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Prucalopride for the treatment of women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief

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Contributions of authors
Pennant, Routh, Meads – critical appraisal of clinical effectiveness, Orlando, Barton, critical appraisal of economic modelling, Bayliss – searches, all - writing the report

Contents

1 SUMMARY

1.1 Scope of the submission

The NICE scope of this project was to assess the clinical effectiveness and cost effectiveness of prucalopride in the treatment of chronic constipation in women in whom laxatives fail to provide adequate relief.

1.2 Summary of submitted clinical effectiveness evidence

There were 36 trials/studies listed and information from nine of these was used to inform the clinical effectiveness part of the submission. Trial participants were adult and elderly men and women with chronic constipation. It appears that many participants in these trials had not failed previous laxative use and the spread of baseline predicted EQ-5D scores suggested than all patients were unlikely to have had severe chronic constipation. The intervention in the studies was oral prucalopride at dose 1mg, 2mg or 4mg per day and the comparators were placebo or a different dose of prucalopride. Rescue treatment with a laxative (bisacodyl) or an enema was used in both arms of the pivotal RCTs. Outcome results given were spontaneous complete bowel movements (SCBMs), spontaneous bowel movements (SBMs), bisacodyl/enema use, symptoms (including PAC-Sym), quality of life (PAC-QOL, SF-36) and adverse events. The primary outcome was the proportion of patients with average ≥3 SCBMs/week at weeks 4 and 12 and there was a statistically significant improvement in this outcome in the 2mg prucalopride arm (licensed dose in adult women) compared to placebo for adults in the three pivotal RCTs (INT-6, USA-11, USA-13). Although two RCTs used to inform the economic model were in elderly patients, only one was fully described in the submission (INT-12) and this did not show a significant improvement in the primary outcome measure of the proportion of patients with ≥3 SCBMs/week at week 4 in the 1mg prucalopride arm (licensed dose in elderly women) compared to placebo.

1.3 Summary of submitted cost effectiveness evidence

There were no published economic evaluations of prucalopride in chronic constipation. A de novo cost effectiveness model was submitted. This model had a one year time horizon and stated that it estimated increased costs and QALY gain from the use of prucalopride in a population for whom laxative treatment had failed. The only cost included in the model was the cost of prucalopride: it was assumed that other costs would be at least as high without prucalopride as with prucalopride, and therefore the costing assumption was stated to be conservative. QALY gains were estimated by a range of regression equations. Two different stopping rules were applied to determine whether patients had responded to treatment. Non-responders at 4 weeks were assumed to stop treatment at 4 weeks, and to have gained no benefit from the treatment. The model structure calculated an ICER for a large number of simulated individual patients: the variation here is a mixture of parameter uncertainty and variability in individual patient characteristics. The quoted ICERs were based on two separate patient groups: Adults (under 65) at a dose of 2mg daily, and Elderly (over 65) at a dose of 1mg daily. Overall ICERs were given as well as the ICERs for these two groups separately. The manufacturer's base case result using the primary clinical endpoint of at least 3 spontaneous complete bowel movements (SCBM) per week gave an overall ICER of £15,700/QALY (£16,800/QALY for adults, £11,700/QALY for elderly). Using the secondary endpoint (an increase of at least 1 SCBM per week) gave reported ICERs of £18,000/QALY overall (£18,000/QALY for adults, £15,800/QALY for elderly).

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

There is a considerable quantity of clinical effectiveness evidence in adults that consistently suggests an improvement in constipation from prucalopride compared to placebo. Some of the prucalopride RCTs are available as peer-reviewed publications.

Prucalopride is a relatively inexpensive drug at £2.13 per 2mg tablet.

1.4.2 Weaknesses

There are a number of weaknesses in the clinical evidence and the economic modelling

- The trials were conducted in adults rather than women only and it appears that the licence was based on a post-hoc subgroup analysis. There were approximately 10% of men and 90% of women in the pivotal RCTs.
- It appears that many patients responded to the use of bisacodyl treatment during the trials. Therefore many patients did not appear to be laxative-refractory and so do not fall into the licensed indication.
- Results for adverse events were only given where they affected more than 5% of participants in any arm of the pivotal trials. Therefore, rarer serious side effects, such as cardiovascular events, might be missed.
- EQ-5D was not measured in the pivotal trials and no literature on EQ-5D results were available for chronic constipation. SF-36 was measured but this was not used in the economic modelling. Most of the SF-36 results for the pivotal trials showed no significant differences. A disease-specific quality of life measure was used instead (PAC-QOL) which was then converted to EQ-5D using a mapping equation. This mapping equation appears to have been specifically developed for prucalopride.
- A large number of scenarios were explored in the economic model but these were not described in the submission.
- The design of the economic model has a number of weaknesses.
- The probabilistic sensitivity analysis (PSA) is based on a mixture of patient variability (in terms of baseline EQ-5D) and parameter uncertainty (in terms of regression coefficients). The ICERs reported in the submission are the 50% points from this PSA and not based on the mean results, although the difference is small.
- No account has been taken of adverse events
- Some results were only given in terms of the overall population. It is important to separate the two age groups: adult and elderly

- The model only allowed for variation in the response rate and mean treatment rates to be addressed through the “compliance” figure. Uncertainty in this figure was not included in the probabilistic analysis.
- No explicit allowance was made for withdrawal from treatment at any time after 4 weeks.

1.4.3 Areas of uncertainty

- Since trials were not conducted in the appropriate type of patients, it is uncertain how effective prucalopride is in the patient group for which it is licensed: women who are refractory to laxatives.
- It is uncertain how effective prucalopride is compared to the other comparators specified in the NICE scope decision problem, i.e. invasive procedures and bowel surgery.
- The relative long-term effectiveness of prucalopride compared to placebo is uncertain. The effectiveness results suggested a small comparative reduction in effectiveness between 4 and 12 weeks. High rates of patient drop-out from extension studies were likely to give an optimistic estimate of long-term effectiveness. Extension studies were only in patients given prucalopride (and not placebo) so no comparative evidence is available beyond 12 weeks.
- No meta-analysis of trial results was conducted, yet “pooling of clinical data” was conducted for the economic modelling. It is uncertain how this was done.
- It is uncertain how the differences in trial populations compared to the scope of the appraisal would affect cost-effectiveness. However, if 20% of participants in the pivotal trials had not previously used laxatives, they would be more likely to respond to any treatment, compared to those who had tried a number of previous laxatives. Therefore, the effectiveness would appear to be greater, which would improve the cost effectiveness.
- It is unclear how using the SF-36 results would have affected the cost effectiveness estimates. As there were mostly no significant differences in SF-36 results for the pivotal trials, it is possible that the calculated cost effectiveness results would have been higher.

- The clinical effectiveness results actually used in the economic modelling are unclear, as several of the studies used in the model (INT-1, INT-2, USA-3, GBR-4, FRA-1, USA-26) are not fully described in the submission.
- The assumption that the last measured QALY gain is sustained for the rest of the year is not tested in the model

1.5 Key issues

- It is likely that the effectiveness of prucalopride has been overestimated, due to issues to do with patient selection, comparator used, outcomes used or not used and extension study issues in the trials and studies where this information was made available.
- There are unsubstantiated assumptions relating to the long-term (52 weeks) effectiveness of prucalopride.
- There is a lack of transparency around patients and trial and study results used to inform the economic model
- The data used for mapping effectiveness to EQ-5D was not made available.
- If the regression results are to be believed, it is possible that prucalopride is cost-effective. However, the lack of transparency in the results from the 10 prucalopride trials and studies feeding into the economic model and the lack of transparency over the EQ-5D mapping means that it is not possible to establish a more accurate estimate of cost effectiveness.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

Section 2 (pg 18-21) of the submission gives an adequate description of the aetiology of chronic constipation. The submission briefly describes the different underlying causes and then gives the definition of chronic constipation as classified according to the Rome III criteria. These criteria are

the presence of two or more of the following symptoms for at least three months with symptom onset at least six months prior to diagnosis:

- Straining during at least 25% of defecations;
- Lumpy or hard stools in at least 25% of defecations;
- Sensation of incomplete evacuation for at least 25% of defecations;
- Sensation of anorectal obstruction/blockage for at least 25% of defecations;
- Manual manoeuvres to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor);
- Fewer than 3 defecations per week.

These criteria define chronic constipation but the description of underlying health problem lacks further detail on the aetiology of disease in the specific group of patients for whom prucalopride may be indicated: those with chronic constipation that is refractory to laxative treatment. Although there may not be clearly defined criteria for the classification of these types of patients, a better distinction could have been drawn between those suffering from chronic constipation in whom laxative treatments bring some degree of success and those patients in whom a range of types of laxatives have been tried with no success. These patients, in whom prucalopride may be a last option to avoid invasive treatments, have more severe disease than the general population with chronic constipation and this distinction should have been made clear in the description of the underlying health problem.

In the submission (p 19) it is assumed that10% of constipation patients are dissatisfied or refractory to laxatives. This suggests that people who are dissatisfied with laxatives should be considered as those who are refractory to laxitives. The prucalopride SPC lists the indication as “women in whom laxatives fail to provide adequate relief”. It may be more appropriate to consider just those patients who are refractory to a number of laxatives, in whom there are no other treatments available.

2.2 Critique of manufacturer's overview of current service provision

The introduction section of the submission is not referenced and it is therefore unclear on what basis assertions have been made. Details of the conventional clinical pathway for patients with chronic constipation are not properly described and there is no description of the classes and specific types of laxative treatment that are used in current practice. This would have been helpful in order to give a clear impression of the patients that would be eligible for treatment with prucalopride (licensed for those failing previous laxative treatments).

In the British National Formulary 2010[1] laxatives and bowel cleansing preparations are divided into five classes as follows:

- Bulk-forming laxatives – Relieve constipation by increasing faecal mass which stimulates peristalsis. These laxatives include ispaghula husk, methylcellulose and sterculia.
- Stimulant laxatives – increase intestinal motility and include bisacodyl, dantron, docusate sodium, glycerol, senna and sodium picosulfate.
- Faecal softeners - Act by softening faeces. They can also lubricate the faecal matter, enabling it to pass more easily through the intestine and include Arachis oil and liquid paraffin.
- Osmotic laxatives – These increase the amount of water in the large bowel, either by drawing fluid from the body into the bowel or by retaining the fluid with which they were administered. Osmotic laxatives can be administered orally, for example lactulose, macrogols and magnesium salts or as rectal solutions, for example phosphates and sodium citrate (enemas).
- Peripheral opioid-receptor antagonists – for people with opioid-induced constipation in palliative care, for example methylnaltrexone.

Bulk-forming laxatives may be the safest type of laxatives for long-term use because their action is similar to the natural action of fibre in food. People

[1] Anon. British National Formulary 59. BMJ Group/ Parmaceutical Press, London 2010.

need to drink plenty of water when taking these laxatives because the bulky stools may otherwise eventually block the intestine. Side effects of bulk-forming laxatives may include excess intestinal gas, abdominal pain and bloating.

3 Critique of manufacturer's definition of decision problem

This critique of the manufacturer's definition of the decision problem relates to the manufacturer's statement of the decision problem in comparison with the scope set out by NICE. A discussion of the appropriateness of populations, interventions, comparators and outcomes used for the submission and the included prucalopride trials can be found in the 'critique of submitted evidence synthesis' (section 4.2.2.1) part of this report.

3.1 Population

In the NICE scope, the population is defined as: "Women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief and for whom more invasive procedures such as direct rectal intervention, are being considered" whereas, in the submission, this is amended to: "Women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief."

In clinical practice, following failure of treatments with laxatives, treatment strategies may vary between patients. However, for most patients, if all laxative strategies have been tried, direct rectal intervention is likely to be considered. Although the decision problem is not inaccurate, the change made from the scope to the decision problem relaxes the scope's emphasis that the patients for consideration in this submission should be those that have undergone numerous laxative treatments and end-of-the-line measures are being considered.

However, as discussed later in the critique of submitted evidence (see section 4.2.2), of greater concern in relation to the population is that patients in the

included trials do not meet the requirements of the decision problem and do not reflect patients for whom this drug is licensed.

3.2 Intervention

The technology is Prucalopride (trade name Resolor). Prucalopride is not considered to fall into one of the five classes of laxative treatments. It belongs to a subgroup of drugs that act on serotonin receptors (serotonin (5-HT4) receptor agonist) that act on the colon to stimulate motility. It has marketing authorisation for the symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief but is not licensed in men. However, since it does not appear to have a hormone-related mode of action, it is unclear why there would be a different level of effectiveness in men. It is licensed at doses of 1mg in adult women and elderly women (over 65) and 2mg in adult women.

3.3 Comparators

The comparators outlined in the scope were a) standard therapy without prucalopride, b) invasive procedures such as rectal interventions (including enemas, suppositories and manual evacuation), c) bowel surgery. In the submission decision problem, this is reduced to only a) standard therapy without prucalopride.

The justification in the submission for removal of invasive procedures and bowel surgery as comparators is that these are not direct comparators. However, after failure with all laxative treatments, it is likely that more invasive treatments would be used (personal communication, Dr J Goh, Queen Elisabeth Hospital Birmingham, May 2010) and the removal of these procedures as comparators appears unjustified. However, of greater concern is that the comparator used in the trials on which this submission is based does not fit the decision problem, as discussed later in this report (section 4.2.2).

3.4 Outcomes

No significant changes in outcomes were made in the decision problem from those set out in the scope.

In the decision problem, a cut off of ≥3 spontaneous complete bowel movements (SCBM) per week is used as a primary outcome measure and this may be justified since ≥3 bowel movements per week is considered to be within normal limits. However, the term 'spontaneous' describes bowel movements that are considered not to be brought about by laxative treatment or an enema. The use of this criterion may be a flaw in the trials in this submission because it could result in an overestimation of the effectiveness of prucalopride. This is discussed in the critique of clinical effectiveness (section 4.2.2.1).

In the scope, quality of life is specified as an outcome. In the submission decision problem, a more specific measure of quality of life is given (PAC-QOL). Relief of symptoms of chronic constipation and quality of life were to be measured using the PAC-Sym and PAC-QOL questionnaires. These questionnaires provide detailed information on symptoms and quality of life, especially related to constipation. The submission decision problem specifies the use of PAC-QOL results only, but the trials included in the submission also measured SF-36 (see section 4).

The decision problem states that adverse events were to be presented in the submission and the manufacturer particularly state that cardiovascular and central nervous system-related events would be highlighted. Although the decision problem was appropriate, full results for adverse events were not presented and this is discussed in section 4.1.6 (Description and critique of manufacturer's outcome selection).

3.5 Time frame

The time frame used in the economic model is 52 weeks. Data is extrapolated from 12 week trials and, in some cases, results from 4 week trials are extrapolated to 52 weeks. This is justified on page 118 of the manufacturer's submission:

Observational study data collected in adult female patients for an additional 40 weeks beyond the initial trial period emphasised the patients satisfaction with prucalopride therapy was maintained over the initial year (52 weeks) of prucalopride therapy in adult female patients.

However, it does not appear to have been appropriate to make this assumption based on data from the single-arm extension studies. Three long-term studies (INT-10, INT-17, USA-22), containing mixed groups of patients from different clinical trials, form the basis for this assumption. These studies are appraised in section 4.2.2 of this report. The use of this data was inappropriate because:

1) No information is available for patients receiving placebo treatment and assumptions cannot therefore be made about long-term comparative effectiveness and, more importantly,

2) The high attrition from these studies (average >50% at 12 months) was likely to have resulted in biased data since patients who were more satisfied with their treatment were more likely to remain in the studies.

