
Antimicrobial prophylaxis in total hip replacement: a systematic review.
By Glenny AM, Song F.

No. 22
Health promoting schools and health promotion in schools: two systematic reviews.
By Lister-Sharp D, Chapman S, Stewart-Brown S, Sowden A.

No. 23
Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee.
A review by Lord J, Victor C, Littlejohns P, Ross FM, Axford JS.

Volume 4, 2000

No. 1
The estimation of marginal time preference in a UK-wide sample (TEMPUS) project.
A review by Cairns JA, van der Pol MM.

No. 2
Geriatric rehabilitation following fractures in older people: a systematic review.
By Cameron I, Crotty M, Currie C, Finnegan T, Gillespie L, Gillespie W, *et al*.

No. 3
Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research.
By Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C.

No. 4
Community provision of hearing aids and related audiology services.
A review by Reeves DJ, Alborz A, Hickson FS, Bamford JM.

No. 5
False-negative results in screening programmes: systematic review of impact and implications.
By Petticrew MP, Sowden AJ, Lister-Sharp D, Wright K.

No. 6
Costs and benefits of community postnatal support workers: a randomised controlled trial.
By Morrell CJ, Spiby H, Stewart P, Walters S, Morgan A.

No. 7
Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness.
By French RS, Cowan FM, Mansour DJA, Morris S, Procter T, Hughes D, *et al*.

No. 8
An introduction to statistical methods for health technology assessment.
A review by White SJ, Ashby D, Brown PJ.

No. 9
Disease-modifying drugs for multiple sclerosis: a rapid and systematic review.
By Clegg A, Bryant J, Milne R.

No. 10
Publication and related biases.
A review by Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ.

No. 11
Cost and outcome implications of the organisation of vascular services.
By Michaels J, Brazier J, Palfreyman S, Shackley P, Slack R.

No. 12
Monitoring blood glucose control in diabetes mellitus: a systematic review.
By Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R.

No. 13
The effectiveness of domiciliary health visiting: a systematic review of international studies and a selective review of the British literature.
By Elkan R, Kendrick D, Hewitt M, Robinson JJA, Tolley K, Blair M, *et al*.

No. 14
The determinants of screening uptake and interventions for increasing uptake: a systematic review.
By Jepson R, Clegg A, Forbes C, Lewis R, Sowden A, Kleijnen J.

No. 15
The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth.
A rapid review by Song F, O'Meara S, Wilson P, Golder S, Kleijnen J.

No. 16
Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views.
By Bricker L, Garcia J, Henderson J, Mugford M, Neilson J, Roberts T, *et al*.

No. 17
A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer.
By Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J.

No. 18
Liquid-based cytology in cervical screening: a rapid and systematic review.
By Payne N, Chilcott J, McGoogan E.

No. 19
Randomised controlled trial of non-directive counselling, cognitive–behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care.
By King M, Sibbald B, Ward E, Bower P, Lloyd M, Gabbay M, *et al*.

No. 20
Routine referral for radiography of patients presenting with low back pain: is patients' outcome influenced by GPs' referral for plain radiography?
By Kerry S, Hilton S, Patel S, Dundas D, Rink E, Lord J.

No. 21
Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration.
By O'Meara S, Cullum N, Majid M, Sheldon T.

No. 22
Using routine data to complement and enhance the results of randomised controlled trials.
By Lewsey JD, Leyland AH, Murray GD, Boddy FA.

No. 23
Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review.
By Meads C, Cummins C, Jolly K, Stevens A, Burls A, Hyde C.

No. 24
Outcome measures for adult critical care: a systematic review.
By Hayes JA, Black NA, Jenkinson C, Young JD, Rowan KM, Daly K, *et al*.

No. 25
A systematic review to evaluate the effectiveness of interventions to promote the initiation of breastfeeding.
By Fairbank L, O'Meara S, Renfrew MJ, Woolridge M, Sowden AJ, Lister-Sharp D.

No. 26
Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review.
By Parkes J, Bryant J, Milne R.

No. 27
Treatments for fatigue in multiple sclerosis: a rapid and systematic review.
By Brañas P, Jordan R, Fry-Smith A, Burls A, Hyde C.

No. 28
Early asthma prophylaxis, natural history, skeletal development and economy (EASE): a pilot randomised controlled trial.
By Baxter-Jones ADG, Helms PJ, Russell G, Grant A, Ross S, Cairns JA, *et al*.

No. 29
Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis.
By Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HAW.

No. 30
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina.
By McDonagh MS, Bachmann LM, Golder S, Kleijnen J, ter Riet G.

No. 31
A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma.
By Turner J, Nicholl J, Webber L, Cox H, Dixon S, Yates D.

No. 32
Intrathecal pumps for giving opioids in chronic pain: a systematic review.
By Williams JE, Louw G, Towlerton G.

No. 33
Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review.
By Shepherd J, Waugh N, Hewitson P.

No. 34
A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies.
By MacLehose RR, Reeves BC, Harvey IM, Sheldon TA, Russell IT, Black AMS.

No. 35
Intravascular ultrasound-guided interventions in coronary artery disease: a systematic literature review, with decision-analytic modelling, of outcomes and cost-effectiveness.
By Berry E, Kelly S, Hutton J, Lindsay HSJ, Blaxill JM, Evans JA, *et al*.

No. 36
A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression.
By Simpson S, Corney R, Fitzgerald P, Beecham J.

No. 37
Systematic review of treatments for atopic eczema.
By Hoare C, Li Wan Po A, Williams H.

No. 38
Bayesian methods in health technology assessment: a review.
By Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR.

No. 39
The management of dyspepsia: a systematic review.
By Delaney B, Moayyedi P, Deeks J, Innes M, Soo S, Barton P, *et al*.

No. 40
A systematic review of treatments for severe psoriasis.
By Griffiths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC.

Volume 5, 2001

No. 1
Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review.
By Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, *et al*.

No. 2
The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review.
By Stewart A, Sandercock J, Bryan S, Hyde C, Barton PM, Fry-Smith A, *et al*.

No. 3
Equity and the economic evaluation of healthcare.
By Sassi F, Archard L, Le Grand J.

No. 4
Quality-of-life measures in chronic diseases of childhood.
By Eiser C, Morse R.

No. 5
Eliciting public preferences for healthcare: a systematic review of techniques.
By Ryan M, Scott DA, Reeves C, Bate A, van Teijlingen ER, Russell EM, *et al*.

No. 6
General health status measures for people with cognitive impairment: learning disability and acquired brain injury.
By Riemsma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J.

No. 7
An assessment of screening strategies for fragile X syndrome in the UK.
By Pembrey ME, Barnicoat AJ, Carmichael B, Bobrow M, Turner G.

No. 8
Issues in methodological research: perspectives from researchers and commissioners.
By Lilford RJ, Richardson A, Stevens A, Fitzpatrick R, Edwards S, Rock F, *et al*.

No. 9
Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy.
By Cullum N, Nelson EA, Flemming K, Sheldon T.

No. 10
Effects of educational and psychosocial interventions for adolescents with diabetes mellitus: a systematic review.
By Hampson SE, Skinner TC, Hart J, Storey L, Gage H, Foxcroft D, *et al*.

