



Febuxostat for the treatment of hyperuricaemia in people with gout: a single technology appraisal

M Stevenson* and A Pandor

School of Health and Related Research (ScHARR), University of Sheffield, UK

*Corresponding author

Declared competing interests of authors: none

Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of febuxostat for the management of hyperuricaemia in patients with gout based upon a review of the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The submission's evidence came from two randomised controlled trials comparing the efficacy and safety of febuxostat with allopurinol. The trials were of reasonable methodological quality and measured a clinically relevant range of outcomes. A pooled clinical efficacy analysis showed that a daily dose of 80 mg or 120 mg of febuxostat was significantly more effective than fixed-dose allopurinol (300/100 mg/day) at lowering serum uric acid (sUA) levels to therapeutic targets (< 6 mg/dl); however, a large percentage of febuxostat patients did not achieve the primary end point and the fixed-dose allopurinol regimen may have introduced bias. There were no differences between treatments in more clinically important outcomes such as gout flares and tophi resolution after 52 weeks of treatment. No subgroup analyses were conducted for patients with renal impairment, non-responders to allopurinol or patients with severe disease. Supplementary data from a 2-year open-label extension study were also provided, but were difficult to interpret and poorly reported. The incidence of adverse events was similar between treatments, although more febuxostat recipients discontinued treatment prematurely. A decision tree model was

HTA 07/69/01

Date of ERG submission:

March 2008

TAR Centre(s):

The School of Health and Related Research (ScHARR)

List of authors:

M Stevenson and A Pandor

Contact details:

Matt Stevenson, Technical Director ScHARR-TAG, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA, UK

E-mail: m.d.stevenson@shef.ac.uk

The research reported in this article of the journal supplement was commissioned and funded by the HTA programme on behalf of NICE as project number 07/69/01. The assessment report began editorial review in October 2008 and was accepted for publication in April 2009. See the HTA programme web site for further project information (www.hta.ac.uk). This summary of the ERG report was compiled after the Appraisal Committee's review.

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

developed to determine the cost-effectiveness of febuxostat. The scope was limited to the comparison of continual febuxostat treatment with continual allopurinol treatment. Switching between treatments or withdrawing treatment in patients whose sUA levels had not decreased was not permitted. The model predicted a cost-effectiveness of £16,324 [95% confidence interval (CI) £6281 to £239,928] per quality-adjusted life-year (QALY) gained for febuxostat compared with allopurinol after 2 years of treatment. The incremental cost per QALY was below £20,000 in 63% of the simulations undertaken. Changes in the time horizon did not materially affect the results. The ERG believes that the modelling structure employed was not appropriate to estimate the cost-effectiveness of febuxostat within a treatment algorithm. In addition, there were concerns about the methodology used for collecting data on key model inputs. Given these reservations the cost-effectiveness of febuxostat could not be determined. The guidance issued by NICE in August 2008 as a result of the STA states that febuxostat is recommended as an option for the management of chronic hyperuricaemia in gout only for people who are intolerant of allopurinol or for whom allopurinol is contraindicated.

Introduction

The National Institute of Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.^{1,2} Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the manufacturer's evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of febuxostat for the management of hyperuricaemia in patients with gout.³

Description of the underlying health problem

Gout is a metabolic disorder that causes acute, intermittent and painful attacks of arthritis in the joints of the foot (especially the big toe), knee, hand and wrist. Gout occurs when there is a sudden onset of inflammation as a result of excess uric acid (crystals of monosodium urate) in the blood (hyperuricaemia) and tissues. Urate crystals deposited in and around joints and tissue are known as tophi,⁴ which can cause significant pain.

The incidence of gout has been estimated to range from 11.9 to 18.0 cases per 10,000 patient-years.⁵ Incidence is affected by both age and gender, with men aged from 65 to 84 years having an incidence rate approximately 60 times greater than that in women aged below 45 years.⁵ The overall prevalence of gout in the UK has been estimated at 1.4%,^{5,6} with this value being 7.3% among men aged from 65 to 75 years.⁵

Scope of the ERG report

The objective of the appraisal was to assess the clinical effectiveness and cost-effectiveness of febuxostat for the management of hyperuricaemia in adults with gout in whom urate deposition has already occurred (including a history or presence of tophus and/or gouty arthritis). The comparators included: allopurinol, alternative standard care (including sulphinyprazole, benzbromarone, probenecid or a combination of these) for adults unresponsive to or with hypersensitivity to allopurinol, and allopurinol (dose adjusted according to glomerular filtration rate), benzbromarone or a combination of these for adults with renal impairment. The outcomes measured included surrogate [serum uric acid levels (sUA)] and clinical outcomes (gout flares, reduction in tophi size), tolerance and health-related quality of life.