3.6 Other relevant factors

None identified.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturers search strategy

The submission section 9.2 Appendix 2 Search strategy for section 5.1 (Identification of studies) states that "a systematic review was not performed as part of this submission." Thus no strategies were submitted.

As a result of submitting clarification questions the ERG was informed that an in-house database (The Prucalopride Clinical Development Database of Movetis) was searched for phase II-III placebo-controlled studies.

The manufacturer also stated in response to the clarification questions that searches on MEDLINE and ClinicalTrials.gov using the keyword prucalopride failed to identify any additional trials on prucalopride.

Having clarified that some searches were in fact conducted but given that these appeared to be quite limited (the ERG would suggest at least searching EMBASE and CENTRAL in addition, and including synonym name Resolor in the strategy), the ERG carried out their own searches (see Appendix 1) and the results were examined by the ERG team. However, as the manufacturer had not referenced the studies used in the submission it was difficult to establish whether any additional references were found.

4.1.2 Inclusion/exclusion criteria used for study selection

No formal inclusion/exclusion criteria for study selection are stated in the submission. This information would normally be expected in the sections where manufacturers are requested to give information on how they identified studies and their methods of study selection (section 5.1 and 5.2).

However, in part of the 'context' section (paragraph 2, page 20), the patient group that is described as forming the basis for the submission is defined. The four criteria for defining the target population for prucalopride in this submission are:

1. Onset of symptoms at least 6 months prior to diagnosis
2. Should have tried at least one laxative with unsatisfactory symptomatic response
3. Fewer then three satisfactory defecations per week on laxative treatment
4. Breakthrough symptoms on laxative treatment must included two or more of the following in at least 20% of defecations: A) Straining, B) Lumpy or hard stools, C) Sensation of incomplete evacuation, D) Sensation of anorectal obstruction/blockage

These criteria do not appear to fit the patient population in the licensed indication because:

1) The target population, patients with severe chronic constipation who have undergone a variety of unsuccessful treatments, are likely to have been undergoing treatment for far longer than 6 months and this cut off is likely to be too short.

2) To define the population as only having necessarily taken one type of laxative treatment is inappropriate since the target population for this guidance are patients that have failed on a range of previous laxative medications. In normal clinical practice, numerous treatments would be applied before a patient is defined as not responding to laxative treatment.

3) Patients having one or two defecations per week whilst on laxative treatment are likely to be having beneficial effects from laxatives. This definition is therefore inappropriate since it is likely to include patients who have not truly failed previous laxative treatment and these patients are outside of the intended scope for this submission.

4) The criteria used to define failure of previous laxative treatments (see A-D above) are inappropriate because two of these criteria alone would be unlikely to be sufficient evidence of treatment failure with laxatives.

4.1.3 Included and excluded studies

A table of identified phase II and phase III trials and other studies is given on page 27 of the submission. Identified studies are shown below (see Table 1) but it was not possible to tell for some of these whether they are RCTs or other study designs. Of these trials and studies, nine are described in the submission and data from ten are used to inform the economic model. However, trials and studies used to inform the economic model do not fully correspond with those described in the submission. Table 1 below shows all the identified trials and studies and indicates which were fully described and which were used for the economic model. It appears that five used for the economic model are not fully described in the submission (INT-1, INT-2 and USA-3 (phase II dose response studies), FRA-1 (subjects with objective chronic constipation) and GBR-4 (phase II study, 1mg prucalopride).

Table 1. Trials and studies identified in the submission

	Trial/Study		
Type of trial/study	Identified in submission	Described in submission	Used to inform economic model
Dose-response trials	INT-1 INT-2 USA-3		INT-1 INT-2 USA-3
Pivotal trials - Phase III, double-blind, placebo-controlled trials	INT-6 USA-11 USA-13	INT-6 USA-11 USA-13	INT-6 USA-11 USA-13
Other phase II/III, double-blind, placebo-controlled trials	USA-25 USA-28 BEL-6 GBR-4 FRA-1 Part 1 USA-21 NED-13 NED-2	USA-28	GBR-4 FRA-1 Part 1
Phase II/III, double-blind, placebo-controlled , trials in elderly patients	USA-26 INT-12	INT-12	USA-26 INT-12
Phase II/III open-label studies in patients with chronic constipation	INT-10 USA-22 BEL-8 INT-3 INT-4 NED-4 FRA-1 Part 2 INT-13 SWE-2	INT-10 USA-22	FRA-1 Part 2
Phase II/III double-blind, placebo-controlled, trials in patients with opioid-induced	USA-8 INT-14 INT-8	INT-8	

chronic constipation	USA-27		
Phase II open-label studies in patients with opioid-induced chronic constipation	INT-17	INT-17	
Phase II trials in patients with multiple sclerosis or spinal cord injury	BEL-18 DEN-2 INT-9		
Phase II, double-blind, placebo-controlled trial in subjects with chronic intestinal pseudo-obstruction	GBR-7		
Phase II, double-blind, placebo-controlled trials with i.v./s.c. formulations for the treatment of postoperative ileus in patients undergoing major abdominal surgery of elective partial colectomies	GER-1 USA-5		

It is unclear why some trials in the number series are missing. Three trials were identified by the manufacturers as being ‘pivotal’ (INT-6, USA-11, USA-13) and these trials form the basis for much of the assessment of clinical effectiveness. However, the rationale for the particular focus on these three trials is not given.

4.1.4 Details of any relevant studies that were not included

A systematic search for randomised controlled trials was conducted to identify any additional studies to those included in the current submission (see section 4.1.1 and appendix 1). However, since no references were given for indentified trials/studies in the submission, it was not possible to cross match with the ERG’s systematic search. A true assessment of whether any relevant trials/studies were not included was therefore not possible.

Details of trials identified in the submission that were not then described or used to inform the economic model are given in Table 1 (see also table 1 on pages 27-31 of the submission). Since these trials and studies were not used in the submission, they may be considered to be excluded. However, five of the ten trials included for economic modelling are also not fully described in the submission (no full description of study methodology and no baseline characteristics or study findings).

4.1.5 Description and critique of manufacturers approach to validity assessment

The manufacturer gives details of the methods used in the trials described in the submission (see submission tables 4-7, pgs 36-38). Critical appraisal was conducted for the three pivotal trials (submission table 24, pg 58). This included items of study quality related to randomisation, allocation concealment, baseline similarity, blinding of care providers, participants and outcome assessors, differential attrition, selective outcome reporting and intention to treat analysis. The quality assessment method appears to have been satisfactory. However, this was only applied to the three pivotal trials and not to the other trials and other studies that are listed in the submission and to those used to inform the economic model.

4.1.6 Description and critique of manufacturers outcome selection

The primary outcomes of the trials selected by the manufacturer were similar to those outlined in the decision problem and, in this respect, selected outcomes are satisfactory. The use of the SCBM outcome in trials may have been inappropriate but this is discussed later in section 4.2.2.1 of this report.

However, one outcome listed in the decision problem, adverse events, was not listed as an outcome measure. Findings for adverse events in one safety study (USA-26) and for the other nine trials described in the submission are presented in the submission but these were only given for events occurring in ≥5% of patients. On request of the ERG, full details of adverse events occurring in five of the trials were provided.

4.1.7 Describe and critique of the statistical approach used

For many of the presented results, statistical analysis was not applied and results of trials were simply presented separately. Results from three pivotal trials were “pooled” in order to inform the summary statements (pg 25-26 of the submission) but full pooled results and statistical tests conducted across the three pivotal trials were not presented.

It was stated that “A meta-analysis was not considered appropriate for this submission as there are no active comparators to prucalopride” (p79) but, in response to questions for clarification, manufacturers state that, “If the pooling of clinical data as required for regulatory submissions is considered as meta-analysis, we indeed performed meta-analyses.”

It was stated that, “For the first 12 weeks of the economic model for adults an analysis of individual patient level data is undertaken for all female patients treated with 2mg dose of prucalopride.” On further clarification, manufacturers confirmed that an individual patient data analysis was in fact not conducted. Patient data from trials was used to inform baseline utility values that were mapped across the representative UK population (oral communication from manufacturers, May 2010). Change in utility was calculated from regression equations that used data collected from clinical trials (see page 123 of submission).

4.1.8 Summary statement

Despite being a non-systematic search, relevant studies appear to have been identified in the submission. The ERG presumes that the majority of data from relevant studies is included in the submission. However, the included studies do not appear to match the decision problem in terms of the population under investigation or the comparator. Although the included trials do appear to match the decision problem in terms of the outcomes assessed, these outcomes may introduce bias.

4.2 Summary of submitted evidence

4.2.1 Summary of results

In the clinical effectiveness section, evidence was submitted on nine trials: three pivotal trials in adults (18-65 years) (INT-6, USA-11, USA-13), one trial in elderly patients (>65 years) (INT-12), one trial in patients with opioid-induced constipation (INT-8), one retreatment study (USA-28) (4mg prucalopride/day) and three extended, single-arm, observational studies (INT-10, USA-22, INT17) (see Table 1).

Data from three dose-response trials (INT-1, INT-2, USA-3), one trial in elderly patients (USA-26) and two 'other' phase II trials (FRA-1, GBR-4) are used to inform the model but no methods or results for these trials are detailed in the submission.

The outcomes considered in the NICE scope are given below for the studies detailed in the submission that were relevant to the proposed indication. Results for the study in patients with opioid-induced constipation and the retreatment study (4mg prucalopride/day) are not presented in this ERG report since patients with opioid-induced chronic constipation and prucalopride taken at 4mg/day are not in the current licensed indication. Results for adverse events in the trials for which full data was supplied on request from the manufacturers (three pivotal trials in adults, one retreatment study and one trial in elderly patients) are also given.

4.2.1.1 Effectiveness in the general adult population: Pivotal trials

Data from three trials considered to be pivotal were used to inform the assessment of clinical effectiveness in the adult female population. Adult patients in these trials were those with a history of chronic constipation and were largely dissatisfied with previous laxative treatments. Before the start of the intervention, all patients underwent a two-week run-in period where no laxative medication (except for rescue medication) was allowed. Patients were then randomised to receive prucalopride (2 or 4mg) or placebo. On both treatment arms, if patients had not had a bowel movement for ≥3 days, rescue

medication could be requested. This consisted of a single dose of 15mg bisacodyl. If this was unsuccessful, the dose could be increased and, if there was still no success, an enema could be used. Patients were followed up for 12 weeks and data was collected at 4 and 12-week time points. Outcome measures in these trials were similar to those in the NICE scope and the decision problem.

Summary of results:

Over 12 weeks, for the 2mg prucalopride group, in the three pivotal trials:

Spontaneous Complete Bowel Movements (SCBM).

- All trials showed significantly more patients with mean of ≥3 SCBM per week for prucalopride compared to placebo.
- All trials showed significantly greater mean number of SCBM per week for prucalopride compared to placebo.

Symptoms

- 2 out of 3 trials showed significantly greater improvements in PAC SYM symptoms score for prucalopride compared to placebo.

Quality of life

- All trials showed significantly greater improvement in PAC-QOL quality of life score for prucalopride compared to placebo.
- No trials showed significantly greater improvement in SF-36 PCS quality of life score for prucalopride compared to placebo.
- No trials showed significantly greater improvement in SF-36 MCS quality of life score for prucalopride compared to placebo

Since, in most cases, pooled results across trials were not given in the submission, weighted pooled results have been calculated by the ERG. These were weighted by study size and calculated using excel (no statistical testing was conducted by the ERG). Results for the pivotal trials for the outcomes given in the NICE scope are given below:

a) Number of patients with mean ≥3 SCBMs per week

Measurements for pivotal trials were taken during the run-in period and at weeks 4 and 12. Pooled results for the number of patients with a mean number of ≥3 SCBM per week are calculated during the periods of weeks 1-4 and weeks 1-12.

Table 2. ***Number (percentage) patients with mean ≥3 SCBMs per week for all patients in pivotal trials*** **(INT-6, USA-11, USA-13)**

Trial	Time point	Prucalopride 2mg	Placebo
INT-6 (Tack 2009)	Weeks 1-4	56/236 (23.7%)***	25/240 (10.4%)
	Weeks 1-12	46/236 (19.5%)**	23/240 (9.6%)
USA-11 (Camilleri 2008)	Weeks 1-4	61/190 (32.1%)***	19/193 (9.8%)
	Weeks 1-12	55/190 (28.9%)***	25/193 (13.0%)
USA-13 (Quigley 2009)	Weeks 1-4	61/209 (29.2%)***	24/208 (11.5%)
	Weeks 1-12	50/209 (23.9%)**	25/207 (12.1%)
$Pooled results			
	Weeks 1-4	**28.0%**	10.6%
	Weeks 1-12	23.8%	11.4%

***p<0.001 compared to placebo

**p<0.01 compared to placebo

$As calculated by the ERG

In the ERG questions for clarification, the manufacturer was asked to confirm whether men, and patients who were satisfied with their previous treatments, were included in these trial results. The manufacturer confirmed that this was the case and provided the following results for mean ≥3 SCBM per week for female patients who were not satisfied with their previous laxative treatment:

Table 2b Number (percentage) patients with mean ≥3 SCBM per week, combined pivotal trial results, subgroup analysis: women only, not satisfied with previous treatment

	Placebo		**PRU 2 mg**	
Time-point	**N**	**n (%)**	**N**	**n (%)**
Female n (%)				
Run-in	466	2 (0.4)	451	4 (0.9)
Weeks-1-4	468	39 (8.3)	452	138 (30.5)
Weeks 1-12	468	44 (9.4)	452	109 (24.1)

b) Number of patients with mean increase of ≥ 1 SCBM per week

Measurements for the three pivotal trials were taken during the run-in period and at weeks 4 and 12. Results for the number of patients with a mean increase of ≥1 SCBM per week are calculated during the periods of weeks 1-4 and weeks 1-12.

Table 3. Number (percentage) patients with mean increase of ≥1 SCBMs per week for all patients in pivotal trials (INT-6, USA-11, USA-13)

Trial	Time point	Prucalopride 2mg	Placebo
INT-6 (Tack 2009)	Weeks 1-4	93/227 (41.0%)***	49/235 (20.9%)
	Weeks 1-12	86/226 (38.1%)***	49/234 (20.9%)
USA-11 (Camilleri 2008)	Weeks 1-4	100/177 (56.5%)***	46/189 (24.3%)
	Weeks 1-12	89/177 (50.3%)***	49/189 (25.9%)
USA-13 (Quigley 2009)	Weeks 1-4	102/209 (48.8%)***	53/208 (25.5%)
	Weeks 1-12	89/209 (42.6%)***	57/207 (27.5%)
$Pooled results			
	Weeks 1-4	**48.2%**	23.4%
	Weeks 1-12	43.2%	24.6%

***p<0.001 compared to placebo

$As calculated by the ERG

c) Mean number of spontaneous complete bowel movements per week

Measurements were taken during the run-in period (counted as baseline) and at weeks 4 and 12. Results for the mean number of SCBM per week are calculated during the periods of weeks 1-4 and weeks 1-12 (mean change from baseline is displayed in brackets).