No. 11
Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review.
By Jobanputra P, Parry D, Fry-Smith A, Burls A.

No. 12
Statistical assessment of the learning curves of health technologies.
By Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT.

No. 13
The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review.
By Dinnes J, Cave C, Huang S, Major K, Milne R.

No. 14
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of debriding agents in treating surgical wounds healing by secondary intention.
By Lewis R, Whiting P, ter Riet G, O'Meara S, Glanville J.

No. 15
Home treatment for mental health problems: a systematic review.
By Burns T, Knapp M, Catty J, Healey A, Henderson J, Watt H, *et al*.

No. 16
How to develop cost-conscious guidelines.
By Eccles M, Mason J.

No. 17
The role of specialist nurses in multiple sclerosis: a rapid and systematic review.
By De Broe S, Christopher F, Waugh N.

No. 18
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 19
The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review.
By Chilcott J, Wight J, Lloyd Jones M, Tappenden P.

No. 20
Extended scope of nursing practice: a multicentre randomised controlled trial of appropriately trained nurses and preregistration house officers in pre-operative assessment in elective general surgery.
By Kinley H, Czoski-Murray C, George S, McCabe C, Primrose J, Reilly C, *et al*.

No. 21
Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) Acute day hospital versus admission; (2) Vocational rehabilitation; (3) Day hospital versus outpatient care.
By Marshall M, Crowther R, Almaraz-Serrano A, Creed F, Sledge W, Kluiter H, *et al*.

No. 22
The measurement and monitoring of surgical adverse events.
By Bruce J, Russell EM, Mollison J, Krukowski ZH.

No. 23
Action research: a systematic review and guidance for assessment.
By Waterman H, Tillen D, Dickson R, de Koning K.

No. 24
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer.
By Ward S, Morris E, Bansback N, Calvert N, Crellin A, Forman D, *et al*.

No. 25
A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.
By Lloyd Jones M, Hummel S, Bansback N, Orr B, Seymour M.

No. 26
Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature.
By Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, *et al*.

No. 27
The cost-effectiveness of magnetic resonance imaging for investigation of the knee joint.
By Bryan S, Weatherburn G, Bungay H, Hatrick C, Salas C, Parry D, *et al*.

No. 28
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer.
By Forbes C, Shirran L, Bagnall A-M, Duffy S, ter Riet G.

No. 29
Superseded by a report published in a later volume.

No. 30
The role of radiography in primary care patients with low back pain of at least 6 weeks duration: a randomised (unblinded) controlled trial.
By Kendrick D, Fielding K, Bentley E, Miller P, Kerslake R, Pringle M.

No. 31
Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients.
By McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, *et al*.

No. 32
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer.
By Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N.

No. 33
Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.
By Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G.

No. 34
Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes.
By David AS, Adams C.

No. 35
A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression.
By Churchill R, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, *et al*.

No. 36
Cost analysis of child health surveillance.
By Sanderson D, Wright D, Acton C, Duree D.

Volume 6, 2002

No. 1
A study of the methods used to select review criteria for clinical audit.
By Hearnshaw H, Harker R, Cheater F, Baker R, Grimshaw G.

No. 2
Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment.
By Hyde C, Wake B, Bryan S, Barton P, Fry-Smith A, Davenport C, *et al*.

No. 3
Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation.
By Wake B, Hyde C, Bryan S, Barton P, Song F, Fry-Smith A, *et al*.

No. 4
A systematic review of discharge arrangements for older people.
By Parker SG, Peet SM, McPherson A, Cannaby AM, Baker R, Wilson A, *et al*.

No. 5
The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation.
By Peters J, Stevenson M, Beverley C, Lim J, Smith S.

No. 6
The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 7
The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review.
By Berry E, Kelly S, Westwood ME, Davies LM, Gough MJ, Bamford JM, *et al*.

No. 8
Promoting physical activity in South Asian Muslim women through 'exercise on prescription'.
By Carroll B, Ali N, Azam N.

No. 9
Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation.
By Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, *et al*.

No. 10
A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models.
By Richards RG, Sampson FC, Beard SM, Tappenden P.

No. 11
Screening for gestational diabetes: a systematic review and economic evaluation.
By Scott DA, Loveman E, McIntyre L, Waugh N.

No. 12
The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: a systematic review and economic evaluation.
By Clegg AJ, Colquitt J, Sidhu MK, Royle P, Loveman E, Walker A.

No. 13
The clinical effectiveness of trastuzumab for breast cancer: a systematic review.
By Lewis R, Bagnall A-M, Forbes C, Shirran E, Duffy S, Kleijnen J, *et al*.

No. 14
The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation.
By Lewis R, Bagnall A-M, King S, Woolacott N, Forbes C, Shirran L, *et al*.

No. 15
A systematic review of the effectiveness and cost-effectiveness of metal-on-metal hip resurfacing arthroplasty for treatment of hip disease.
By Vale L, Wyness L, McCormack K, McKenzie L, Brazzelli M, Stearns SC.

No. 16
The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation.
By Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, *et al*.

No. 17
A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept.
By Cummins C, Connock M, Fry-Smith A, Burls A.

No. 18
Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation.
By Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, *et al*.

No. 19
Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: a systematic review and economic evaluation.
By Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, *et al*.

No. 20
Clinical medication review by a pharmacist of patients on repeat prescriptions in general practice: a randomised controlled trial.
By Zermansky AG, Petty DR, Raynor DK, Lowe CJ, Freementle N, Vail A.

No. 21
The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation.
By Jobanputra P, Barton P, Bryan S, Burls A.

No. 22
A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety.
By Kaltenthaler E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J.

No. 23
A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer.
By Forbes C, Wilby J, Richardson G, Sculpher M, Mather L, Reimsma R.

No. 24
A systematic review of the effectiveness of interventions based on a stages-of-change approach to promote individual behaviour change.
By Riemsma RP, Pattenden J, Bridle C, Sowden AJ, Mather L, Watt IS, *et al*.

No. 25
A systematic review update of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists.
By Robinson M, Ginnelly L, Sculpher M, Jones L, Riemsma R, Palmer S, *et al*.

No. 26
A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS.
By Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, *et al*.

No. 27
A randomised controlled crossover trial of nurse practitioner versus doctor-led outpatient care in a bronchiectasis clinic.
By Caine N, Sharples LD, Hollingworth W, French J, Keogan M, Exley A, *et al*.

No. 28
Clinical effectiveness and cost – consequences of selective serotonin reuptake inhibitors in the treatment of sex offenders.
By Adi Y, Ashcroft D, Browne K, Beech A, Fry-Smith A, Hyde C.

No. 29
Treatment of established osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M.

No. 30
Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial.
By Elliott RA Payne K, Moore JK, Davies LM, Harper NJN, St Leger AS, *et al*.

No. 31
Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice.
By Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, *et al*.

No. 32
The measurement of satisfaction with healthcare: implications for practice from a systematic review of the literature.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Storey L, *et al*.

No. 33
The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.
By Garside R, Round A, Dalziel K, Stein K, Royle R.

No. 34
A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis.
By Suri R, Wallis C, Bush A, Thompson S, Normand C, Flather M, *et al*.