The main evidence presented in support of the clinical effectiveness of febuxostat was based on two head-to-head, phase III, randomised controlled trials [the Febuxostat Allopurinol Controlled Trial (FACT) study⁷ and the Allopurinol and Placebo-controlled Efficacy study of febuxostat (APEX) trial⁸] comparing the efficacy and safety of febuxostat with fixed-dose allopurinol. The manufacturer did not present comparisons with alternative comparators (such as sulphinyprazole,

benzbromarone, probenecid or a combination of these) for adults unresponsive to, or intolerant of, allopurinol or with renal impairment.

The scope of the manufacturer's cost-effectiveness submission was limited to the comparison of continual febuxostat treatment with continual allopurinol treatment. Switching between treatments was not permitted, nor was there the possibility of withdrawing treatment in patients whose sUA levels had not decreased. Although the dosage level of febuxostat was allowed to vary, increasing from 80 mg daily to 120 mg daily in patients not initially responding to treatment, the dose of allopurinol was assumed fixed at 300 mg per day. Costs were considered from an NHS and personal social services perspective. Cost-effectiveness was expressed in terms of incremental cost per quality-adjusted life-year (QALY) gained, with a time horizon of 2 years used for the base-case results.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process. A narrative critique of the submitted evidence was presented. The economic model submitted by the manufacturer was regarded as inappropriate to assess the decision problem.

Results

Summary of submitted clinical evidence

A pooled (not meta-analysed) clinical efficacy analysis of two head-to-head, multiarm, randomised, double-blind, controlled trials (52-week FACT study⁷ and 28-week APEX trial⁸) comparing the efficacy and safety of febuxostat with fixed-dose allopurinol in 1689 patients with hyperuricaemia (sUA levels ≥ 8 mg/dl) and gout showed that febuxostat (80 mg/day and 120 mg/day) was significantly more effective than fixed-dose allopurinol (300/100 mg/day) at reducing sUA levels to < 6 mg/dl. However, a large percentage of patients on febuxostat did not achieve the primary end point and the fixed-dose regimen employed for allopurinol patients may have introduced bias.

Despite the significantly greater effect on sUA levels with febuxostat (including mean percentage reduction from baseline) than with allopurinol,

there were generally no differences between treatments in more clinically important outcomes such as gout flares and tophi resolution (secondary end points).

A post hoc subgroup analysis showed that febuxostat was more effective than allopurinol in decreasing sUA levels to < 6 mg/dl in patients with baseline sUA concentrations of < 9 mg/dl, between 9 and 10 mg/dl and > 10 mg/dl. In addition, significantly more febuxostat recipients than fixed-dose allopurinol recipients achieved a reduction in sUA levels to therapeutic targets (< 5 mg/dl). No subgroup analyses were conducted for patients with renal impairment, non-responders to allopurinol or patients with severe disease.

Supplementary data from an ongoing, long-term, open-label extension study (EXCEL – fEbuXostat/allopurinol Comparative Extension Long-term study) of the two head-to-head trials showed that more patients on febuxostat (80 mg/day and 120 mg/day) than on fixed-dose allopurinol (300/100 mg/day) remained on initial treatment after more than 24 months of follow-up, and the number of tophi and gout flares were reduced over time in these patients. However, these data need to be interpreted with caution as the manufacturer's submission does not provide statistical analysis of event rates over time or data on withdrawals because of gout flares, adverse events or non-response.

Although the adverse event profile was similar in those receiving febuxostat compared with those receiving allopurinol, more febuxostat recipients discontinued treatment prematurely [the statistical analysis comparing the rates of discontinuation between the treatment groups was not reported in the manufacturer's submission or in the requested supplementary data; however, the primary published peer-reviewed clinical paper for the FACT study reports that the rates of discontinuation were significantly higher in febuxostat recipients ($p < 0.04$) than in those receiving allopurinol]. Reasons for withdrawal included gout flares and adverse events such as liver function test abnormalities.

Summary of submitted cost-effectiveness evidence

A decision tree model was developed in Microsoft EXCEL. The model subdivided patients into four mutually exclusive categories of sUA levels, which were related to both the expected number of gout flares and the underlying utility of a patient. Two

identical cohorts of men and women entered the model with an assumed baseline sUA acid level of ≥ 8 mg/dl. One cohort was assumed to receive 80 mg/day of febuxostat treatment, increased to 120 mg/day in those patients who did not adequately respond; the remaining cohort was assumed to receive 300 mg/day of allopurinol. The primary analysis was for a period of 2 years; however, sensitivity analyses were undertaken using different time periods.