Table 4. Mean number (mean change from baseline) of SCBMs per week for all patients in pivotal trials (INT-6, USA-11, USA-13)

Trial	Time point	Prucalopride 2mg	Placebo
INT-6 (Tack 2009)	Weeks 1-4	1.7 (1.4)*** n=236	0.9 (0.5) n=240
	Weeks 1-12	1.6 (1.2)*** n=236	1.0 (0.5) n=240
USA-11 (Camilleri 2008)	Weeks 1-4	2.5 (2.1)*** n=190	1.1 (0.7) n=193
	Weeks 1-12	2.3 (1.9)*** n=190	1.3 (0.8) n=193
USA-13 (Quigley 2009)	Weeks 1-4	2.1 (1.6)*** n=209	1.0 (0.6) n=208
	Weeks 1-12	1.9 (1.5)*** n=209	1.2 (0.8) n=207
$Pooled results (weighted by study size)			
	Weeks 1-4	2.1 (1.7)	1.0 (0.6)
	Weeks 1-12	1.9 (1.5)	1.2 (0.7)

***p<0.001 compared to placebo **p<0.01 compared to placebo

$As calculated by the ERG

d) Symptoms of constipation – PAC-SYM symptom score

A questionnaire to assess patient symptoms, the PAC-SYM symptom score, was developed for use in patients with constipation. Measurements were taken during the run-in period (taken as baseline) and at weeks 4 and 12 (mean change in score from baseline is displayed in brackets).

Table 5. Mean PAC-SYM score (mean change from baseline) for all patients in pivotal trials (INT-6, USA-11, USA-13)

Trial	Time point	Prucalopride 2mg	Placebo
INT-6 (Tack 2009)	Week 4	1.46 (-0.67)***	1.73 (-0.34)
	Week 12	1.44 (-0.66)	1.69 (-0.37)
USA-11 (Camilleri 2008)	Week 4	1.26 (-0.65)***	1.57 (-0.38)
	Week 12	1.26 (-0.63)*	1.49 (-0.46)
USA-13 (Quigley 2009)	Week 4	1.40 (-0.65)***	1.59 (-0.38)
	Week 12	1.26 (-0.78)***	1.52 (-0.45)
$Pooled results (weighted by study size)			
	Weeks 1-4	1.38 (-0.66)	1.64 (-0.37)
	Weeks 1-12	1.33 (-0.69)	1.57 (-0.42)
***p≤0.001 compared to placebo *p≤0.05 compared to placebo $As calculated by the ERG			

e) Quality of life

PAC-QOL

The PAC-QOL survey of quality of life was taken during the run-in period and at weeks 4 and 12 (mean change in score from baseline is displayed in brackets). (Note that a decrease in PAL-QOL represents an improved quality of life score).

Table 6. Mean PAC-QOL score (mean change from baseline) for all patients in pivotal trials (INT-6, USA-11, USA-13)

Trial	Time point	Prucalopride 2mg	Placebo
INT-6 (Tack 2009)	Week 4	1.37 (-0.65)***	1.72 (-0.31)
	Week 12	1.36 (-0.65)***	1.66 (-0.38)
USA-11 (Camilleri 2008)	Week 4	1.28 (-0.87)***	1.83 (-0.38)
	Week 12	1.29 (-0.84)***	1.73 (-0.47)
USA-13 (Quigley 2009)	Week 4	1.43 (-0.77)***	1.67 (-0.43)
	Week 12	1.34 (-0.85)***	1.65 (-0.47)
$Pooled results (weighted by study size)			
	Weeks 1-4	1.36 (-0.76)	1.74 (-0.37)
	Weeks 1-12	1.33 (-0.77)	1.68 (-0.44)
***p<0.001 compared to placebo $As calculated by the ERG			

SF-36 PCS and MCS

Measurements of SF-36 PCS were taken during the run-in period and at weeks 4 and 12 (mean change in score from baseline is displayed in brackets).

Table 7. Mean SF-36 PCS score (mean change from baseline) for all patients in pivotal trials (INT-6, USA-11, USA-13)

Trial	Time point	Prucalopride 2mg	Placebo
INT-6 (Tack 2009)	Week 4	46.7 (2.6)*	44.9 (1.1)
	Week 12	46.3 (2.1)	45.6 (1.8)
USA-11 (Camilleri 2008)	Week 4	48.5 (2.3)	47.1 (0.9)
	Week 12	49.4 (2.7)	47.9 (1.4)
USA-13 (Quigley 2009)	Week 4	48.9 (2.5)	48.7 (1.6)
	Week 12	49.1 (2.7)	49.4 (2.5)
$Pooled results (weighted by study size)			
	Weeks 1-4	48.0 (2.5)	46.8 (1.2)
	Weeks 1-12	48.2 (2.5)	47.5 (1.9)
*p≤0.05 compared to placebo $As calculated by the ERG			

Surveys of SF-36 MCS were taken during the run-in period and at weeks 4 and 12 (mean change in score from baseline is displayed in brackets).

Table 8. Mean SF-36 MCS score (mean change from baseline) for all patients in pivotal trials (INT-6, USA-11, USA-13)

Trial	Time point	Prucalopride 2mg	Placebo
INT-6 (Tack 2009)	Week 4	46.4 (2.2)	45.9 (0.7)
	Week 12	47.6 (3.2)	46.1 (1.5)
USA-11 (Camilleri 2008)	Week 4	48.8 (3.5)	46.7 (1.3)
	Week 12	48.0 (2.1)	47.3 (2.0)
USA-13 (Quigley 2009)	Week 4	47.6 (2.7)	47.4 (1.3)
	Week 12	48.6 (3.4)	47.3 (1.4)
$Pooled results (weighted by study size)			
	Weeks 1-4	47.5 (2.8)	46.6 (1.1)
	Weeks 1-12	48.1 (2.9)	46.9 (1.6)
*p≤0.05 compared to placebo $As calculated by the ERG			

4.2.1.2 Clinical effectiveness in elderly patients (INT-12)

Results for one trial in elderly patients (INT-12) are presented in the clinical effectiveness section of the submission but the results for the other trial in elderly patients that was used to inform baseline utility in the economic model (USA-26) were not presented. Methods for the INT-12 trial were identical to those of the three pivotal trials except that patients were randomised to placebo or doses of 1, 2 or 4mg prucalopride and that the duration of the study was only 4 weeks. Results are presented for a) number of patients with mean ≥3 spontaneous complete bowel movements per week, b) number of patients with mean increase of ≥1 SCBM per week, c) mean number of spontaneous complete bowel movements per week, d) PAC-SYM symptom score and e) PAC-QOL score (no SF-36 measurements were taken in this study).

Table 9. Results for SCBMs, symptoms and quality of life for elderly patients in the INT-12 trial

	Prucalopride 1 mg (n = 76)	Prucalopride 2 mg (n = 75)	Placebo (n = 70)
a) Mean of ≥ 3 SCBMs/week, n (%)			
Run-in	0/76	0/75	2/70 (2.9)
Week 1-4	30/76 (**39.5**)	24/75 (32.0)	14/70 (20.0)
b) Average increase of ≥ 1 SCBM/week, n (%)			
Week 1-4	44/72 (**61.1**)*	41/72 (56.9)*	22/65 (33.8)
c) Average number of SCBM/week, mean (mean change from baseline)			
Week 1-4	2.7 (1.9)*	2.4 (1.7)*	1.7 (0.6)
d) Overall PAC-SYM symptoms score, mean (mean change from baseline)			
Week 4	0.88 (-0.53)*	1.10 (-0.37)	1.22 (-0.23)
e) Overall PAC-QOL score, mean (mean change from baseline)			
Week 4	0.95 (-0.53)*	1.12 (-0.30)	1.26 (-0.20)
*p≤0.05 compared to placebo			

4.2.1.3 Long-term efficacy

Three studies were designed to assess the long-term tolerability and safety of prucalopride. These were single arm studies and were made up of patients who had completed the following studies:

1) **INT-10** – Patients from INT-6 (pivotal trial) and INT-12 (elderly patient trial)

2) **USA-22** – Patients from USA-3 (phase II, does response trial), USA-11 and USA-13 (pivotal trials), USA-21 (phase II 'other' dose response trial), USA-25 (phase III, 'other' dose titration trial), USA-27 (opioid-induced chronic constipation trial), USA-28 (phase III retreatment trial).

3) **INT-17** – INT-8 and INT-14 (both opioid-induced chronic constipation trials)

INT 10, USA-22 and INT-17 lasted for 24, 36 and 12 months respectively. All patients received prucalopride during these studies but some of these patients had received placebo in their previous studies. Doses ranged from 0-4mg. Full details of results are not given in the submission but the following summary statements were made:

Table 10: Summary of efficacy results for long term, single arm studies (INT-10, USA-22, INT-17)

INT-10	**PAC-QOL** • There was statistically significant improvement from baseline in total and individual PAC-QOL scores at all time-points • The mean (SE) improvement in total PAC-QOL satisfaction subscale score at month 3 was –1.14 (0.054), –1.41 (0.062) at month 12 and –1.68 (0.132) at month 21 • Mean decrease from baseline in total and individual items of PAC-QOL satisfaction subscale scores were maximal at month 21, ranging from –1.39 to –1.86 • 54.9% patients had an improvement in total PAC-QOL satisfaction subscale score ≥ 1 on a 5-point scale at month 3, this proportion increased to 65.3% at month 12 and 72.0% at month 21 • Results showed that patient's satisfaction with his/her bowel function and treatment improved over time when receiving treatment with 2 mg to 4 mg prucalopride for a long-term period **Patient's Daily Diary** • Mean daily dose of prucalopride was 2.56 mg (range 0-4 mg) during the entire study period. For the first 11 weeks of the study 2 mg was the more frequent pattern of use, from week 15 onwards 4 mg became more common • Use of laxatives decreased during prucalopride treatment, the decrease was more pronounced in patients who previously received placebo
USA-22	**PAC-QOL** • There was statistically significant improvement from baseline in total and individual PAC-QOL scores at all time-points • The mean (SE) improvement in total PAC-QOL satisfaction subscale score at month 3 was –1.04 (0.040), –1.38 (0.059) at month 12 and –1.33 (0.099) at month 21 • Mean decrease from baseline in total and individual items of PAC-QOL satisfaction subscale scores were maximal at month 15 or month 18, ranging from –1.27 to –1.61 • 50.8% patients had an improvement in total PAC-QOL satisfaction subscale score ≥ 1 on a 5-point scale at month 3, this proportion increased to 65.3% at month 12 and 61.9% at month 21 • Results showed that patient's satisfaction with his/her bowel function and treatment improved over time when receiving treatment with 2 mg to 4 mg prucalopride for a long-term period **Patient's Daily Diary** • The most frequent weekly pattern of prucalopride use was 4 mg daily for 5 days or more • Use of laxatives decreased during prucalopride treatment, generally the decrease was more pronounced in patients who previously received placebo

INT-17	**PAC-QOL** • There was improvement from baseline in total and individual PAC-QOL scores at all time-points • 45.3% patients had an improvement in total PAC-QOL satisfaction subscale score ≥ 1 on a 5-point scale at month 1, this proportion improved further throughout the study • The mean (SE) improvement in total PAC-QOL satisfaction subscale score at month 1 was –0.95 (0.134), –0.85 (0.149) at month 3 and –1.17 (0.195) at month 6 • Results showed that patient's satisfaction with his/her bowel function and treatment improved over time when receiving treatment with 1 mg to 4 mg prucalopride for a long-term period **Patient's Daily Diary** • Generally patients use of laxatives decreased during prucalopride treatment, the decrease was more pronounced in patients who previously received placebo • The proportion of patients who indicated that treatment was moderately to extremely effective was high at month 1 (69.8%) and remained high throughout the study 66.7% at month 3, 68.8% at month 6 and 90.0% at month 9 (although only a small number of patients had data at month 9) • At month 1, 39.1% of patients had no or mild constipation, 35.6% at month 3, 38.8% at month 6 and 60% at month 9, compared with 7.9% of patients at baseline • The percentage of patients that indicated they were bothered by their constipation decreased from 60.7% at baseline to 29.9% at month 1, 34.2% at month 3 and 26.5% at month 6

Satisfaction scores at 12 months from these trials were used to justify the assumption of the sustained effectiveness of prucalopride from 12 to 52 weeks for the economic model. However, at 12 months, on average, <50% of patients remained in these trials (table 11 below (Table 38 on p82 of submission) shows patient disposition over time). These studies were continued until all patients had dropped out and although discontinuations were mainly due to "the decision of the previous sponsor (JRF) to stop the prucalopride developmental program worldwide", many patients also dropped out due to insufficient response (17%), withdrawal of consent (15%) and adverse events (8%). Full details of reasons for discontinuation are given below (table 12, Table 39 on p82 of submission).

Table 11: Patient disposition over time (PRU-INT-10, PRU-USA-22, PRU-INT-17)

Number of patients ongoing with data	PRU-INT-10		PRU-USA-22		PRU-INT-17	
	Previously on placebo (N=224)	Previously on prucalopride (N=469)	Previously on placebo (N=656)	Previously on prucalopride (N=1119)	Previously on placebo (N=31)	Previously on prucalopride (N=65)
Month 3	208 (92.9)	440 (93.8)	578 (88.1)	1007 (90.0)	29 (93.5)	60 (92.3)
Month 6	171 (76.3)	351 (74.8)	405 (61.7)	726 (64.9)	23 (74.2)	53 (81.5)
Month 9	151 (67.4)	312 (66.5)	301 (45.9)	555 (49.6)	17 (54.8)	35 (53.8)
Month 12	134 (59.8)	276 (58.8)	200 (30.5)	409 (36.6)	5 (16.1)	7 (10.8)
Month 15	105 (46.9)	199 (42.4)	161 (24.5)	339 (30.3)	0	0
Month 18	80 (35.7)	132 (28.1)	116 (17.7)	264 (23.6)	-	-
Month 21	39 (17.4)	64 (13.6)	74 (11.3)	167 (14.9)	-	-
Month 24	18 (8.0)	21 (4.5)	12 (1.8)	18 (1.6)	-	-
Month 27	0	0	-	-	-	-

Table 12: Patient demographic data and reasons for discontinuation (PRU-INT-10, PRU-USA-22, PRU-INT-17)

	PRU-INT-10	PRU-USA-22	PRU-INT-17
Number of patients enrolled (M/F)	693 (100/593)	1775 (199/1576)	96 (33/63)
Mean age years (range)	50.8 (18-92)	47.2 (18-89)	52.4 (24-83)
Mean duration of treatment days (range)	342.2 (1-733)	231.17 (1-721)	127.32 (2-286)
Discontinuations (n[%])	658 (95)	1775 (100)	96 (100)
Insufficient response	119 (17)	316 (17.8)	12 (12.5)
Adverse event	70 (10)	140 (7.9)[†]	6 (6.3)
Withdrew consent	53 (8)	326 (18.4)	7 (7.3)
Lost to follow-up	29 (4)	209 (11.8)	1 (1.0)
Non-compliant	11 (2)	59 (3.3)	1 (1.0)
Ineligible to continue	4 (1)	17 (1.0)	-
Asymptomatic/cured	3 (<1)	13 (<1)	-
Death	1 (<1)	-	4 (4.2)
Other	368 (53)[‡]	695 (39.2)[‡]	65 (67.7)[‡]

[†]Three deaths included

[‡]Mostly discontinuation due to the decision of previous sponsor (JRF) to stop the prucalopride developmental program worldwide

4.2.1.4 Adverse events

One RCT that was specifically designed to assess the safety of treatment with prucalopride is presented in the submission (USA 26). This was a four-week trial of safety/tolerability in elderly patients (>65 years) living in a nursing facility. Results are only presented for types of adverse events occurring in ≥5% of patients in the trial. In a similar way, safety results for the three pivotal trials (INT-6, USA-11, USA-13), the other trial in elderly patients (INT-12), the trial in patients with opioid-induced constipation, the retreatment study (USA-28) and the long-term, single arm studies (INT-10, USA-22, INT-17) are presented only for types of adverse events occurring in ≥5% of patients in the trials. The ERG therefore requested full results for all adverse events and results for the three pivotal trials (INT-10, USA-22, INT-17), one study in elderly patients (INT-12) and one re-treatment study (USA-28) were provided.