No. 35
A systematic review of the costs and effectiveness of different models of paediatric home care.
By Parker G, Bhakta P, Lovett CA, Paisley S, Olsen R, Turner D, *et al*.

Volume 7, 2003

No. 1
How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study.
By Egger M, Jüni P, Bartlett C, Holenstein F, Sterne J.

No. 2
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure.
By Mowatt G, Vale L, Perez J, Wyness L, Fraser C, MacLeod A, *et al*.

No. 3
Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease.
By Clark W, Raftery J, Barton P, Song F, Fry-Smith A, Burls A.

No. 4
A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus negative.
By Chilcott J, Lloyd Jones M, Wight J, Forman K, Wray J, Beverley C, *et al*.

No. 5
Systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing's sarcoma and neuroblastoma.
By Riley RD, Burchill SA, Abrams KR, Heney D, Lambert PC, Jones DR, *et al*.

No. 6
The cost-effectiveness of screening for *Helicobacter pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model.
By Roderick P, Davies R, Raftery J, Crabbe D, Pearce R, Bhandari P, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of routine dental checks: a systematic review and economic evaluation.
By Davenport C, Elley K, Salas C, Taylor-Weetman CL, Fry-Smith A, Bryan S, *et al*.

No. 8
A multicentre randomised controlled trial assessing the costs and benefits of using structured information and analysis of women's preferences in the management of menorrhagia.
By Kennedy ADM, Sculpher MJ, Coulter A, Dwyer N, Rees M, Horsley S, *et al*.

No. 9
Clinical effectiveness and cost–utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation.
By Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C.

No. 10
Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities.
By Grimshaw GM, Szczepura A, Hultén M, MacDonald F, Nevin NC, Sutton F, *et al*.

No. 11
First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS).
By Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM.

No. 12
The effectiveness and cost-effectiveness of ultrasound locating devices for central venous access: a systematic review and economic evaluation.
By Calvert N, Hind D, McWilliams RG, Thomas SM, Beverley C, Davidson A.

No. 13
A systematic review of atypical antipsychotics in schizophrenia.
By Bagnall A-M, Jones L, Lewis R, Ginnelly L, Glanville J, Torgerson D, *et al*.

No. 14
Prostate Testing for Cancer and Treatment (ProtecT) feasibility study.
By Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, *et al*.

No. 15
Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation.
By Boland A, Dundar Y, Bagust A, Haycox A, Hill R, Mujica Mota R, *et al*.

No. 16
Screening for fragile X syndrome: a literature review and modelling.
By Song FJ, Barton P, Sleightholme V, Yao GL, Fry-Smith A.

No. 17
Systematic review of endoscopic sinus surgery for nasal polyps.
By Dalziel K, Stein K, Round A, Garside R, Royle P.

No. 18
Towards efficient guidelines: how to monitor guideline use in primary care.
By Hutchinson A, McIntosh A, Cox S, Gilbert C.

No. 19
Effectiveness and cost-effectiveness of acute hospital-based spinal cord injuries services: systematic review.
By Bagnall A-M, Jones L, Richardson G, Duffy S, Riemsma R.

No. 20
Prioritisation of health technology assessment. The PATHS model: methods and case studies.
By Townsend J, Buxton M, Harper G.

No. 21
Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence.
By Cody J, Wyness L, Wallace S, Glazener C, Kilonzo M, Stearns S, *et al*.

No. 22
The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation.
By Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N.

No. 23
The role of modelling in prioritising and planning clinical trials.
By Chilcott J, Brennan A, Booth A, Karnon J, Tappenden P.

No. 24
Cost–benefit evaluation of routine influenza immunisation in people 65–74 years of age.
By Allsup S, Gosney M, Haycox A, Regan M.

No. 25
The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors.
By Wight J, Chilcott J, Holmes M, Brewer N.

No. 26
Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment.
By Williams JG, Cheung WY, Cohen DR, Hutchings HA, Longo MF, Russell IT.

No. 27
Evaluating non-randomised intervention studies.
By Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, *et al*.

No. 28
A randomised controlled trial to assess the impact of a package comprising a patient-orientated, evidence-based self-help guidebook and patient-centred consultations on disease management and satisfaction in inflammatory bowel disease.
By Kennedy A, Nelson E, Reeves D, Richardson G, Roberts C, Robinson A, *et al*.

No. 29
The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review.
By Dinnes J, Loveman E, McIntyre L, Waugh N.

No. 30
The value of digital imaging in diabetic retinopathy.
By Sharp PF, Olson J, Strachan F, Hipwell J, Ludbrook A, O'Donnell M, *et al*.

No. 31
Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.
By Law M, Wald N, Morris J.

No. 32
Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation.
By Ward S, Kaltenthaler E, Cowan J, Brewer N.

No. 33
Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review.
By Hummel S, Paisley S, Morgan A, Currie E, Brewer N.

No. 34
Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system.
By Royle P, Waugh N.

No. 35
Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.
By Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K.

No. 36
A randomised controlled trial to evaluate the clinical and cost-effectiveness of Hickman line insertions in adult cancer patients by nurses.
By Boland A, Haycox A, Bagust A, Fitzsimmons L.

No. 37
Redesigning postnatal care: a randomised controlled trial of protocol-based midwifery-led care focused on individual women's physical and psychological health needs.
By MacArthur C, Winter HR, Bick DE, Lilford RJ, Lancashire RJ, Knowles H, *et al*.

No. 38
Estimating implied rates of discount in healthcare decision-making.
By West RR, McNabb R, Thompson AGH, Sheldon TA, Grimley Evans J.

No. 39
Systematic review of isolation policies in the hospital management of methicillin-resistant *Staphylococcus aureus*: a review of the literature with epidemiological and economic modelling.
By Cooper BS, Stone SP, Kibbler CC, Cookson BD, Roberts JA, Medley GF, *et al*.

No. 40
Treatments for spasticity and pain in multiple sclerosis: a systematic review.
By Beard S, Hunn A, Wight J.

No. 41
The inclusion of reports of randomised trials published in languages other than English in systematic reviews.
By Moher D, Pham B, Lawson ML, Klassen TP.

No. 42
The impact of screening on future health-promoting behaviours and health beliefs: a systematic review.
By Bankhead CR, Brett J, Bukach C, Webster P, Stewart-Brown S, Munafo M, *et al*.

Volume 8, 2004

No. 1
What is the best imaging strategy for acute stroke?
By Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock PAG, Dennis MS, *et al*.

No. 2
Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care.
By Mant J, McManus RJ, Oakes RAL, Delaney BC, Barton PM, Deeks JJ, *et al*.

No. 3
The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling.
By Garside R, Stein K, Wyatt K, Round A, Price A.

No. 4
A systematic review of the role of bisphosphonates in metastatic disease.
By Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, *et al*.

No. 5
Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer.
By Jones L, Hawkins N, Westwood M, Wright K, Richardson G, Riemsma R.

No. 6
Effectiveness and efficiency of guideline dissemination and implementation strategies.
By Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, *et al*.

No. 7
Clinical effectiveness and costs of the Sugarbaker procedure for the treatment of pseudomyxoma peritonei.
By Bryant J, Clegg AJ, Sidhu MK, Brodin H, Royle P, Davidson P.