The manufacturer's submission predicted a cost-effectiveness of £16,324 (95% CI £6281 to £239,928) per QALY gained for febuxostat compared with allopurinol after 2 years of treatment. The incremental cost per QALY was below £20,000 in 63% of the simulations undertaken. Changes in the time horizon did not materially affect the results.

Commentary on the robustness of submitted evidence

The manufacturer conducted an adequate systematic search for clinical effectiveness and cost-effectiveness studies of febuxostat for the treatment of gout. It appears unlikely that any additional trials would have met the inclusion criteria had the search been widened to include other databases. The processes undertaken by the manufacturer for screening studies, data extraction and applying quality criteria to included studies are not explicitly clear in the submission. These factors limit the robustness of the systematic review.

The two identified trials, which represent the main clinical efficacy evidence, were of reasonable methodological quality (with some limitations) and measured a range of outcomes that are as appropriate and clinically relevant as possible. Although a simple pooled analysis of the individual patient level data from the two head-to-head trials was undertaken by the manufacturer, the methods for this type of data pooling were not explicitly described. The statistical approach for combining the data appears to be inappropriate as it fails to preserve randomisation and introduces bias and confounding. The resulting pooled data should therefore be treated with caution. A meta-analysis undertaken by the ERG showed that the methodology used by the manufacturer to synthesise the data was unlikely to alter the conclusions on efficacy.

The ERG considered the modelling structure inappropriate. Given the nature of the disease and the interventions it was deemed likely that a treatment algorithm that started all patients on the relatively inexpensive allopurinol and which treated those who did not respond with the more expensive febuxostat would be more cost-effective than the strategies evaluated in the submission. The ERG requested that the following analysis be undertaken at a minimum: allopurinol – febuxostat – no treatment; febuxostat – allopurinol – no treatment; allopurinol – no treatment and febuxostat – no treatment; however, the manufacturer did not comply with this request.

Even overlooking the inappropriateness of the model structure there were a number of errors within the analyses presented. For example, the price of allopurinol was incorrect and the price of febuxostat was altered within the probabilistic sensitivity analyses. Reanalyses were not undertaken by the manufacturer despite these issues being raised.

The ERG has serious concerns regarding the data selected to estimate the relationship between sUA levels and the number of gout flares expected. A large portion of the data collected to develop this linkage was excluded (accounting for 51% of all patients and 77% of UK patients), and the ERG was not convinced by the arguments provided to exclude these data.

The ERG has additional serious concerns about the interpretation of the multivariate analyses. It is indicated that there is no significant association between sUA levels and the number of gout flares reported within the data set used. This analysis has apparently been overlooked in favour of a bivariate analysis that does not include other confounders. Note that, although no statistically significant relationship was found within this data set, this does not mean that such a relationship does not exist, as indicated in clinical guidelines.

The ERG noted that the chronic utility gain associated with reduced sUA levels was a key driver in the cost per QALY gained ratio. It was noted that the relationship between sUA level and chronic utility had been modelled assuming a linear relationship. The evidence for this assumption was uncertain and not clearly established.

The ERG noted that the derivation of the disutility associated with a gout flare came from data that did

not appear internally consistent, with some people giving greater utility to a health state associated with a gout flare than to one without such a flare.

The ERG further noted that the dose of allopurinol was assumed to be fixed, whereas guidelines allow for the upwards titration of this dose. Although the manufacturer reported that the dose of allopurinol commonly used was 300 mg/day, this does not represent best practice, which allows for doses of 900 mg/day of allopurinol.

Conclusions

The clinical evidence, based on a simple pooled analysis of the patient level data from two randomised controlled trials, showed that a daily dose of 80 mg or 120 mg of febuxostat was significantly more efficacious than allopurinol at the commonly used fixed daily dose of 300 mg in lowering sUA levels to therapeutic targets (< 6 mg/dl). However, a large percentage of patients on febuxostat did not achieve the primary end point and the fixed-dose regimen employed for allopurinol patients may have introduced bias. In general, there were no differences between treatments in more clinically important outcomes such as gout flares and tophi resolution after 52 weeks of treatment. No subgroup analyses were conducted for patients with renal impairment, non-responders to allopurinol or patients with severe disease. Supplementary data from a 2-year open-label extension study were also provided, but were difficult to interpret (no statistical analysis undertaken) and poorly reported.