Across these five trials/studies there were higher total numbers of subjects with adverse events for patients taking prucalopride compared to patients on placebo treatment. Across all trials/studies, there were higher numbers of gastrointestinal disorders, nervous system disorders, general disorders and administration, renal and urinary disorders and metabolism and nutrition disorders in the prucalopride arm of trials compared to placebo arms as highlighted in Table 13 below. There were no consistent differences in the prevalence of cardiac disorders across trials/studies.

Table 13: Number (percentage) of adverse events in elderly patient (INT-12) and pivotal (INT-6, USA-11, USA-13) trials and a retreatment (USA-28) study

	Elderly patient trial		Pivotal trials						Retreatment study	
	INT-12		INT-6		USA-11		USA-13		USA-28	
	Placebo	Prucalopride	Placebo	Prucalopride	Placebo	Prucalopride	Placebo	Prucalopride	Placebo	Prucalopride
TOTAL NO. SUBJ. WITH ADVERSE EVENT	32 (44.4)	104 (45.0)	161 (67.1)	348 (73.1)	149 (71.3)	326 (79.3)	140 (66.0)	336 (78.3)	171 (66.5)	196 (77.5)
GASTROINTESTINAL DISORDERS	6 (8.3)	38 (16.5)	96 (40.0)	225 (47.3)	80 (38.3)	211 (51.3)	53 (25.0)	189 (44.1)	84 (32.7)	128 (50.6)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DIS	6 (8.3)	20 (8.7)	22 (9.2)	57 (12.0)	26 (12.4)	50 (12.2)	26 (12.3)	52 (12.1)	22 (8.6)	20 (7.9)
NERVOUS SYSTEM DISORDERS	6 (8.3)	19 (8.2)	49 (20.4)	160 (33.6)	35 (16.7)	148 (36.0)	41 (19.3)	126 (29.4)	39 (15.2)	87 (34.4)
GENERAL DISORDERS AND ADMINISTRATION SITE	4 (5.6)	15 (6.5)	25 (10.4)	62 (13.0)	16 (7.7)	47 (11.4)	8 (3.8)	43 (10.0)	16 (6.2)	20 (7.9)
INFECTIONS AND INFESTATIONS	7 (9.7)	15 (6.5)	61 (25.4)	97 (20.4)	45 (21.5)	105 (25.5)	51 (24.1)	119 (27.7)	55 (21.4)	57 (22.5)
INVESTIGATIONS	6 (8.3)	11 (4.8)	13 (5.4)	47 (9.9)	22 (10.5)	50 (12.2)	14 (6.6)	31 (7.2)	26 (10.1)	29 (11.5)

	Elderly patient trial		Pivotal trials						Retreatment study	
	INT-12		INT-6		USA-11		USA-13		USA-28	
	Placebo	Prucalopride	Placebo	Prucalopride	Placebo	Prucalopride	Placebo	Prucalopride	Placebo	Prucalopride
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (2.8)	8 (3.5)	12 (5.0)	34 (7.1)	7 (3.3)	18 (4.4)	10 (4.7)	22 (5.1)	16 (6.2)	11 (4.3)
CARDIAC DISORDERS	3 (4.2)	7 (3.0)	6 (2.5)	20 (4.2)	2 (1.0)	9 (2.2)	4 (1.9)	7 (1.6)	3 (1.2)	6 (2.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0)	6 (2.6)	3 (1.3)	10 (2.1)	3 (1.4)	17 (4.1)	13 (6.1)	21 (4.9)	15 (5.8)	9 (3.6)
VASCULAR DISORDERS	0 (0.0)	5 (2.2)	10 (4.2)	10 (2.1)	3 (1.4)	7 (1.7)	3 (1.4)	8 (1.9)	2 (0.8)	4 (1.6)
EAR AND LABYRINTH DISORDERS	0 (0.0)	4 (1.7)	3 (1.3)	8 (1.7)	3 (1.4)	9 (2.2)	0 (0.0)	2 (0.5)	1 (0.4)	1 (0.4)
EYE DISORDERS	1 (1.4)	4 (1.7)	2 (0.8)	14 (2.9)	1 (0.5)	9 (2.2)	5 (2.4)	4 (0.9)	2 (0.8)	3 (1.2)
RENAL AND URINARY DISORDERS	1 (1.4)	4 (1.7)	4 (1.7)	22 (4.6)	9 (4.3)	22 (5.4)	0 (0.0)	16 (3.7)	12 (4.7)	13 (5.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (2.8)	4 (1.7)	21 (8.8)	26 (5.5)	14 (6.7)	32 (7.8)	12 (5.7)	34 (7.9)	14 (5.4)	16 (6.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (1.4)	3 (1.3)	2 (0.8)	10 (2.1)	2 (1.0)	2 (0.5)	1 (0.5)	3 (0.7)	3 (1.2)	0 (0.0)

	Elderly patient trial		Pivotal trials						Retreatment study	
	INT-12		INT-6		USA-11		USA-13		USA-28	
	Placebo	Prucalopride	Placebo	Prucalopride	Placebo	Prucalopride	Placebo	Prucalopride	Placebo	Prucalopride
METABOLISM AND NUTRITION DISORDERS	0 (0.0)	2 (0.9)	6 (2.5)	17 (3.6)	7 (3.3)	18 (4.4)	1 (0.5)	15 (3.5)	5 (1.9)	11 (4.3)
PSYCHIATRIC DISORDERS	2 (2.8)	2 (0.9)	11 (4.6)	22 (4.6)	10 (4.8)	25 (6.1)	8 (3.8)	20 (4.7)	10 (3.9)	8 (3.2)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (1.4)	2 (0.9)	5 (2.1)	16 (3.4)	6 (2.9)	16 (3.9)	5 (2.4)	7 (1.6)	13 (5.1)	7 (2.8)
SURGICAL AND MEDICAL PROCEDURES	0 (0.0)	1 (0.4)	4 (1.7)	4 (0.8)	7 (3.3)	15 (3.6)	5 (2.4)	13 (3.0)	9 (3.5)	4 (1.6)
IMMUNE SYSTEM DISORDERS	1 (1.4)	0 (0.0)	1 (0.4)	2 (0.4)	1 (0.5)	4 (1.0)	4 (1.9)	1 (0.2)	3 (1.2)	1 (0.4)
HEPATOBILIARY DISORDERS			0 (0.0)	1 (0.2)						
NEOPLASMS BENIGN, MALIGNANT AND UNSPEC.			0 (0.0)	1 (0.2)	3 (1.4)	1 (0.2)	0 (0.0)	3 (0.7)	1 (0.4)	4 (1.6)
ENDOCRINE DISORDERS							1 (0.5)	0 (0.0)	1 (0.4)	1 (0.4)

4.2.2 Critique of submitted evidence syntheses

The following critique first looks at the quality of the trials used for the summary of the clinical effectiveness of prucalopride and then considers the way that this trial information has been incorporated into the economic model.

4.2.2.1 Critique of trials in the clinical effectiveness section

4.2.2.1.1 Pivotal trials

There are several issues associated with the trial evidence on which this submission is based and these are discussed below:

Patients

It appears that the patients studied in the pivotal trials were not those with laxative-refractory chronic constipation as per the licensed indication. This is evidenced in a number of ways:

1) Before the trials, in response to the question “overall assessment of therapeutic efficacy of previous treatment of constipation”, across the three pivotal trials, 17.0% of patients answered that they had found their previous treatment adequate. The types of patients for whom prucalopride is indicated, those with severe chronic constipation and refractory to laxative treatments, would be extremely unlikely to have found previous treatments adequate. Additionally, even amongst patients finding previous treatments inadequate (as presented by manufacturers in clarification responses, table 2b of this report), there are likely to be many for whom laxatives are continuing to give some benefits and may not be true candidates for treatment with prucalopride.

2) Bisacodyl was used as a rescue medication in all three pivotal trials and findings suggest that it was effective. Results for the total number of bowel movements (induced by all causes), were not available in publications or the initial manufacturer’s submission but were supplied by the manufacturer on request. The average number of bowel movements (BM) per week induced by bisacodyl/enemas (spontaneous BM minus all BM) was 1.34 in weeks 1-4 and

1.26 in weeks 1-12. In publications and the manufacturer's submission, results for the frequency of use of bisacodyl and enemas are pooled. However, in response to our questions for clarification, the manufacturers state that 60-70% of patients took bisacodyl whilst only 10-15% of patients underwent enemas. In addition, from the graphs provided by the manufacturer in the clarifications document (see below) it appears that, in patients who did have enemas, only one or two were performed over the whole study period:

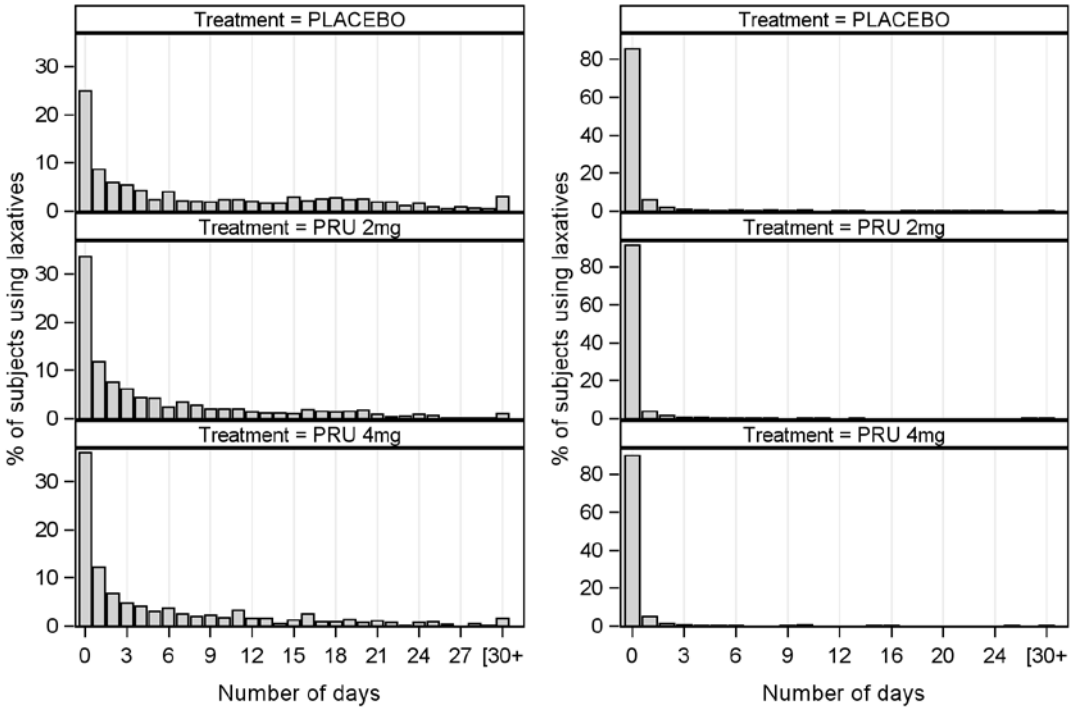

Figure 1 Bisacodyl (left) and enema (right) use in pivotal trials

It therefore appears likely that, for participants in the pivotal trials, at least one BM per week was induced by bisacodyl. It is not possible to determine whether these were 'complete' bowel movements. However, since some effect was clearly induced by bisacodyl use and, since bisacodyl is a type of laxative, this suggests that not all patients in these trials were resistant to laxatives.

3) At the end of the pivotal trials, patients were asked to rate their treatments and results are provided for the number of patients rating their treatments as "quite a bit or extremely effective". Although these ratings are higher in the prucalopride arms, over the 12 week trials, 17.5% of patients in the placebo arm rated their treatment as quite a bit or extremely effective. It appears that

these patients either a) required little medical intervention or b) responded to laxative (bisacodyl) treatment. This further suggests that patients in these trials did not all have severe chronic constipation and trial results are unlikely to properly reflect results for prucalopride in the proposed indication.

Comparator group

The comparator group in the pivotal trials was inappropriate on two counts:

I) If the population under investigation are assumed to be those with severe chronic constipation who have failed on all previous laxative therapy, a placebo group may be an appropriate comparator. However, even with this assumption, the placebo comparator in the pivotal trials is biased because of the rescue medication and how the outcomes were counted. In both the placebo and prucalopride arms of these trials, rescue treatment with biscodyl/enema is given. Any bowel movements that occurred due to these treatments were considered to be non-spontaneous and were discounted from the count of SCBMs (the primary outcomes for these studies). Since the placebo group will naturally receive more rescue therapy than the prucalopride group, this introduced bias. From information supplied by the manufacturer, it is evident that the number of non-spontaneous bowel movements that were discounted from the placebo group was higher than the number discounted from the prucalopride group. An average of 1.7 non-spontaneous bowel movements per week were deducted from the placebo group compared to 1.0 per week in the prucalopride group and this was likely to have led to an overestimation of the comparative effectiveness of prucalopride.

II) If the actual patient populations in these trials is considered (many patients were likely to have been responsive to laxative treatment), a placebo is not an appropriate comparator. An appropriate comparator may have been a variety of laxative treatments, at the discretion of the treating clinician. In these trials, if patients did not have bowel movements for ≥3 consecutive days, rescue treatment of a single dose of bisacodyl was prescribed. The use of limited access to a single laxative treatment does not represent clinical practice in the

general group of patients with chronic constipation and, in this respect, the comparator group is also inappropriate.

Outcomes

The primary outcome in these trials, ≥3 spontaneous complete bowel movements (SCBM) per week, was likely to have given a biased impression of the effectiveness of prucalopride. BMs occurring within 24 hours of rescue medication in either the placebo or prucalopride arm were discounted. However, as would be anticipated, patients receiving placebo required more courses of rescue treatment compared to those receiving prucalopride and this resulted in a greater number of discounted BMs in the placebo arm. On request, manufacturers supplied data for the total number of SBMs and BMs and, from these results, it can be determined that, over 12 weeks, 1.74 non-spontaneous BMs per week were discounted from the placebo group compared to 1.03 non-spontaneous BMs in the 2mg prucalopride group. Since this discounting is more than 50% higher in the placebo group, this was likely to have had some impact on the apparent effectiveness of prucalopride compared to placebo.

4.2.2.1.2 Trials in elderly patients

Elderly patients may suffer chronic constipation but the causes may be different in this type of population. Elderly people are more likely to have constipation secondary to other causes such as poor diet, limited physical exercise and other medications. Two trials of elderly patients are used to inform the economic modelling but details for only one of these trials is given in the submission (INT-12).

Patients

Although patients with constipation due to secondary factors were excluded, it seems likely that, as with the pivotal trials, the patient group were not restricted only to those warranting treatment with prucalopride. In the INT-12 trial, 21% of patients assessed their previous treatment as adequate suggesting that they had not previously failed laxative treatment. Also, it appears that treatment arms may not have been balanced at baseline since

28.6% of the patients in the 2mg prucalopride group rated their previous treatment as adequate compared to 12.7% of patients in the placebo group. As for the pivotal trials, bisacodyl was used as a rescue therapy and, similarly, the use of a laxative as the rescue therapy suggests that these patients were still responsive to laxative treatment. Post-intervention, 16% of patients in the placebo group rated their treatment as “quite a bit or extremely effective”, suggesting that many patients had found the rescue therapy (laxative treatment) to be effective.