No. 8
Psychological treatment for insomnia in the regulation of long-term hypnotic drug use.
By Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M.

No. 9
Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome.
By Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ.

No. 10
A systematic review and economic evaluation of magnetic resonance cholangiopancreatography compared with diagnostic endoscopic retrograde cholangiopancreatography.
By Kaltenthaler E, Bravo Vergel Y, Chilcott J, Thomas S, Blakeborough T, Walters SJ, *et al*.

No. 11
The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis.
By Barton P, Jobanputra P, Wilson J, Bryan S, Burls A.

No. 12
Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review.
By Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S.

No. 13
Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation.
By Czoski-Murray C, Warren E, Chilcott J, Beverley C, Psyllaki MA, Cowan J.

No. 14
Routine examination of the newborn: the EMREN study. Evaluation of an extension of the midwife role including a randomised controlled trial of appropriately trained midwives and paediatric senior house officers.
By Townsend J, Wolke D, Hayes J, Davé S, Rogers C, Bloomfield L, *et al*.

No. 15
Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach.
By Oliver S, Clarke-Jones L, Rees R, Milne R, Buchanan P, Gabbay J, *et al*.

No. 16
A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery.
By Reeves BC, Angelini GD, Bryan AJ, Taylor FC, Cripps T, Spyt TJ, *et al*.

No. 17
Does early magnetic resonance imaging influence management or improve outcome in patients referred to secondary care with low back pain? A pragmatic randomised controlled trial.
By Gilbert FJ, Grant AM, Gillan MGC, Vale L, Scott NW, Campbell MK, *et al*.

No. 18
The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis.
By Clark W, Jobanputra P, Barton P, Burls A.

No. 19
A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder.
By Bridle C, Palmer S, Bagnall A-M, Darba J, Duffy S, Sculpher M, *et al*.

No. 20
Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis.
By Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N.

No. 21
Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.
By Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, *et al*.

No. 22
Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus.
By Dretzke J, Cummins C, Sandercock J, Fry-Smith A, Barrett T, Burls A.

No. 23
Clinical effectiveness and cost-effectiveness of prehospital intravenous fluids in trauma patients.
By Dretzke J, Sandercock J, Bayliss S, Burls A.

No. 24
Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation.
By Dündar Y, Boland A, Strobl J, Dodd S, Haycox A, Bagust A, *et al*.

No. 25
Development and validation of methods for assessing the quality of diagnostic accuracy studies.
By Whiting P, Rutjes AWS, Dinnes J, Reitsma JB, Bossuyt PMM, Kleijnen J.

No. 26
EVALUATE hysterectomy trial: a multicentre randomised trial comparing abdominal, vaginal and laparoscopic methods of hysterectomy.
By Garry R, Fountain J, Brown J, Manca A, Mason S, Sculpher M, *et al*.

No. 27
Methods for expected value of information analysis in complex health economic models: developments on the health economics of interferon-β and glatiramer acetate for multiple sclerosis.
By Tappenden P, Chilcott JB, Eggington S, Oakley J, McCabe C.

No. 28
Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.
By Dalziel K, Round A, Stein K, Garside R, Price A.

No. 29
VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers.
By Iglesias C, Nelson EA, Cullum NA, Torgerson DJ on behalf of the VenUS Team.

No. 30
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.
By Mowatt G, Vale L, Brazzelli M, Hernandez R, Murray A, Scott N, *et al*.

No. 31
A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme.
By Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S.

No. 32
The Social Support and Family Health Study: a randomised controlled trial and economic evaluation of two alternative forms of postnatal support for mothers living in disadvantaged inner-city areas.
By Wiggins M, Oakley A, Roberts I, Turner H, Rajan L, Austerberry H, *et al*.

No. 33
Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review.
By Green JM, Hewison J, Bekker HL, Bryant, Cuckle HS.

No. 34
Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status.
By Critchley HOD, Warner P, Lee AJ, Brechin S, Guise J, Graham B.

No. 35
Coronary artery stents: a rapid systematic review and economic evaluation.
By Hill R, Bagust A, Bakhai A, Dickson R, Dündar Y, Haycox A, *et al*.

No. 36
Review of guidelines for good practice in decision-analytic modelling in health technology assessment.
By Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*.

No. 37
Rituximab (MabThera®) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation.
By Knight C, Hind D, Brewer N, Abbott V.

No. 38
Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation.
By Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, *et al.*

No. 39
Pegylated interferon α-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J.

No. 40
Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation.
By Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, *et al.*

No. 41
Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups.
By Beswick AD, Rees K, Griebsch I, Taylor FC, Burke M, West RR, *et al.*

No. 42
Involving South Asian patients in clinical trials.
By Hussain-Gambles M, Leese B, Atkin K, Brown J, Mason S, Tovey P.

No. 43
Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes.
By Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N.

No. 44
Identification and assessment of ongoing trials in health technology assessment reviews.
By Song FJ, Fry-Smith A, Davenport C, Bayliss S, Adi Y, Wilson JS, *et al*.

No. 45
Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine
By Warren E, Weatherley-Jones E, Chilcott J, Beverley C.

No. 46
Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis.
By McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, *et al*.

No. 47
Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation.
By Green C, Colquitt JL, Kirby J, Davidson P, Payne E.

No. 48
Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis.
By Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N, *et al*.

No. 49
Generalisability in economic evaluation studies in healthcare: a review and case studies.
By Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, *et al*.

No. 50
Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations.
By Wallace P, Barber J, Clayton W, Currell R, Fleming K, Garner P, *et al*.

Volume 9, 2005

No. 1
Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne.
By Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill C, Simpson NB, *et al*.

No. 2
Do the findings of case series studies vary significantly according to methodological characteristics?
By Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L.

No. 3
Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions.
By Wilson BJ, Torrance N, Mollison J, Wordsworth S, Gray JR, Haites NE, *et al*.

No. 4
Randomised evaluation of alternative electrosurgical modalities to treat bladder outflow obstruction in men with benign prostatic hyperplasia.
By Fowler C, McAllister W, Plail R, Karim O, Yang Q.

No. 5
A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer.
By Shenfine J, McNamee P, Steen N, Bond J, Griffin SM.

No. 6
Impact of computer-aided detection prompts on the sensitivity and specificity of screening mammography.
By Taylor P, Champness J, Given-Wilson R, Johnston K, Potts H.

No. 7
Issues in data monitoring and interim analysis of trials.
By Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, *et al*.

No. 8
Lay public's understanding of equipoise and randomisation in randomised controlled trials.
By Robinson EJ, Kerr CEP, Stevens AJ, Lilford RJ, Braunholtz DA, Edwards SJ, *et al*.

No. 9
Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies.
By Greenhalgh J, Knight C, Hind D, Beverley C, Walters S.

No. 10
Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology.
By Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, *et al*.

No. 11
Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation.
By Green C, Dinnes J, Takeda A, Shepherd J, Hartwell D, Cave C, *et al*.

No. 12
A methodological review of how heterogeneity has been examined in systematic reviews of diagnostic test accuracy.
By Dinnes J, Deeks J, Kirby J, Roderick P.

No. 13
Cervical screening programmes: can automation help? Evidence from systematic reviews, an economic analysis and a simulation modelling exercise applied to the UK.
By Willis BH, Barton P, Pearmain P, Bryan S, Hyde C.