The ERG believes that the modelling structure employed was not appropriate to estimate the cost-effectiveness of febuxostat within a treatment algorithm. In addition, there were concerns about the methodology used for collecting data on key model inputs. Given these reservations the cost-effectiveness of febuxostat could not be determined.

Key issues

The head-to-head trials presented in the manufacturer's submission directly compared febuxostat with fixed-dose allopurinol. However, gout management guidelines and the allopurinol summary of product characteristics generally recommend dose titration of allopurinol according to therapeutic targets (usual maintenance dose in mild conditions 100–200 mg/day, in moderately severe conditions 300–600 mg/day, in severe

conditions 700–900 mg/day). Nevertheless, the manufacturer's submission and our clinical advisors suggest that dose escalation is rarely used by most clinicians in clinical practice.

Although measures such as gout flares and tophi resolution were secondary outcomes, these are more clinically important. Randomised controlled trial evidence shows that even though more febuxostat recipients achieved the recommended biochemical goal (< 6 mg/dl) this did not translate into an advantage over allopurinol in clinically important outcomes.

As previously described, the ERG has serious concerns regarding the model structure (and choice of treatment algorithms compared) and the robustness of key parameters within the model.

Areas of uncertainty

There is uncertainty around the clinical effectiveness and cost-effectiveness of febuxostat in comparison to other relevant treatments (including sulphinyprazole, benzbromarone, probenecid or a combination of these) for adults unresponsive to, or intolerant of, allopurinol or with renal impairment. In addition, long-term efficacy and safety data are limited on febuxostat and there is uncertainty around the relationship between sUA levels and the expected number of gout flares.

The incremental costs per QALY of sequential approaches of treatment are uncertain as these approaches have not been modelled. The inclusion of sequential treatments is likely to produce a more cost-effective solution than allowing only one treatment for the duration of the model. Moreover, there is uncertainty in the relationship between sUA levels and underlying patient utility.

Summary of NICE guidance issued as a result of the STA

The appraisal consultation document issued by NICE in May 2008 stated that:

Febuxostat is not recommended for the management of chronic hyperuricaemia in people with gout.

The manufacturer appealed against the preliminary decision and produced additional evidence not contained in the STA submission that compared febuxostat with no treatment. This evidence was not formally critiqued by the ERG.

In August 2008 the final appraisal determination was released with the guidance that febuxostat, within its marketing authorisation, is recommended as an option for the management of chronic hyperuricaemia in gout only for people who are intolerant of allopurinol or for whom allopurinol is contraindicated.

Intolerance of allopurinol was defined as:

adverse effects that are sufficiently severe to warrant its discontinuation, or to prevent full dose escalation for optimal effectiveness as appropriate within its marketing authorisation.

At the time of writing the manufacturer was appealing this decision.

Key references

1. National Institute for Health and Clinical Excellence. *Single technology appraisal (STA) – specification for manufacturer/sponsor submission of evidence*. URL: www.nice.org.uk/niceMedia/pdf/STASpecManufacturerSubofEvidence.pdf.
2. National Institute for Health and Clinical Excellence. *Guide to the single technology (STA) process*. 19 September 2006. URL: www.nice.org.uk/page.aspx?o=STAprcessguide.
3. Stevenson M, Pandor A. *Febuxostat for the management of hyperuricaemia in patients with gout: a single technology appraisal*. 2008. URL: www.ncchta.org/erg/reports/1704.pdf.
4. Falasca GF. Metabolic diseases: gout. *Clin Dermatol* 2006;**24**:498–508.
5. Mikuls TR, Farrar JT, Bilker WB, Fernandes S, Schumacher HR, Saag KG. Gout epidemiology: results from the UK General Practice Research Database, 1990–1999. *Ann Rheum Dis* 2005;**64**:267–72.
6. Annemans L, Spaepen E, Gaskin M, Bonnemaire M, Malier V, Gilbers T, *et al*. Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000–2005. *Ann Rheum Dis* 2007;**8**:67:960–6.
7. Becker MA, Schumacher R, Wortmann RL, MacDonald PA, Eustace D, Palo WA, *et al*. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med* 2005;**353**:2450–61.
8. Schumacher HR, Becker MA, Wortmann RL, MacDonald PA, Hunt B, Streit J, *et al*. Febuxostat vs allopurinol and placebo in subjects with hyperuricemia and gout: the 28-week APEX study. Poster presented at the Annual Scientific meeting of the American College of Rheumatology, San Diego, CA, 16–17 November 2005.