Comparator

As with the pivotal studies (section *4.2.2.1.1, ‘Comparator’*), the comparator group in the trial of elderly patients could be seen to be inappropriate because: 1) the placebo group was disadvantaged by the selection of only spontaneous BMs. Greater discounting of BMs from the comparator compared to the prucalopride arms was likely to have resulted in bias in the results. 2) Since the general chronic constipation elderly population were the group being considered, an appropriate comparator treatment would have been laxatives. However, the rescue medication on the trial was too restrictive to be a true representation of laxative use in clinical practice.

Outcomes

See as previously described in the critique of the pivotal trials.

4.2.2.1.3 Long-term studies

The use of this study data to inform the assumption that prucalopride maintains the same comparative advantage in quality of life from 12-52 weeks in the economic model is likely to have been inappropriate for a number of reasons.

Patients

Patients in the long-term studies of efficacy and safety (INT-10, USA-22, INT-17) were those who had previously taken part in prucalopride trials. It is unclear how participants from those trials were selected for follow-up studies and baseline data for these patients is not given in the manufacturer’s submission. However, it appears likely that, as with the pivotal trials, these

patients were not necessarily refractory to laxative treatment. The patient group in these studies is a mixture of elderly patients and those with opioid-induced chronic constipation and the results have not been separated.

As discussed below (section 4.2.2.2), the high rate of attrition of patients from these studies (>50% at 12 months) was likely to have resulted in a patient group continuing with treatment who were relatively more satisfied with their treatment compared to those dropping out and who were therefore not representative of all patients treated with prucalopride.

Comparator

No comparator group was used in these open-label studies. However, these results have been used to justify the assumption that the improvement in quality of life in patients on prucalopride compared to those on placebo treatment is maintained at 52 weeks. The absence of placebo data for this period of time invalidates this assumption because it is not possible to determine quality of life at 52 weeks in patients receiving placebo treatment.

4.2.2.2 Clinical effectiveness evidence used to inform the economic model

There are problems associated with the trials presented in this submission but, of greater importance is the effectiveness data that was used to inform the economic model and the way that this data has been applied. In order to inform the economic model, patient results from certain trials were selected. This was used to determine baseline quality of life (EQ-5D) and change from baseline appears to have been determined using mean changes in quality of life in the selected patients of the selected trials. Several issues lie around the estimate of effectiveness used for the economic model:

1) It is apparent that many of the patients with data used to inform the economic model did not have laxative-refractory chronic constipation. Patient data from the pivotal trials formed a major part of data for economic modelling and, as discussed above (section 4.2.2.1.1), it appears that many of these patients were still responsive to laxative treatment. At baseline, some patients were satisfied with their current treatments and, in many patients, bisacodyl

was effective as a rescue therapy, suggesting that patients were unlikely to be representative of those in the licensed indication.

Precise details of which patients, from which trials, that were used to inform the model, were not given in the submission. Upon request for further information about the source of patient data, a histogram of simulated baseline EQ-5D scores for adult (18-65) and elderly (≥65) patient data was provided by the manufacturers:

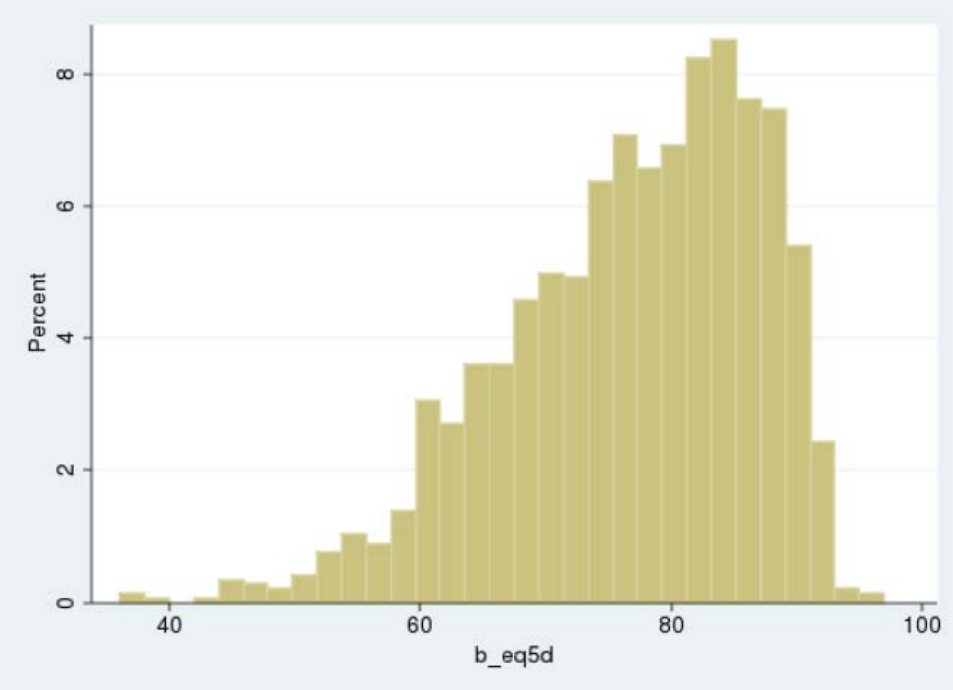

Figure 2 Baseline EQ-5D scores for adults (18-65) patient data used in the economic model

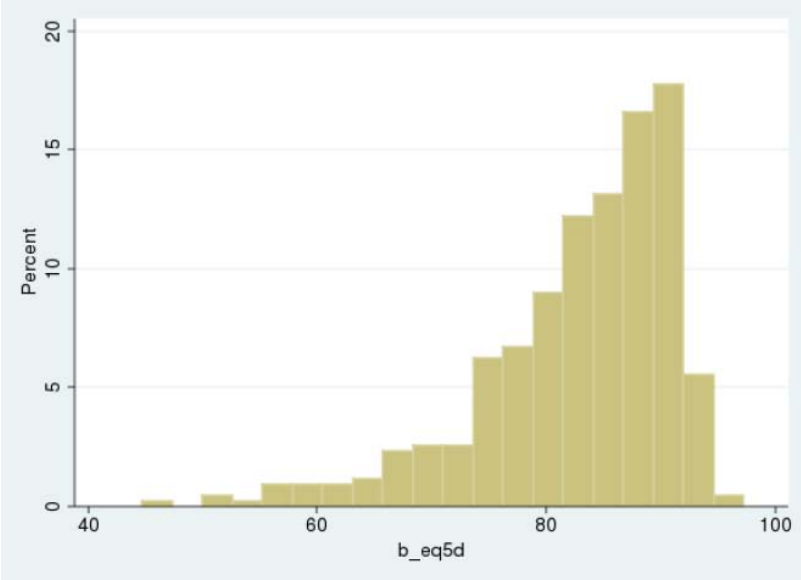

Figure 3 Baseline EQ-5D scores for elderly patient data used in the economic model

The ERG does not have research evidence to determine whether these baseline EQ-5D scores are likely to represent patients with severe, laxative-refractory, chronic constipation. However, the wide range of baseline scores suggests that this was not a homogenous group. If those at the lower end of the spectrum are assumed to be patients with severe chronic constipation that have failed to respond to all other treatments, it is reasonable to assume that those at the higher end of the spectrum tend in some way to be less severe cases. The distributions are skewed towards the higher end and some values are above 90. It would therefore appear likely that many patients whose data was used to inform the economic model did not have chronic constipation that could be classed as severe and may not fall in the category of those who may be eligible for treatment with prucalopride.

2) The comparator group in the model is inappropriate because a key assumption of the economic model (pg 130 of the submission) is that "Placebo data from the prucalopride clinical trial were taken as an approximation for the efficacy of response for patients on laxatives." If the model is considering laxative treatment as the comparator to prucalopride, the comparator data taken from trials is inappropriate. Placebo rescue therapy was not equivalent to laxative treatment that would be used in clinical practice

since it was limited to one laxative and patients had restricted access to that treatment.

3) As discussed above, certain selected trials, and certain selected patient results from those trials, were used to inform the economic model (Table 53 pg 124 of the submission) but there is no justification for why these trials, and why particular patients from these trials, were selected. There is no way of discerning whether appropriate information has been used to inform the economic model.

4) There is no description of five of the trials that have contributed data to the economic model and no results from these trials are given in the submission.

5) The model assumption that the relative advantage in quality of life in prucalopride patients at the end of study follow up is maintained at 52 weeks is inappropriate. Trials used as the basis for this assumption had, on average, >50% attrition at 12 months and the reasons for discontinuation included insufficient response (17%), withdrawal of consent (15%) and adverse events (8%). In the three pivotal trials, for all SCBM and quality of life measures, there were decreases in efficacy from 1-4 to 1-12 weeks compared to the placebo suggesting that, in fact, effectiveness was likely to decrease with time. In the long-term studies, considering that many patients were likely to have dropped out due to dissatisfaction, patients remaining in the trial were likely to have been those that were relatively more satisfied. These trials therefore give a biased reflection of long-term patient satisfaction and it is not possible to judge whether patient satisfaction would have been maintained at 12 months.

The assumption of maintenance of quality of life up to 52 weeks is also not valid due to the lack of data for long-term patient satisfaction in the placebo group. If relative quality of life is to be compared, follow-up data in the placebo group would also be required.

Additionally, patients in these long-term follow-up trials included patients that were not refractory to laxatives and patient groups were mixtures of adult and elderly patients and patients with opioid-induced constipation.

6) The submission states that individual patient results were used to inform the model. However, manufacturers later clarified that this was not the case. Patient data from trials was used to inform baseline EQ-5D data for the model by mapping them onto UK population data. Changes in EQ-5D were informed by results of relevant trials. However, this process is not transparent and it is still unclear what information and what assumptions were used to inform the effectiveness results in the economic model.

7) In order to generate EQ-5D data for the economic model, data from PAC-QOL and PAC-Sym were extrapolated to EQ-5D. This was done by first establishing the relationship between PAC and SF-36 data within patients. The known relationship between SF-36 and EQ-5D was then used to extrapolate PAC data directly to EQ-5D and the following equation was used:

EQ-5D = 97.7-9.8 (PAC-QOL) (see page 225 of the submission)

It appears that the SF-36 data did not directly contribute to EQ-5D scores although these results were available from the trials. Sensitivity analysis could have been conducted to examine model results when EQ-5D data was derived directly from SF-36 data since this is a validated method.

4.2.3 Summary

This submission is based on trials that do not properly inform on the effectiveness of prucalopride in the laxative-refractory patients for whom this drug has marketing authorisation. Results from these trials have not been incorporated into the economic model in a transparent way.

5 ECONOMIC EVALUATION

5.0.0. Manufacturer's search strategy

Search for cost effectiveness studies

Although a Search strategy for cost effectiveness studies was included in section 9.10 (appendix 10 of the submission), neither the date on which the search was conducted nor the date span of the search were included in the initial submission (both required by the NICE template) and it was not obvious on which database this was run (format suggested MEDLINE 1950-2010).

Further information provided post clarification questions established that both MEDLINE and EMBASE were searched from 2000-2009, as was NHS EED (the ERG assumes the same dates were used). No cost effectiveness analyses relating to the specific patient group were located.

The strategy does not include a detailed cost filter, but simply uses the term (cost*). Line 3 was redundant and would be captured by line 4. The searches used a combination of text word and index terms (MeSH) and used Boolean operators. No language limit appears to have been employed, which is inconsistent with the searches in submission appendix 12 (measurement and valuation of health effects) which were limited to English language.

Following clarification questions, it transpired that more resources had been searched than first stated but, as the range of search terms used was limited, the ERG ran further searches (see appendix 1) using the Haynes cost filter. No additional relevant references were found.

Search strategy for measurement and valuation of health effects

The search strategy for measurement and valuation of health effects is given in section 9.12 of the submission (appendix 12). Manufacturers searched via PubMED which they stated would cover MEDLINE which in turn includes Cochrane and the manufacturer states that the searches were carried out on 19 March 2010 and cover the period January 1990 – March 2010.

Although MEDLINE does include the Cochrane CDSR database it does not cover DARE, HTA, NHS EED or the CENTRAL database which all form part

of the Cochrane Library. So the manufacturers may have unwittingly introduced bias to the searches. They did not state they had searched EMBASE which covers more European-based journals and a wider range of pharmaceutical-related resources than MEDLINE, which again may have been advisable. (Alternatively they may have searched it but omitted to report this, as EMBASE was included in the cost effectiveness and resource identification measurement and valuation searches (see submission appendix 13)).

In submission section 9.12.4, the search strategy detailed does indeed combine free text and MeSH terms using Boolean operators. It covered a comprehensive range of terms likely to capture matters relating to measurement and valuation of health effects. The search terms used to describe the condition were limited (the manufacturer acknowledges this in section 9.12.6) and the decision not to search on the free text term constipation will necessarily have restricted the yield of this search (just 25 references). There is a 52% overlap between the studies located by the cost search (9.10.4) and this search, which is not surprising given the overlap of the topic areas. The decision to make these searches relatively narrow and limit by date and language may have been driven by time-constraints and concern over the size of the topic area.

The ERG ran some more comprehensive strategies to locate cost-effectiveness and measurement/valuation of health effects (see appendix 6.1) and the results (152 unduplicated refs) were screened for relevance. However, no relevant references were located.

Search strategy for resource identification, measurement and valuation

The search strategy for resource identification, measurement and valuation is given in submission section 9.13 (Appendix 13). The initial submission stated that a comprehensive literature search was undertaken to identify economic literature relevant to the therapeutic area. Although it states that the search strategy used and literature identified are outlined at the end of this section, it is not clear whether this means section 9.13 or section 6.5. In any case, there did not appear to be anything relevant in section 6.5 or at the end of 9.13. It is

possible that this statement should have referred to appendix 10 and appendix 12 of the submission.

As regards resource identification, measurement and valuation, the manufacturer stated that “such searches were not applicable because resource use data were not available for prucalopride and hence no search was undertaken. The remaining sections are therefore not considered applicable.” In response to clarification questions, the manufacturer stated that a detailed search was undertaken of MEDLINE and EMBASE from 2000 onwards to identify potential changes in resource use resulting from effective control of the symptoms of chronic constipation and that the resource analysis emphasised that patients suffering ineffectively treated chronic constipation impose significant costs on the NHS. They went on to state “unfortunately the Prucalopride trials did not collect resource data and hence direct evidence from the trials was unavailable to support resource savings from the use of Prucalopride”

No search terms were provided for the searches to identify potential changes in resource use so the ERG assume that, as no additional strategies were provided, this literature was derived from the cost-effectiveness and measurement and valuation of health effects searches (sections 9.10 and 9.12 of the submission). The ERG searches located a range of literature on costs incurred by patients suffering from severe constipation and the manufacturer commented on the evidence found from this type of literature in their reply to clarification questions (referring to significant costs imposed on the NHS by such patients). They go on to state, however, that the prucalopride trials did not collect resource data, so they made a conservative assumption that no savings would result from effectively controlling the symptoms of chronic constipation and resource analysis was therefore entirely confined to acquisition costs of prucalopride.

5.1 Overview of manufacturer’s economic evaluation

Including 1-page summary of structure, assumptions and sources, with signposting to tables with numerical inputs and their distributions where appropriate.