No. 14
Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation.
By McCormack K, Wake B, Perez J, Fraser C, Cook J, McIntosh E, *et al*.

No. 15
Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation.
By Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, *et al*.

No. 16
A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine.
By Peveler R, Kendrick T, Buxton M, Longworth L, Baldwin D, Moore M, *et al*.

No. 17
Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation.
By Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N, *et al*.

No. 18
A randomised controlled comparison of alternative strategies in stroke care.
By Kalra L, Evans A, Perez I, Knapp M, Swift C, Donaldson N.

No. 19
The investigation and analysis of critical incidents and adverse events in healthcare.
By Woloshynowych M, Rogers S, Taylor-Adams S, Vincent C.

No. 20
Potential use of routine databases in health technology assessment.
By Raftery J, Roderick P, Stevens A.

No. 21
Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study.
By Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, *et al*.

No. 22
A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis.
By Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J.

No. 23
A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma.
By Smith JR, Mugford M, Holland R, Candy B, Noble MJ, Harrison BDW, *et al*.

No. 24
An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales.
By Roderick P, Nicholson T, Armitage A, Mehta R, Mullee M, Gerard K, *et al*.

No. 25
Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation.
By Wilson J, Connock M, Song F, Yao G, Fry-Smith A, Raftery J, *et al*.

No. 26
Indirect comparisons of competing interventions.
By Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, *et al*.

No. 27
Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling.
By Robinson M, Palmer S, Sculpher M, Philips Z, Ginnelly L, Bowens A, *et al*.

No. 28
Outcomes of electrically stimulated gracilis neosphincter surgery.
By Tillin T, Chambers M, Feldman R.

No. 29
The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.
By Garside R, Stein K, Castelnuovo E, Pitt M, Ashcroft D, Dimmock P, *et al*.

No. 30
Systematic review on urine albumin testing for early detection of diabetic complications.
By Newman DJ, Mattock MB, Dawnay ABS, Kerry S, McGuire A, Yaqoob M, *et al*.

No. 31
Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis.
By Cochrane T, Davey RC, Matthes Edwards SM.

No. 32
Longer term clinical and economic benefits of offering acupuncture care to patients with chronic low back pain.
By Thomas KJ, MacPherson H, Ratcliffe J, Thorpe L, Brazier J, Campbell M, *et al*.

No. 33
Cost-effectiveness and safety of epidural steroids in the management of sciatica.
By Price C, Arden N, Coglan L, Rogers P.

No. 34
The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis.
By Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL.

No. 35
Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials.
By King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, *et al*.

No. 36
The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review.
By Bryant J, Brodin H, Loveman E, Payne E, Clegg A.

No. 37
A trial of problem-solving by community mental health nurses for anxiety, depression and life difficulties among general practice patients. The CPN-GP study.
By Kendrick T, Simons L, Mynors-Wallis L, Gray A, Lathlean J, Pickering R, *et al*.

No. 38
The causes and effects of socio-demographic exclusions from clinical trials.
By Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, *et al*.

No. 39
Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis.
By Epps H, Ginnelly L, Utley M, Southwood T, Gallivan S, Sculpher M, *et al*.

No. 40
A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study.
By Hobbs FDR, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, *et al*.

No. 41
Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty.
By Keating JF, Grant A, Masson M, Scott NW, Forbes JF.

No. 42
Long-term outcome of cognitive behaviour therapy clinical trials in central Scotland.
By Durham RC, Chambers JA, Power KG, Sharp DM, Macdonald RR, Major KA, *et al*.

No. 43
The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.
By Castelnuovo E, Stein K, Pitt M, Garside R, Payne E.

No. 44
Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis.
By Knowles R, Griebsch I, Dezateux C, Brown J, Bull C, Wren C.

No. 45
The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation.
By Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, *et al*.

No. 46
The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma.
By Kwartz AJ, Henson DB, Harper RA, Spencer AF, McLeod D.

No. 47
Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation.
By Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, *et al*.

No. 48
Systematic review of effectiveness of different treatments for childhood retinoblastoma.
By McDaid C, Hartley S, Bagnall A-M, Ritchie G, Light K, Riemsma R.

No. 49
Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis.
By Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, *et al*.

No. 50
The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children.
By Dretzke J, Frew E, Davenport C, Barlow J, Stewart-Brown S, Sandercock J, *et al*.

Volume 10, 2006

No. 1
The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease.
By Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, *et al*.

No. 2
FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke.
By Dennis M, Lewis S, Cranswick G, Forbes J.

No. 3
The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews.
By Black C, Bagust A, Boland A, Walker S, McLeod C, De Verteuil R, *et al*.

No. 4
A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery.
By Whiting P, Gupta R, Burch J, Mujica Mota RE, Wright K, Marson A, *et al*.

No. 5
Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies.
By Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR.

No. 6
Systematic review and evaluation of methods of assessing urinary incontinence.
By Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review.
By Connock M, Frew E, Evans B-W, Bryan S, Cummins C, Fry-Smith A, *et al*.

No. 8
Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling.
By Garside R, Pitt M, Somerville M, Stein K, Price A, Gilbert N.

No. 9
Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation.
By Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, *et al*.

No. 10
Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients.
By Szczepura A, Westmoreland D, Vinogradova Y, Fox J, Clark M.

No. 11
Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study.
By Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Greaves M, *et al*.

No. 12
A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers.
By Nelson EA, O'Meara S, Craig D, Iglesias C, Golder S, Dalton J, *et al*.

No. 13
Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial).
By Michaels JA, Campbell WB, Brazier JE, MacIntyre JB, Palfreyman SJ, Ratcliffe J, *et al*.

No. 14
The cost-effectiveness of screening for oral cancer in primary care.
By Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M *et al*.

No. 15
Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis.
By Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, *et al*.

No. 16
Systematic review of the effectiveness and cost-effectiveness of HealOzone® for the treatment of occlusal pit/fissure caries and root caries.
By Brazzelli M, McKenzie L, Fielding S, Fraser C, Clarkson J, Kilonzo M, *et al*.

No. 17
Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment.
By Lewis SW, Davies L, Jones PB, Barnes TRE, Murray RM, Kerwin R, *et al*.

No. 18
Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation.
By Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, *et al*.

No. 19
Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial.
By Kennedy TM, Chalder T, McCrone P, Darnley S, Knapp M, Jones RH, *et al*.

No. 20
A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1.
By Connock M, Juarez-Garcia A, Frew E, Mans A, Dretzke J, Fry-Smith A, *et al*.

No. 21
Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.
By Wright M, Grieve R, Roberts J, Main J, Thomas HC on behalf of the UK Mild Hepatitis C Trial Investigators.

No. 22
Pressure relieving support surfaces: a randomised evaluation.
By Nixon J, Nelson EA, Cranny G, Iglesias CP, Hawkins K, Cullum NA, *et al*.

No. 23
A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents.
By King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, *et al*.

No. 24
The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review.
By Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, *et al*.

No. 25
Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model.
By Thomas KS, Keogh-Brown MR, Chalmers JR, Fordham RJ, Holland RC, Armstrong SJ, *et al*.

No. 26
A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use.
By Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, *et al*.