5.1.1 Natural history

Chronic constipation can become a public health concern when it is not adequately controlled with current laxatives. Chronic constipation inflicts a heavy burden to the patients (in terms of an impaired psychological well-being and overall quality of life (QOL)), to the society (due to work absenteeism) and to the health system (due to the substantial and inefficient health resource use by patients who remain dissatisfied and often unsuccessfully seek an alternative treatment that may provide better relief for their constipation). This translates into frequent visits to the treating physician and the unnecessary performance of expensive diagnostic procedures to rule out other causes of constipation. The majority of patients with constipation are managed in primary care.

Prucalopride is intended to be used in those patients for whom laxatives have been identified as being ineffective or inadequate. The outcome in the trials was the number of Spontaneous Complete Bowel Movements (SCBM) per week. Patients who reached ≥3SCBM per week were considered responders to the treatment of prucalopride. As the manufacturer did not build a Markov model, it was difficult to see the clinical pathway for patients.

5.1.2 Treatment effectiveness within the submission

The model submitted by Movetis is a de novo economic evaluation designed to evaluate the cost effectiveness of treatment with prucalopride (plus rescue medication) in two separate female populations: adults (18-65 years, 2 mg/daily dosage) and elderly (65+ years, 1mg/daily dosage). In both groups the comparator was placebo (plus rescue medication).

The following chart was included in the description of the model that was provided by the manufacturer.

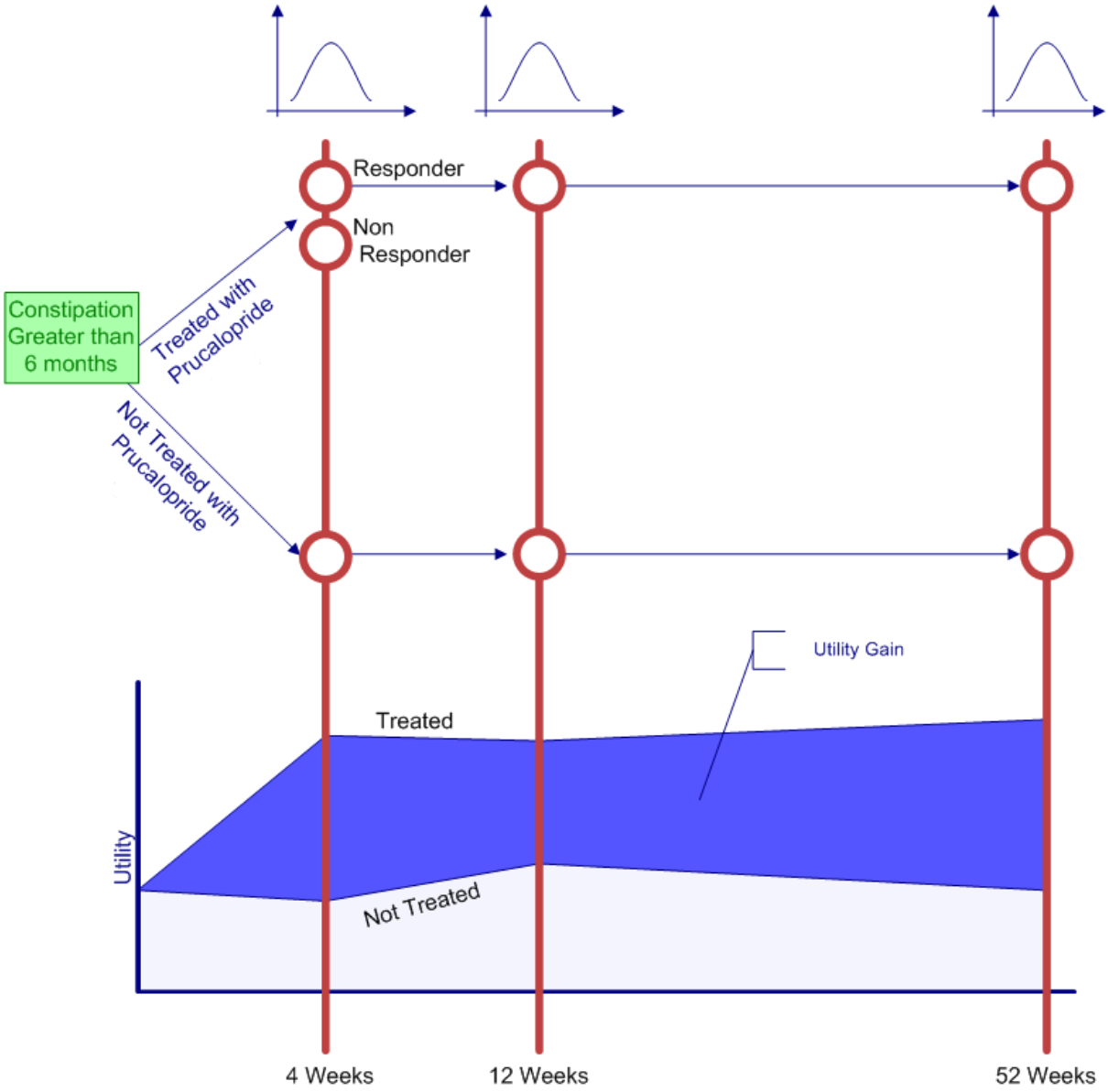

Figure 4 Figure 8 (p118) of manufacturers submission, entitled “Costs and outcomes of constipation treatment – decision tree analysis, UK model”

RCT results were collected for the 2 mg dosage population (<65 years) for 12 weeks, while 1mg dosage population (>65 years) results were collected for a period of four weeks. For the following months up to one year observational study results were collected. It was found that patient satisfaction was maintained over the year in patients who continued to take prucalopride. It

was stated on p130 of the submission that “Patient drop out due to lack of efficacy after 12 weeks was low (< 5%)” but that is contradicted by table 38 of the submission on p82 showing high rates of dropout between 40-90% and table 39 showing that ~17% dropped out from insufficient response (tables 11 and 12 of this report). The time-points in the model are 4-weeks, 12-weeks and 52-weeks. Treatment outcome was the frequency of spontaneous complete bowel movements (SCBM). A patient who experienced 3 or more SCBM in one week was defined as having achieved normalised bowel movements and hence categorised as being a “responder”. Patients who achieved “normality” in bowel movements were considered responders in this context and were reassessed after 12 weeks to ensure that treatment effectiveness was sustained. In patients who did not maintain the target treatment response of 3 or more SCBMs, treatment was discontinued.

The manufacturer provided in the clarifications responses an illustrative graph generated by the model in the base case situation with actual utility scores on the vertical axis (scale goes from 78 to 90) and weeks 4, 12 and 52 on the horizontal axis. The top line (yellow) is treated responder, next line (red) treated but not responder and lowest line (blue) is not treated. Both prucalopride groups start at the same utility level with a mean index score of 82.22 (on a scale where full health is scored at 100). The group of patients not treated with prucalopride do get slightly better between 0 to 12 weeks; this is explained by Movetis to be typical of a placebo effect. The adult group was assessed at weeks 4 and 12, the improvement between week 0 and week 12 was taken to be sustained to week 52. The elderly group was assessed at week 4 and the improvement at week 4 was taken to be sustained to week 52.

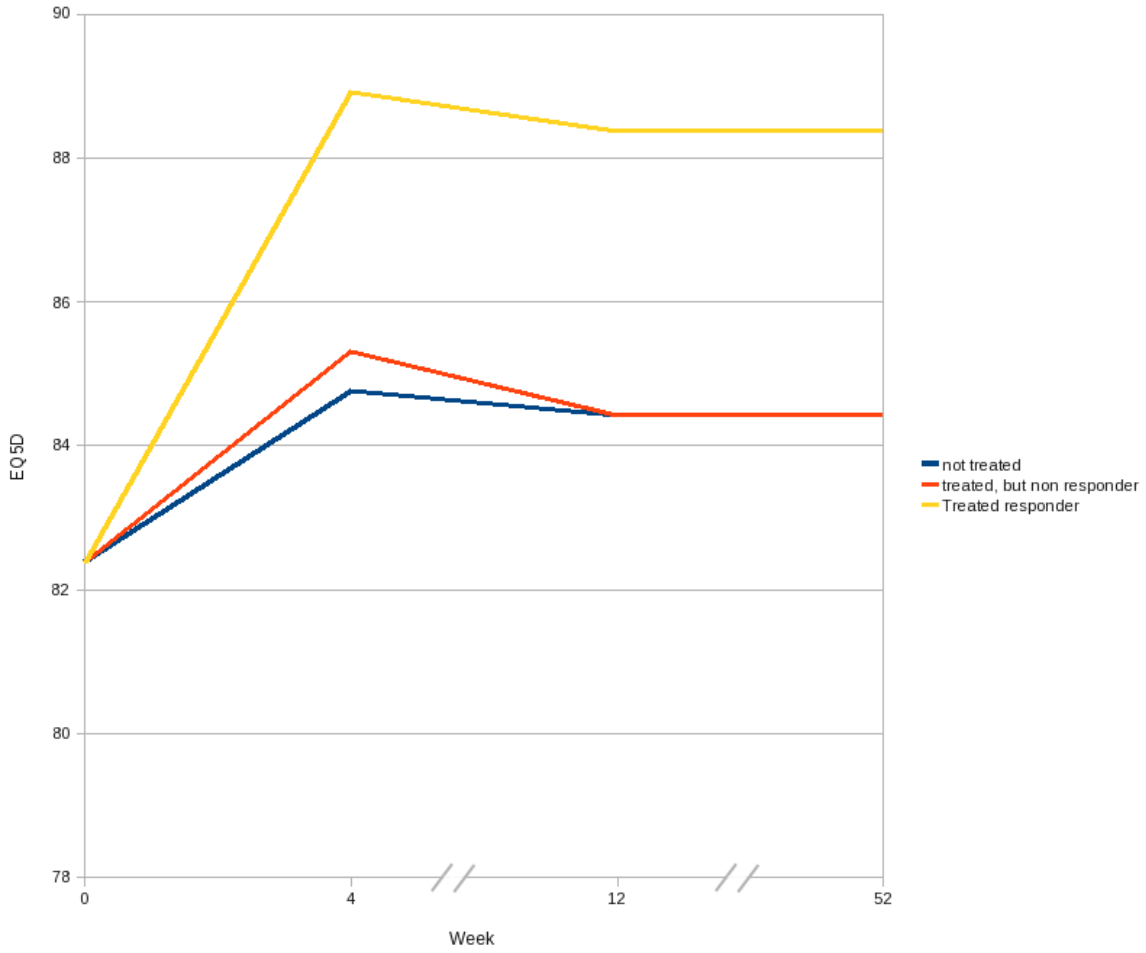

Figure 5 Changes in EQ-SD generated by the economic model in the base case situation

5.1.3 Health related quality of life

EQ-5D outcomes were not collected directly in the prucalopride trials, they collected SF-36 and PAC-QOL together at various time points, obtaining 5488 sets of values altogether. SF-36 has been mapped onto the EQ-5D index in a previously published paper by Rowen et al 2009[2] where EQ-5D was estimated for each SF36 sample using a generalised least squares model. The prucalopride model then used a mapping process to convert PAC-QOL to EQ-5D which was carried out by Haycox et al, whose paper was included in the submission (see appendix 14 starting on p216 “The economic evaluation of Prucalopride in Chronic Constipation”)..

[2] Rowen D, Brazier J, Roberts J. Mapping SF-36 onto the EQ-5D index: how reliable is the relationship? Health and Quality of Life Outcomes 2009;7(27):1-9

The estimated equation for deriving EQ-5D from PAC-QOL was:

EQ-5D = 97.7 – 9.8 (PAC-QOL)

Note that the PAC-QOL is an inverse measure from 1 (mild symptoms) to 4 (severe symptoms). A patient suffering from severe chronic constipation (4) would map onto an EQ-5D score of 0.585 (on the 0 - 1 EQ-5D scale). This is illustrated by the diagram below, from the Haycox et al paper in appendix 14, p222.

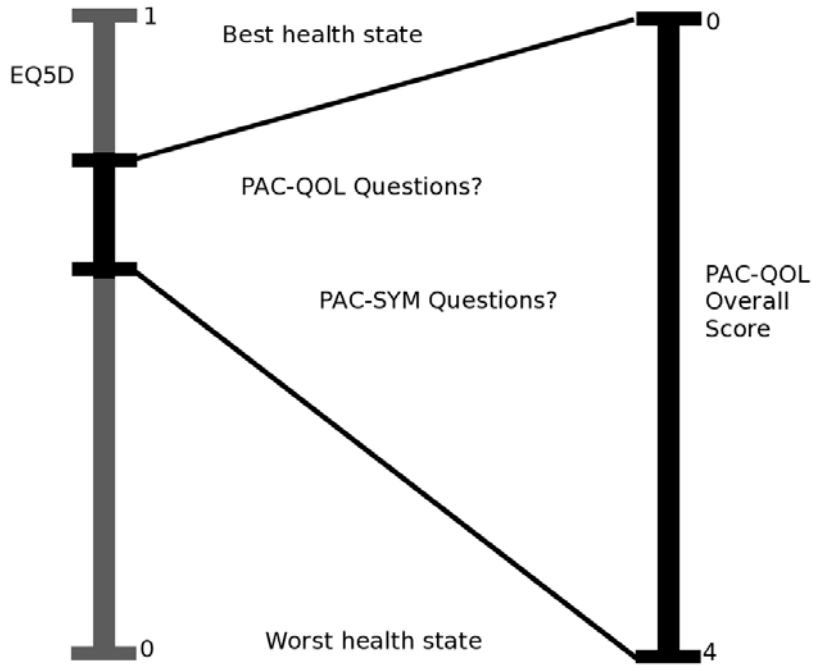

Figure 6 Relationship between PAC-QOL quality of life score and EQ-5D

Also please note that the EQ-5D estimate of severe chronic constipation of 0.585 contrasts with the baseline EQ-5D scores provided in the clarifications document and reproduced in figures 2 and 3 of this ERG report.

A chart representative of the mapping process, provided by the manufacturer, is shown below. It is similar to the diagram from p224 of the Haycox et al paper, but enlarged, and it does not have any explanatory comment:

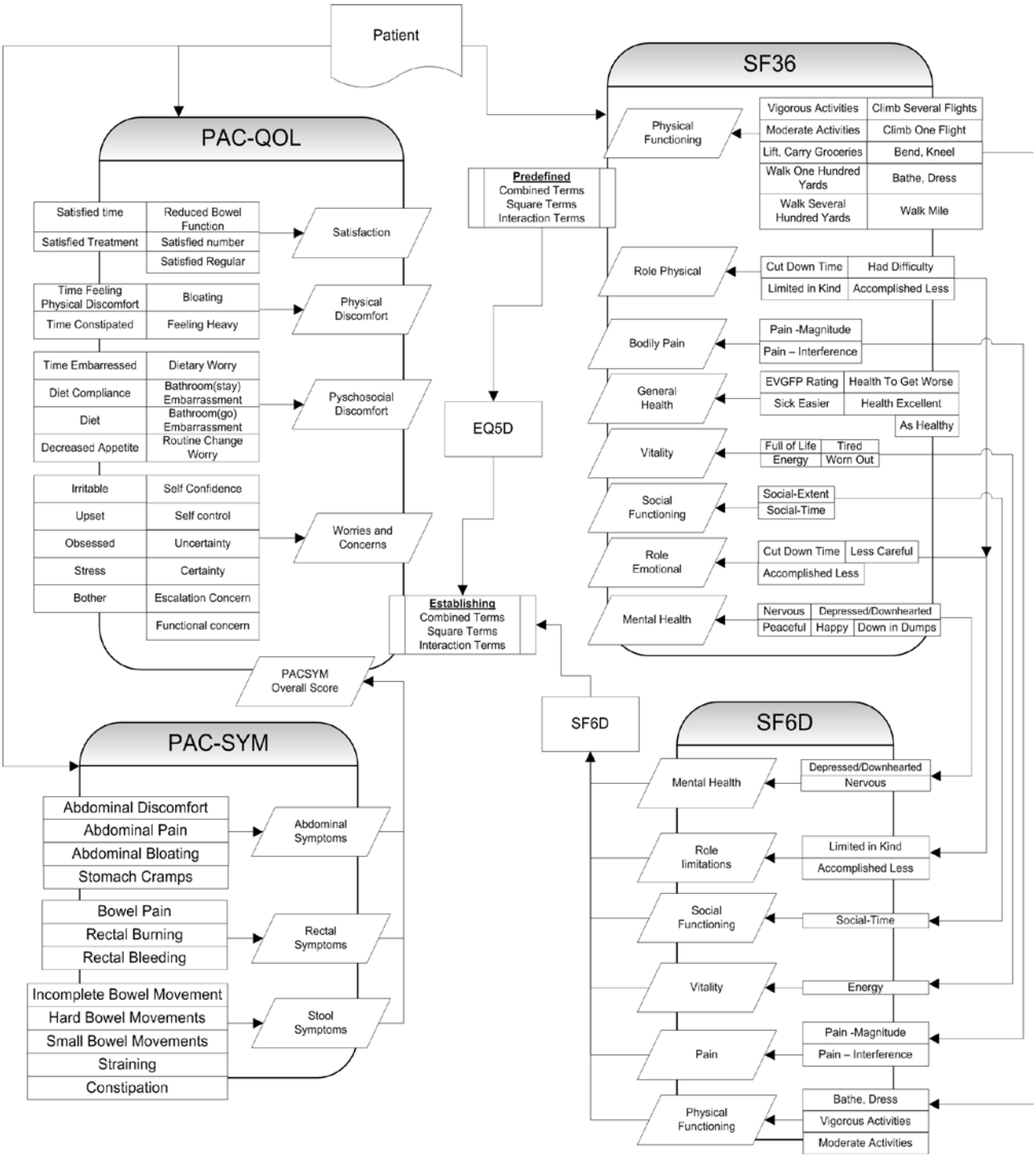

Figure 7 Mapping process of PAC-QOL to EQ-5D

5.1.4 Resources and costs

The only resource/cost incorporated into the economic model is the full list price of prucalopride to the NHS (cost of prucalopride: 2mg tablet is priced at £2.13 and 1mg tablet at £1.38). The clinical trials did not collect data on resources used.

5.1.5 Discounting

The time frame used in the model covered a period of 12 months so discounting has not been applied.

5.1.6 Sensitivity analyses

Sensitivity Analysis was presented on alternative response:

- ≥ 3 SCBMs (spontaneous complete bowel movements) per week
- an increase of ≥1 SCBM per week

Both response analyses were carried out for all female patients, adult female and elderly female. No other sensitivity analysis results were presented in the original submission. Some further scenarios were included in the clarification document.

5.1.7 Model validation

The manufacturer's submission (submission pp 152-153) describes in detail a validation process relating to the mapping of quality of life scores. For the rest of the model, the following remarks were made (see p153 of the submission):

Design of the economic model focused on keeping the structure as simple as possible, providing a structure which aligned as closely with real world clinical practice as possible. The first step in the process was to identify the effect of treatment upon a patient's quality of life, and how this compared with current practice. One particular issue was the lack of any specific evidence relating to the treatment of chronic constipation. Whilst laxative use is widespread, readily available over the counter and inexpensive, the inclusion criteria for the evaluation of prucalopride defines patients who are both unresponsive to current medication and who have suffered from constipation for longer than

six months.

5.2 Critique of approach used

The only cost incorporated in the model is the acquisition cost of prucalopride. It is assumed that other NHS costs will be at least as high for the comparator arm as for prucalopride. Therefore, the decision not to include these costs is described as a conservative approach. This may well be the case for routine NHS costs, but it is not clear that adverse event costs are no higher with prucalopride than without, bearing in mind that there were more adverse events in the prucalopride arm than placebo arm of the trials (see table 13 of this ERG report).

For outcomes, it was assumed that non-responders do not benefit from prucalopride treatment. Quality of life gained by responders was estimated by one of eight different regression equations, which varied according to all possible combinations of three factors:

- Use of primary endpoint from trials (responders have at least 3 SCBM per week) or secondary endpoint (responders have an increase of at least 1 SCBM per week);
- Inclusion of all patients or only those who answered “yes” to the question relating to previous laxative treatment;
- Treatment effect dependent or not dependent on baseline EQ-5D.

These regression equations were applied to a dataset including EQ-5D scores inferred from the mapping process. The dependent variable is the mapped EQ-5D at 4 weeks or 12 weeks. Again, no account was taken of adverse events.

The manufacturers used an unconventional approach to the cost-effectiveness calculation. However, their approach is equivalent to the more conventional approach. To see this equivalence, it is helpful to start from the

"conventional" approach. The figure below shows a decision tree in which those on treatment are classified as responders or non-responders.

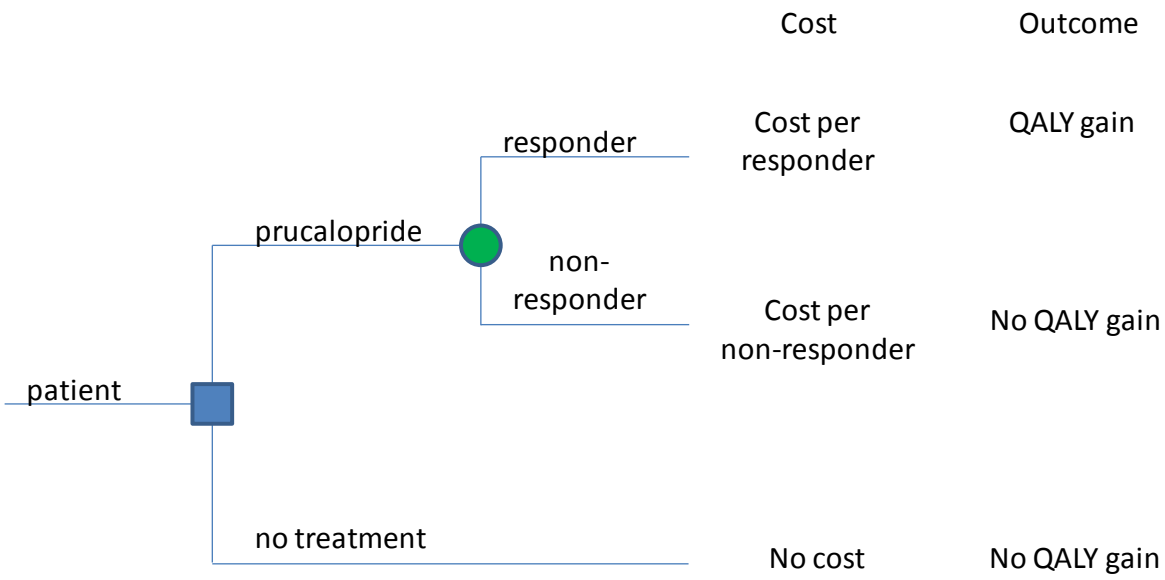

Figure 8 Decision tree for prucalopride treatment

Since the only cost included in the model is the cost of prucalopride, there is a zero cost for the comparator arm, which can be taken as "no treatment". Therefore the mean difference in cost per patient treated is given as:

$$(\text{response rate}) \times (\text{cost per responder}) + (\text{non-response rate}) \times (\text{cost per non-responder}).$$

The manufacturer's response to clarification questions confirmed that non-responders were assumed to have no QALY gain compared to those not treated. Therefore the mean QALY gain per patient treated is simply:

$$(\text{response rate}) \times (\text{mean QALY gain per responder}).$$

The conventional calculation of the ICER divides the mean difference in cost by the mean QALY gain. Therefore the incremental cost-effectiveness ratio (ICER) can be calculated as:

$$\frac{(\text{response rate}) \times (\text{cost per responder}) + (\text{non-response rate}) \times (\text{cost per non-responder})}{(\text{response rate}) \times (\text{mean QALY gain per responder}) + (\text{non-response rate}) \times (0)},$$

which simplifies to:

$$\frac{(\text{response rate}) \times (\text{cost per responder}) + (\text{non-response rate}) \times (\text{cost per non-responder})}{(\text{response rate}) \times (\text{mean QALY gain per responder})}.$$

The conventional approach calculates the mean cost difference and QALY gain per patient treated. The ratio of these two is the “conventional” ICER.

Instead of the “conventional” approach, the manufacturers have calculated the mean cost per responder and divided by the mean QALY gain per responder. There is no need to account for QALYs gained by non-responders, as these are assumed to be zero. However, the cost incurred by non-responders must be included. This has been done by sharing the non-responders’ cost among the responders.

To see the equivalence of the approach taken by the manufacturer to the “conventional” approach requires a certain amount of manipulation of fractions. Starting from the “conventional” ICER formula given above, the first step is to divide top and bottom by (response rate). Then it can be seen that the “conventional” ICER formula is equivalent to:

$$\text{ICER} = \frac{(\text{cost per responder}) + \left(\frac{\text{non-response rate}}{\text{response rate}}\right) \times (\text{cost per non-responder})}{(\text{mean QALY gain per responder})}.$$

Given that the only cost included in the model is the daily cost of treatment, the mean cost incurred by responders is found by multiplying the daily cost of treatment by the mean number of days on treatment. The cost incurred by non-responders is the cost of the 28 days’ treatment taken before the stopping rule was applied. Therefore the ICER can be rewritten as

$$\text{ICER} = \frac{(\text{daily cost}) \times \left[(\text{days per responder}) + \left(\frac{\text{non-response rate}}{\text{response rate}}\right) \times 28\right]}{(\text{mean QALY gain per responder})},$$

where “days per responder” represents the mean number of days for which each responder requires treatment. The figure 28 represents the number of days for which non-responders are treated.

Now it is a mathematical identity that:

$$\left[A + B \times C\right] = 365 \times \frac{1}{365} \times \left[A + B \times C\right] = 365 \times \left[\frac{A + B \times C}{365}\right] = 365 \times \left[\frac{A}{365} + \frac{B \times C}{365}\right]$$

$$= 365 \times \left[\frac{A}{365} + B \times \frac{C}{365}\right].$$

Taking *A* as (days per responder), *B* as $\left(\frac{\text{non - response rate}}{\text{response rate}}\right)$, and *C* as 28,

we have:

$$\text{ICER} = \frac{\left(\text{daily cost}\right) \times 365 \times \left[\left(\frac{\text{days per responder}}{365}\right) + \left(\frac{\text{non - response rate}}{\text{response rate}}\right) \times \frac{28}{365}\right]}{\left(\text{mean QALY gain per responder}\right)}.$$

The expression inside the square brackets in the formula immediately above is described in the model as “compliance”. For example, suppose that responders themselves use an average of 210 days’ treatment per year and that there are two non-responders for every responder. Then the “compliance” is calculated as $\frac{210}{365} + 2 \times \frac{28}{365} = \frac{266}{365} \approx 73\%$.

It should be stressed that “compliance” here does not relate to the fraction of patients who take the medication, but rather to the fraction of a year’s medication overall taken by responders, increased by adding the non-responders’ medication to the responders. For this reason, the “compliance” figure can be over 100%.

In the manufacturers’ model, the “compliance” figure as defined above is used as an input to the model, and the additional cost per patient is then calculated as $\left(\text{daily cost}\right) \times 365 \times \left(\text{"compliance"}\right)$.

QALY gains per responder are estimated by starting with a distribution of baseline EQ-5D scores, which have been designed to match the population observed in the trials. Then the quality of life gain was calculated using only (at most) three terms from the regression equation: the coefficients relating to

treatment, responder, and baseline adjustment for treatment. The last of these coefficients was fixed at zero in some of the models. Instead of using the point estimates of these coefficients, independent samples were taken each time from normal distributions using the standard error from the regression analysis. This means that the distribution of QALY gain includes a mix of first-order uncertainty (or patient variability) reflected in the sampling of baseline EQ-5D scores and second-order uncertainty (or parameter uncertainty) reflected in the sampling for the regression coefficients.

From this “mixed” sampling, a curve described as a cost-effectiveness acceptability curve (CEAC) can be constructed. However, this curve is not a true CEAC as usually understood, because of the mixture of patient variability with parameter uncertainty.

The manufacturer’s model then produces an average incremental cost, an average QALY gained, and an “average” ICER. In the original submission, the average ICERs quoted represented a 50% point on the “CEAC”. In some of the clarification responses, the ICER has been correctly calculated as the ratio of the average incremental cost and the average QALY gained.

However, it should be remembered that, in effect, the average incremental cost given by the manufacturer is a “cost per responder”, sharing the non-responders’ treatment costs among the responders. The average QALY gained is also per responder, with no adjustment required. The ratio of these is indeed equal to the “conventional” ICER, subject to the various assumptions that have been made in the modelling.

5.3 Results included in manufacturer’s submission

The following results were taken directly from the manufacturer’s original submission (see p147-8 of the submission):

As there is only a single intervention compared to placebo (equivalent to standard care) the ICERs and CEACs represent a simple comparison between

treatment with and without prucalopride.

The SmPC (Summary of Product Characteristics) base case is all female patients excluding those who are non-responders by the 4-week stopping rule. This best represents clinical practice and conforms to the recommendations in the SmPC.

Table 57. Cost and QALY data for SmPC Base Case (treatment compliance 80%)

Treatment	Average incremental cost/year (SD)	Average QALY gained per year (SD)	Average cost/QALY (SD)
Prucalopride	£498.01 (108)	0.0316 (0.1124)	£15,700 (961)
Current standard care	—	—	—

This case is associated with an ICER of £15,700 per QALY; this represents the 50% cumulative probability of prucalopride being cost-effective compared to standard care.

And from p149

It conforms to the SmPC to identify at 4 weeks patients who are non-responders and discontinue treatment with prucalopride. Data for non-responders are therefore not presented here.

A range of options are included in the model; the following are presented here:

- A full (or complete) response is defined as patients who achieve ‘normalisation’ of bowel function as defined by the achievement of the primary trial outcome measure of achieving 3 or more SCBMs per week. As this is our ‘base case’ analysis the results for this patient group are provided below for all patients and separately for adult and

elderly patients. Cost/QALY results for this analysis are in Table 58:

Table 58. Cost and QALY data for ≥3 SCBM responders (primary clinical endpoint)

≥3 SCBM responders	Average incremental cost/year (SD)	Average QALY gained per year (SD)	Average cost/QALY (SD)
All females	£498.01 (108)	0.0316 (0.1124)	£15,700 (961)
Adult females	£622.00 (0)	0.0369 (0.0450)	£16,800 (—)
Elderly females	£403 (0)	0.0342 (0.1495)	£11,700 (—)

And from p150:

All patients who achieved an additional bowel movement per week were designated as **partial responders** and the cost-effectiveness of treating all such patients was analysed. Analysis of the relationship between partial responders on medication (PROMs) and this partial outcome measure emphasises that patients who achieve an additional SCBM per week also experience significant improvements in PROMs. Cost and QALY data are in Table 59.