No. 27
A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost–utility for these groups in a UK context.
By Buxton M, Caine N, Chase D, Connelly D, Grace A, Jackson C, *et al*.

No. 28
Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation.
By Shepherd J, Jones J, Takeda A, Davidson P, Price A.

No. 29
An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial.
By Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C, *et al*.

No. 30
Accurate, practical and cost-effective assessment of carotid stenosis in the UK.
By Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, *et al*.

No. 31
Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.
By Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, *et al*.

No. 32
The cost-effectiveness of testing for hepatitis C in former injecting drug users.
By Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, *et al*.

No. 33
Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation.
By Kaltenthaler E, Brazier J, De Nigris E, Tumur I, Ferriter M, Beverley C, *et al*.

No. 34
Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.
By Williams C, Brunskill S, Altman D, Briggs A, Campbell H, Clarke M, *et al*.

No. 35
Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation.
By Brazier J, Tumur I, Holmes M, Ferriter M, Parry G, Dent-Brown K, *et al*.

No. 36
Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model.
By Whiting P, Westwood M, Bojke L, Palmer S, Richardson G, Cooper J, *et al*.

No. 37
Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme.
By O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A.

No. 38
A comparison of the cost-effectiveness of five strategies for the prevention of non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling.
By Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, *et al*.

No. 39
The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review.
By Waugh N, Black C, Walker S, McIntyre L, Cummins E, Hillis G.

No. 40
What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET).
By Williams J, Russell I, Durai D, Cheung W-Y, Farrin A, Bloor K, *et al*.

No. 41
The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation.
By Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P.

No. 42
A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.
By Chen Y-F, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, *et al*.

No. 43
Telemedicine in dermatology: a randomised controlled trial.
By Bowns IR, Collins K, Walters SJ, McDonagh AJG.

No. 44
Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model.
By Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C.

No. 45
Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation.
By Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, *et al*.

No. 46
Etanercept and efalizumab for the treatment of psoriasis: a systematic review.
By Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y, *et al*.

No. 47
Systematic reviews of clinical decision tools for acute abdominal pain.
By Liu JLY, Wyatt JC, Deeks JJ, Clamp S, Keen J, Verde P, *et al*.

No. 48
Evaluation of the ventricular assist device programme in the UK.
By Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, *et al*.

No. 49
A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children.
By Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, *et al*.

No. 50
Amniocentesis results: investigation of anxiety. The ARIA trial.
By Hewison J, Nixon J, Fountain J, Cocks K, Jones C, Mason G, *et al*.

Volume 11, 2007

No. 1
Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation.
By Dundar Y, Bagust A, Dickson R, Dodd S, Green J, Haycox A, *et al*.

No. 2
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer.
By Collins R, Fenwick E, Trowman R, Perard R, Norman G, Light K, *et al*.

No. 3
A systematic review of rapid diagnostic tests for the detection of tuberculosis infection.
By Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, *et al*.

No. 4
The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women.
By Stevenson M, Davis S, Lloyd-Jones M, Beverley C.

No. 5
A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines.
By Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K, *et al*.

No. 6
Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation.
By Adi Y, Juarez-Garcia A, Wang D, Jowett S, Frew E, Day E, *et al*.

No. 7
Glucocorticoid-induced osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M.

No. 8
Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection.
By Low N, McCarthy A, Macleod J, Salisbury C, Campbell R, Roberts TE, *et al*.

No. 9
Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation.
By Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, *et al*.

No. 10
Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only.
By Isaacs AJ, Critchley JA, See Tai S, Buckingham K, Westley D, Harridge SDR, *et al*.

No. 11
Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N.

No. 12
Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.
By Tappenden P, Jones R, Paisley S, Carroll C.

No. 13
A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment.
By Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, *et al*.

No. 14
A systematic review and economic evaluation of statins for the prevention of coronary events.
By Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, *et al*.

No. 15
A systematic review of the effectiveness and cost-effectiveness of different models of community-based respite care for frail older people and their carers.
By Mason A, Weatherly H, Spilsbury K, Arksey H, Golder S, Adamson J, *et al*.

No. 16
Additional therapy for young children with spastic cerebral palsy: a randomised controlled trial.
By Weindling AM, Cunningham CC, Glenn SM, Edwards RT, Reeves DJ.

No. 17
Screening for type 2 diabetes: literature review and economic modelling.
By Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, *et al*.

No. 18
The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Mealing S, Roome C, Snaith A, *et al*.

No. 19
The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation.
By Takeda AL, Jones J, Loveman E, Tan SC, Clegg AJ.

No. 20
A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease.
By Collins R, Cranny G, Burch J, Aguiar-Ibáñez R, Craig D, Wright K, *et al*.

No. 21
The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review.
By Colquitt JL, Kirby J, Green C, Cooper K, Trompeter RS.

No. 22
A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions.
By Fayter D, Nixon J, Hartley S, Rithalia A, Butler G, Rudolf M, *et al*.

No. 23
Systematic review of the effectiveness of preventing and treating *Staphylococcus aureus* carriage in reducing peritoneal catheter-related infections.
By McCormack K, Rabindranath K, Kilonzo M, Vale L, Fraser C, McIntyre L, *et al*.

No. 24
The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis.
By McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, *et al*.

No. 25
A randomised controlled trial and economic evaluation of direct versus indirect and individual versus group modes of speech and language therapy for children with primary language impairment.
By Boyle J, McCartney E, Forbes J, O'Hare A.

No. 26
Hormonal therapies for early breast cancer: systematic review and economic evaluation.
By Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L.

No. 27
Cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review.
By Bryant J, Picot J, Levitt G, Sullivan I, Baxter L, Clegg A.

No. 28
Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation.
By McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, *et al*.

No. 29
Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses.
By Colbourn T, Asseburg C, Bojke L, Philips Z, Claxton K, Ades AE, *et al*.

No. 30
Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review.
By Garrison KR, Donell S, Ryder J, Shemilt I, Mugford M, Harvey I, *et al*.

No. 31
A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial.
By Prescott RJ, Kunkler IH, Williams LJ, King CC, Jack W, van der Pol M, *et al*.

No. 32
Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen.
By Bamford J, Fortnum H, Bristow K, Smith J, Vamvakas G, Davies L, *et al*.

No. 33
The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation.
By Black C, Cummins E, Royle P, Philip S, Waugh N.

No. 34
Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis.
By Thompson Coon J, Rogers G, Hewson P, Wright D, Anderson R, Cramp M, *et al*.

No. 35
The Birmingham Rehabilitation Uptake Maximisation Study (BRUM). Home-based compared with hospital-based cardiac rehabilitation in a multi-ethnic population: cost-effectiveness and patient adherence.
By Jolly K, Taylor R, Lip GYH, Greenfield S, Raftery J, Mant J, *et al*.

No. 36
A systematic review of the clinical, public health and cost-effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food.
By Abubakar I, Irvine L, Aldus CF, Wyatt GM, Fordham R, Schelenz S, *et al*.

No. 37
A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial.
By Marson AG, Appleton R, Baker GA, Chadwick DW, Doughty J, Eaton B, *et al*.

No. 38
Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling.
By Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, *et al*.

No. 39
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder.
By Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, *et al*.

No. 40
Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation.
By Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A.

No. 41
The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation.
By Burr JM, Mowatt G, Hernández R, Siddiqui MAR, Cook J, Lourenco T, *et al*.

No. 42
Acceptability, benefit and costs of early screening for hearing disability: a study of potential screening tests and models.
By Davis A, Smith P, Ferguson M, Stephens D, Gianopoulos I.

No. 43
Contamination in trials of educational interventions.
By Keogh-Brown MR, Bachmann MO, Shepstone L, Hewitt C, Howe A, Ramsay CR, *et al*.

No. 44
Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers.
By Facey K, Bradbury I, Laking G, Payne E.

No. 45
The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Rogers G, Dyer M, Mealing S, *et al*.

No. 46
Drug-eluting stents: a systematic review and economic evaluation.
By Hill RA, Boland A, Dickson R, Dündar Y, Haycox A, McLeod C, *et al*.

No. 47
The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model.
By Fox M, Mealing S, Anderson R, Dean J, Stein K, Price A, *et al*.

No. 48
Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study.
By Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, *et al*.

No. 49
Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial.
By Sharples L, Hughes V, Crean A, Dyer M, Buxton M, Goldsmith K, *et al*.

No. 50
Evaluation of diagnostic tests when there is no gold standard. A review of methods.
By Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM.

No. 51
Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding.
By Leontiadis GI, Sreedharan A, Dorward S, Barton P, Delaney B, Howden CW, *et al*.

No. 52
A review and critique of modelling in prioritising and designing screening programmes.
By Karnon J, Goyder E, Tappenden P, McPhie S, Towers I, Brazier J, *et al*.

No. 53
An assessment of the impact of the NHS Health Technology Assessment Programme.
By Hanney S, Buxton M, Green C, Coulson D, Raftery J.

Volume 12, 2008

No. 1
A systematic review and economic model of switching from non-glycopeptide to glycopeptide antibiotic prophylaxis for surgery.
By Cranny G, Elliott R, Weatherly H, Chambers D, Hawkins N, Myers L, *et al*.

No. 2
'Cut down to quit' with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis.
By Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D.

No. 3
A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management.
By Thornton J, Ashcroft D, O'Neill T, Elliott R, Adams J, Roberts C, *et al*.

No. 4
Does befriending by trained lay workers improve psychological well-being and quality of life for carers of people with dementia, and at what cost? A randomised controlled trial.
By Charlesworth G, Shepstone L, Wilson E, Thalanany M, Mugford M, Poland F.

No. 5
A multi-centre retrospective cohort study comparing the efficacy, safety and cost-effectiveness of hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study.
By Hirst A, Dutton S, Wu O, Briggs A, Edwards C, Waldenmaier L, *et al*.

No. 6
Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling.
By Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, ter Riet G, Duley L, *et al*.

No. 7
The use of economic evaluations in NHS decision-making: a review and empirical investigation.
By Williams I, McIver S, Moore D, Bryan S.

No. 8
Stapled haemorrhoidectomy (haemorrhoidopexy) for the treatment of haemorrhoids: a systematic review and economic evaluation.
By Burch J, Epstein D, Baba-Akbari A, Weatherly H, Fox D, Golder S, *et al*.

No. 9
The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review.
By Loveman E, Frampton GK, Clegg AJ.

No. 10
Payment to healthcare professionals for patient recruitment to trials: systematic review and qualitative study.
By Raftery J, Bryant J, Powell J, Kerr C, Hawker S.

No. 11
Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation.
By Chen Y-F, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, *et al*.

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

HTA Commissioning Board

Members

Current and past membership details of all HTA 'committees' are available from the HTA website (www.hta.ac.uk)

Diagnostic Technologies & Screening Panel

Members

Chair,
Dr Ron Zimmern, Director of the Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Ms Norma Armston, Freelance Consumer Advocate, Bolton

Professor Max Bachmann, Professor of Health Care Interfaces, Department of Health Policy and Practice, University of East Anglia

Professor Rudy Bilous Professor of Clinical Medicine & Consultant Physician, The Academic Centre, South Tees Hospitals NHS Trust

Ms Dea Birkett, Service User Representative, London

Dr Paul Cockcroft, Consultant Medical Microbiologist and Clinical Director of Pathology, Department of Clinical Microbiology, St Mary's Hospital, Portsmouth

Professor Adrian K Dixon, Professor of Radiology, University Department of Radiology, University of Cambridge Clinical School

Dr David Elliman, Consultant in Community Child Health, Islington PCT & Great Ormond Street Hospital, London

Professor Glyn Elwyn, Research Chair, Centre for Health Sciences Research, Cardiff University, Department of General Practice, Cardiff

Professor Paul Glasziou, Director, Centre for Evidence-Based Practice, University of Oxford

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Clinical Director, Medicines & Healthcare Products Regulatory Agency, London

Mr Stephen Pilling, Director, Centre for Outcomes, Research & Effectiveness, Joint Director, National Collaborating Centre for Mental Health, University College London

Mrs Una Rennard, Service User Representative, Oxford

Dr Phil Shackley, Senior Lecturer in Health Economics, Academic Vascular Unit, University of Sheffield

Dr Margaret Somerville, Director of Public Health Learning, Peninsula Medical School, University of Plymouth

Dr Graham Taylor, Scientific Director & Senior Lecturer, Regional DNA Laboratory, The Leeds Teaching Hospitals

Professor Lindsay Wilson Turnbull, Scientific Director, Centre for MR Investigations & YCR Professor of Radiology, University of Hull

Professor Martin J Whittle, Clinical Co-director, National Co-ordinating Centre for Women's and Childhealth

Dr Dennis Wright, Consultant Biochemist & Clinical Director, The North West London Hospitals NHS Trust, Middlesex

Pharmaceuticals Panel

Members

Chair,
Professor Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Ms Anne Baileff, Consultant Nurse in First Contact Care, Southampton City Primary Care Trust, University of Southampton

Professor Imti Choonara, Professor in Child Health, Academic Division of Child Health, University of Nottingham

Professor John Geddes, Professor of Epidemiological Psychiatry, University of Oxford

Mrs Barbara Greggains, Non-Executive Director, Greggains Management Ltd

Dr Bill Gutteridge, Medical Adviser, National Specialist Commissioning Advisory Group (NSCAG), London

Mrs Sharon Hart, Consultant Pharmaceutical Adviser, Reading

Dr Jonathan Karnon, Senior Research Fellow, Health Economics and Decision Science, University of Sheffield

Dr Yoon Loke, Senior Lecturer in Clinical Pharmacology, University of East Anglia

Ms Barbara Meredith, Lay Member, Epsom

Dr Andrew Prentice, Senior Lecturer and Consultant Obstetrician & Gynaecologist, Department of Obstetrics & Gynaecology, University of Cambridge

Dr Frances Rotblat, CPMP Delegate, Medicines & Healthcare Products Regulatory Agency, London

Dr Martin Shelly, General Practitioner, Leeds

Mrs Katrina Simister, Assistant Director New Medicines, National Prescribing Centre, Liverpool

Dr Richard Tiner, Medical Director, Medical Department, Association of the British Pharmaceutical Industry, London

Therapeutic Procedures Panel

Members

Chair,
Professor Bruce Campbell, Consultant Vascular and General Surgeon, Department of Surgery, Royal Devon & Exeter Hospital

Dr Mahmood Adil, Deputy Regional Director of Public Health, Department of Health, Manchester

Dr Aileen Clarke, Consultant in Public Health, Public Health Resource Unit, Oxford

Professor Matthew Cooke, Professor of Emergency Medicine, Warwick Emergency Care and Rehabilitation, University of Warwick

Mr Mark Emberton, Senior Lecturer in Oncological Urology, Institute of Urology, University College Hospital

Professor Paul Gregg, Professor of Orthopaedic Surgical Science, Department of General Practice and Primary Care, South Tees Hospital NHS Trust, Middlesbrough

Ms Maryann L Hardy, Lecturer, Division of Radiography, University of Bradford

Dr Simon de Lusignan, Senior Lecturer, Primary Care Informatics, Department of Community Health Sciences, St George's Hospital Medical School, London

Dr Peter Martin, Consultant Neurologist, Addenbrooke's Hospital, Cambridge

Professor Neil McIntosh, Edward Clark Professor of Child Life & Health, Department of Child Life & Health, University of Edinburgh

Professor Jim Neilson, Professor of Obstetrics and Gynaecology, Department of Obstetrics and Gynaecology, University of Liverpool

Dr John C Pounsford, Consultant Physician, Directorate of Medical Services, North Bristol NHS Trust

Dr Karen Roberts, Nurse Consultant, Queen Elizabeth Hospital, Gateshead

Dr Vimal Sharma, Consultant Psychiatrist/Hon. Senior Lecturer, Mental Health Resource Centre, Cheshire and Wirral Partnership NHS Trust, Wallasey

Professor Scott Weich, Professor of Psychiatry, Division of Health in the Community, University of Warwick

Disease Prevention Panel

Members

Chair,
Dr Edmund Jessop, Medical Adviser, National Specialist Commissioning Advisory Group (NSCAG), London

Mrs Sheila Clark, Chief Executive, St James's Hospital, Portsmouth

Mr Richard Copeland, Lead Pharmacist: Clinical Economy/Interface, Wansbeck General Hospital, Northumberland

Dr Elizabeth Fellow-Smith, Medical Director, West London Mental Health Trust, Middlesex

Mr Ian Flack, Director PPI Forum Support, Council of Ethnic Minority Voluntary Sector Organisations, Stratford

Dr John Jackson, General Practitioner, Newcastle upon Tyne

Mrs Veronica James, Chief Officer, Horsham District Age Concern, Horsham

Professor Mike Kelly, Director, Centre for Public Health Excellence, National Institute for Health and Clinical Excellence, London

Professor Yi Mien Koh, Director of Public Health and Medical Director, London NHS (North West London Strategic Health Authority), London

Ms Jeanett Martin, Director of Clinical Leadership & Quality, Lewisham PCT, London

Dr Chris McCall, General Practitioner, Dorset

Dr David Pencheon, Director, Eastern Region Public Health Observatory, Cambridge

Dr Ken Stein, Senior Clinical Lecturer in Public Health, Director, Peninsula Technology Assessment Group, University of Exeter, Exeter

Dr Carol Tannahill, Director, Glasgow Centre for Population Health, Glasgow

Professor Margaret Thorogood, Professor of Epidemiology, University of Warwick, Coventry

Dr Ewan Wilkinson, Consultant in Public Health, Royal Liverpool University Hospital, Liverpool

Expert Advisory Network

Members

Professor Douglas Altman, Professor of Statistics in Medicine, Centre for Statistics in Medicine, University of Oxford

Professor John Bond, Director, Centre for Health Services Research, University of Newcastle upon Tyne, School of Population & Health Sciences, Newcastle upon Tyne

Professor Andrew Bradbury, Professor of Vascular Surgery, Solihull Hospital, Birmingham

Mr Shaun Brogan, Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE, Chief Executive, Regulation and Improvement Authority, Belfast

Ms Tracy Bury, Project Manager, World Confederation for Physical Therapy, London

Professor Iain T Cameron, Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark, Medical Writer & Consultant Pharmacist, Rossendale

Professor Collette Clifford, Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham, Edgbaston, Birmingham

Professor Barry Cookson, Director, Laboratory of Healthcare Associated Infection, Health Protection Agency, London

Dr Carl Counsell, Clinical Senior Lecturer in Neurology, Department of Medicine & Therapeutics, University of Aberdeen

Professor Howard Cuckle, Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Dr Katherine Darton, Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux, Professor of Paediatric Epidemiology, London

Dr Keith Dodd, Consultant Paediatrician, Derby

Mr John Dunning, Consultant Cardiothoracic Surgeon, Cardiothoracic Surgical Unit, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw, Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles, Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby, Professor of Community Rehabilitation, Institute of General Practice and Primary Care, University of Sheffield

Professor Gene Feder, Professor of Primary Care Research & Development, Centre for Health Sciences, Barts & The London Queen Mary's School of Medicine & Dentistry, London

Mr Leonard R Fenwick, Chief Executive, Newcastle upon Tyne Hospitals NHS Trust

Mrs Gillian Fletcher, Antenatal Teacher & Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn, Professor of Medicine, Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham

Dr Neville Goodman, Consultant Anaesthetist, Southmead Hospital, Bristol

Professor Robert E Hawkins, CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor Allen Hutchinson, Director of Public Health & Deputy Dean of ScHARR, Department of Public Health, University of Sheffield

Professor Peter Jones, Professor of Psychiatry, University of Cambridge, Cambridge

Professor Stan Kaye, Cancer Research UK Professor of Medical Oncology, Section of Medicine, Royal Marsden Hospital & Institute of Cancer Research, Surrey

Dr Duncan Keeley, General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping, Research Degrees Programme Director & Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy, Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay, Professor of Psychiatry for the Elderly, University of Leicester, Leicester General Hospital

Professor Julian Little, Professor of Human Genome Epidemiology, Department of Epidemiology & Community Medicine, University of Ottawa

Professor Rajan Madhok, Consultant in Public Health, South Manchester Primary Care Trust, Manchester

Professor Alexander Markham, Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Professor Alistaire McGuire, Professor of Health Economics, London School of Economics

Dr Peter Moore, Freelance Science Writer, Ashtead

Dr Andrew Mortimore, Public Health Director, Southampton City Primary Care Trust, Southampton

Dr Sue Moss, Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Mrs Julietta Patnick, Director, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler, Professor of Liaison Psychiatry, Royal South Hants Hospital, Southampton

Professor Chris Price, Visiting Professor in Clinical Biochemistry, University of Oxford

Professor William Rosenberg, Professor of Hepatology and Consultant Physician, University of Southampton, Southampton

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Dr Susan Schonfield, Consultant in Public Health, Hillingdon PCT, Middlesex

Dr Eamonn Sheridan, Consultant in Clinical Genetics, Genetics Department, St James's University Hospital, Leeds

Professor Sarah Stewart-Brown, Professor of Public Health, University of Warwick, Division of Health in the Community Warwick Medical School, LWMS, Coventry

Professor Ala Szczepura, Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor, Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster, Consumer member, HTA – Expert Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@hta.ac.uk
http://www.hta.ac.uk

ISSN 1366-5278