Table 59. Cost and QALY data for partial responders (≥1 improvement in SCBM responders = secondary clinical endpoint)

≥1 SCBM responders	Average incremental cost/year (SD)	Average QALY gained per year (SD)	Average cost/QALY (SD)
All females	£498 (108)	0.0277 (0.1133)	£18,000 (934)
Adult females	£622 (0)	0.0342 (0.0430)	£18,000 (—)
Elderly females	£403 (0)	0.0255 (0.1466)	£15,815 (—)

Both of the cases analysed (≥3 and ≥1improvement in SCBMs/week) emphasise the cost-effectiveness of prucalopride in treating patients who are assessed as achieving three or more SCBMs after the initial four weeks of therapy.

Some more results were added in the response to clarification questions:

> The new Excel version of the health economic model also includes a scenario for continuation of treatment in patients who meet the secondary endpoint of an increase of 1 SCBM per week with an improvement in HRQoL. An analysis of patient data that meet this scenario shows an average qaly gain of 0.038 at an average cost per qaly gain of £13,277.
>
> At four weeks (28 days) it is realistic and possible to identify patients who gain no benefit from treatment with prucalopride and discontinue treatment. The model considers both responders and non responders. Non-responders cease treatment at 4 weeks and the cost of the initial four weeks is incorporated into the acquisition costs of the responders. The costs of non-responders are therefore included in the responder analysis
>
> The costs and QALYs of ignoring the stopping rule (i.e. aggregating responders and non responders) is included as scenario four in the new version of the health economic model. The average qaly gain in this scenario is 0.014 at an average cost per qaly gained of £34,606

5.4 Validity of results

As noted in Section 5.2, the average incremental cost and QALY are not those calculated per patient treated, but are in fact per responder, sharing the cost of treatment for non-responders among the responders' costs. The average cost/QALY (ICER) values are in many cases taken from the 50% of the "cost-effectiveness acceptability curves" derived using a mixture of patient variability and parameter uncertainty.

Once the structure of the model and its Excel coding had been understood, the ERG was able to verify the results quoted in Section 5.3 of this report. One error was found in the response to clarification questions. This appears to have been a simple copying error affecting one cell of the spreadsheet. The effect was to change the ICER for the first new scenario from the quoted figure of £13,277/QALY to around £17,500/QALY. It should also be noted that

the use of random numbers in the model means that final ICERs are only reliable to within an error range of about £200/QALY.

A more important point in relation to the results quoted is that many of them relate to a combined population consisting of Adult women (defined as under 65 years of age) and Elderly women (defined as over 65 years of age). The dose of prucalopride was different for the two groups (2mg per day for the Adult group and 1mg per day for the Elderly group). It does not seem appropriate to combine these groups, and it is the view of the ERG that the results separated by age groups are more appropriate.

A key input to the model is the set of regression analysis results. It has not been possible to verify these. Subject to that important proviso, the ERG is satisfied that the model gives a fair reflection of the assumptions used to build it.

5.5 Summary of uncertainties and issues

The main limitations of the analysis are as follows:

- It has not been possible to verify the regression equations used to determine the treatment effects in the model. This includes both the clinical effectiveness and the mapping of patient outcomes to EQ-5D.
- No account has been taken of adverse events.
- Some results were only given in terms of the overall population. It is important to separate the two age groups: adult and elderly.
- The model only allowed for variation in the response rate and mean treatment rates to be addressed through the “compliance” figure. Uncertainty in this figure was not included in the probabilistic analysis.
- No explicit allowance was made for withdrawal from treatment at any time after 4 weeks.
- The assumption that the last measured QALY gain is sustained for the rest of the year is not tested in the model.

The first three of these issues have been addressed through additional work undertaken by the ERG, which is described in the following section.

6 Additional work undertaken by the ERG

A number of alternative analyses on the model have been carried out. The aim of these is to test the effect of changes to various assumptions contained within the manufacturer's submission. It is important to note that the results here do not in any way represent the ERG's view of the "correct" ICER.

Throughout this section, separate analysis has been carried out for the two age groups: Adult (Under 65: dose 2mg per day) and Elderly (Over 65: dose 1mg per day).

6.1 Simplifying the model

The model as supplied uses a very large number of replications (nearly 40,000). Despite this, the estimates of the ICER are still not completely stable. Results from repeated runs differ by hundreds of pounds per QALY. Given the near linearity of the model, the point estimate of the ICER should be equal to that obtained using the point estimates of the regression coefficients and the mean baseline QALY. The only nonlinearity in the model relates to multiplying the individual baseline QALY estimates by sampled values of the "treated baseline adjustment". Since these samplings are independent, and the model is linear in each of these parameters individually, the point estimate of the ICER can indeed be calculated from the mean values of the model parameters. This was verified by actually comparing the results from the full model with this approach.

Once the model had been made deterministic, it could easily be restructured so that response rates and mean days treatment for responders could be made into separate inputs to the model, instead of being combined in the "compliance" parameter. Again, the restructuring was verified by comparing the two versions of the model.

Given the limited time available for this report once the manufacturer's model had been fully understood, it was felt by the ERG that deterministic results varying the appropriate parameters would be sufficient to show the key uncertainties in the model.

6.2 Alternative model runs completed

The ERG carried out the following alternative model runs. Each was repeated for Adult (under 65) and Elderly (over 65) groups separately, using all eight of the regression equations provided by the manufacturer. As noted in Section 5.2 of this report, these equations vary according to all possible combinations of three factors:

- Use of primary endpoint from trials (responders have at least 3 SCBM per week) or secondary endpoint (responders have an increase of at least 1 SCBM per week);
- Inclusion of all patients or only those who answered “yes” to the laxative question;
- Treatment effect dependent or not dependent on baseline EQ-5D.

The model runs completed were as follows:

1. Based on the simplified version of the manufacturer’s model, using the “compliance” figure as a main driver of the cost.

2. Using an assumption that responders would take treatment for a mean of 220 days (based on the manufacturer’s submission page 140), and response rates taken from pooled estimates of the 4 week response rate at the appropriate dose calculated in the effectiveness review. The numbers used were as shown below in Table 14

3. As 2, but assuming that all responders would take the treatment for the full 365 days in the year modelled.

4. As adverse events were not included in the model, we have attempted to allow for the possibility that adverse events may be higher in the treatment arm than the comparator. This was done by increasing costs by 5% and reducing QALY gain by 5% compared to number 2.

5. Given that it was not possible to verify the regression equations, we have provided a range of model runs in which the effectiveness was reduced uniformly. This model run reduced the overall effectiveness (QALY gain) by 25% compared to number 2.

6. For the same reason as number 5, overall QALY gain reduced by 50% compared to number 2.

7. Again for the same reason, overall QALY gain reduced by 75% compared to number 2.

Table 14: Response rates used for the analysis performed by the ERG

Population	Endpoint	Value used	Taken from
Adult	≥3 SCBM per week	28.0%	Table 2 (p 21)
Adult	≥1 SCBM increase per week	48.2%	Table 3 (p 22)
Elderly	≥3 SCBM per week	39.5%	Table 9 (p 26)
Elderly	≥1 SCBM increase per week	61.1%	Table 9 (p 26)

The results of these model runs are summarised in Table 15 and Table 16 for Adult and Elderly groups respectively. It can be seen that there is not much difference between the results using the various different regression equations, shown in different columns in the tables. Using pooled response rates made no difference to the results for the Adult group with the primary endpoint. The “compliance” figure used in the manufacturer’s base case was consistent with this pooled response rate. The same compliance figure was used for all other results in the first analysis. Replacing by the higher response rates from the pooled analysis reduced the ICER somewhat. This is because the cost incurred by non-responders contributes proportionately less to the overall cost.

Assuming that all responders take treatment for the full year makes a substantial increase to the ICER. The only other scenarios in which the ICER was substantially increased were those in which a large reduction was made in the assumed effectiveness of the treatment.

Table 15. Deterministic analysis on adult patients (under 65 years) (ICERs in £/QALY)

	Primary End Point (≥3 SCBM per week)				Secondary End point (Increase ≥1 SCBM per week)			
	All patients		Only patients answered yes to laxative question		All patients		Only patients answered yes to laxative question	
	WITH SRTE*	WITHOUT SRTE*	WITH SRTE*	WITHOUT SRTE*	WITH SRTE*	WITHOUT SRTE*	WITH SRTE*	WITHOUT SRTE*
Manufacturer's modelling assumptions	16800	15400	15400	14200	18600	16900	16300	15000
Use of pooled response rates	16800	15400	15400	14200	15900	14400	13900	12800
Responders treated for 365 days	25000	23000	23100	21200	25100	22800	22000	20200
Allowance for adverse events	18500	16900	17000	15600	17500	15900	15300	14100
QALY gain reduced by 25%	22400	20500	20600	18900	21200	19200	18600	17100
QALY gain reduced by 50%	33600	30700	30800	28300	31800	28900	27900	25600
QALY gain reduced by 75%	67200	61400	61700	56600	63600	57700	55800	51200

*Baseline Constipation Severity Related Treatment Effect

Table 16. Deterministic analysis on elderly patients (over 65 years) (ICERs in £/QALY)

	Primary End Point (≥3 SCBM per week)				Secondary End point (Increase ≥1 SCBM per week)			
	All patients		Only patients answered yes to laxative question		All patients		Only patients answered yes to laxative question	
	WITH SRTE*	WITHOUT SRTE*	WITH SRTE*	WITHOUT SRTE*	WITH SRTE*	WITHOUT SRTE*	WITH SRTE*	WITHOUT SRTE*
Manufacturer's modelling assumptions	13800	14800	11800	12600	17500	18700	14900	16200
Use of pooled response rates	12400	13300	10600	11400	14200	15200	12100	13200
Responders treated for 365 days	19200	20700	16500	17700	22900	24500	19500	21300
Allowance for adverse events	13600	14700	11700	12500	15700	16800	13400	14600
QALY gain reduced by 25%	16500	17800	14200	15200	19000	20300	16200	17600
QALY gain reduced by 50%	24800	26700	21300	22800	28500	30500	24300	26500
QALY gain reduced by 75%	49500	53300	42600	45500	56900	61000	48600	52900

*Baseline Constipation Severity Related Treatment Effect

7 Discussion

There were 36 trials/studies listed and nine of these were fully described in the submission. A different selection of 10 trials and studies were used to inform the economic model but five of these were not described in the submission.

In the trials that were described, participants were adult and elderly men and women with chronic constipation. It appears that many participants in these trials had not failed previous laxative use and the spread of baseline predicted EQ-5D scores suggested than all patients were unlikely to have had severe chronic constipation. In the three pivotal trials, 17.0% of patients at baseline answered that they had found their previous treatment adequate. The types of patients for whom prucalopride is indicated, those with severe chronic constipation and refractory to laxative treatments, would be unlikely to have found previous treatments adequate. Therefore, the patients studied in the pivotal trials were not those with laxative-refractory chronic constipation as per the licensed indication.

The intervention in the studies was oral prucalopride at doses of 1mg, 2mg or 4mg per day and the comparators were placebo or a different dose of prucalopride. Outcome results given were spontaneous complete bowel movements (SCBMs), spontaneous bowel movements (SBMs), bisacodyl/enema use, symptoms (including PAC-Sym), quality of life (PAC-QOL, SF-36) and adverse events. The primary outcome was the proportion of patients with ≥3 SCBMs/week over weeks 1-4 and 1-12. There was a statistically significant improvement in this outcome in the 2mg prucalopride arm (licensed dose in adult women) compared to placebo for adults in the three pivotal RCTs (INT-6, USA-11, USA-13). Although two RCTs used to inform the economic model were in elderly patients, only one was fully described in the submission (INT-12) and this did not show a significant improvement in the primary outcome measure of the proportion of patients

with average ≥3 SCBMs/week at week 4 in the 1mg prucalopride arm (licensed dose in elderly women) compared to placebo.

Rescue treatment with a laxative (bisacodyl) or an enema was used in both arms of the three pivotal RCTs in adults. Any bowel movements that occurred due to these treatments were considered to be non-spontaneous and were discounted from the count of SCBMs (the primary outcomes for these studies). From information supplied by the manufacturer, it is evident that the number of non-spontaneous bowel movements that were discounted from the placebo was higher than the number discounted from the prucalopride group.

7.1 Summary of clinical effectiveness issues

- It is apparent that many of the patients did not have laxative-refractory chronic constipation.
- The comparator group in trials was inappropriate. It was neither a true placebo or a proper representation of treatment with laxatives.
- No justification was given for why particular trials and particular patients from these trials were selected to inform the economic model.
- No description or results for five of the trials that have contributed data to the economic model are given in the submission.
- The assumption that effectiveness data can be extrapolated to one year is unjustified.
- There is a lack of transparency around the data and assumptions that have been used to inform effectiveness results in the economic model.
- There is a lack of transparency around the calculation of EQ-5D scores.

Taking all of the clinical effectiveness issues together, it appears that the estimate of the clinical effectiveness used in the economic modelling is likely to be an overestimate, but, due to lack of transparency, the magnitude of overestimation is uncertain.

7.2 Summary of cost effectiveness issues

The cost effectiveness analysis is based on a new model supplied by the manufacturer. The main limitations of the analysis are as follows:

- It has not been possible to verify the regression equations used to determine the treatment effects in the model. This includes both the clinical effectiveness and the mapping of patient outcomes to EQ-5D
- No account has been taken of adverse events
- Some results were only given in terms of the overall population. It is important to separate the two age groups: adult and elderly
- The model only allowed for variation in the response rate and mean treatment rates to be addressed through the “compliance” figure. Uncertainty in this figure was not included in the probabilistic analysis.
- No explicit allowance was made for withdrawal from treatment at any time after 4 weeks.
- The assumption that the last measured QALY gain is sustained for the rest of the year is not tested in the model.

The first three of these issues have been addressed through additional work undertaken by the ERG. The results of the ERG reanalyses are summarised in Table 17

Table 17. Summary of ERG reanalysis (ICERs in £/QALY)

Scenarios	Adults	Elderly
Manufacturer's modelling assumptions	14200 to 18600	11800 to 18700
Use of pooled response rates	14200 to 16800	10600 to 15200
Responders treated for 365 days	20200 to 25100	16500 to 24500
Allowance for adverse events	14100 to 18500	11700 to 16800
QALY gain reduced by 25%	17100 to 22400	14200 to 20300
QALY gain reduced by 50%	25600 to 33600	21300 to 30500
QALY gain reduced by 75%	51200 to 67200	42600 to 61000

7.3 Implications for research

The main research question to be addressed is the clinical effectiveness of prucalopride in adults with chronic constipation in whom standard laxatives have failed to provide adequate relief, and for whom more invasive procedures, such as direct rectal intervention, are being considered. A 12-month trial in these patients would be useful. Prucalopride should be compared to current treatment (such as direct rectal intervention) in this patient group and the trial should measure costs and EQ-5D so that a direct estimate of quality of life can be made.

Appendix 1: Additional ERG searches

Database: Cochrane Library (Wiley) 2010 Issue 5 (CDSR)

Search strategy:

#1 prucalopride
#2 resolor
#3 #1 or #2

Database: Cochrane Library (Wiley) 2010 Issue 2 (CENTRAL, NHS EED, HTA)

Search strategy:

#1 prucalopride
#2 resolor
#3 #1 or #2

Database: MEDLINE (Ovid) 1950 to May Week 2 2010
Search Strategy:

1 prucalopride.mp. or exp prucalopride/
2 resolor.mp.
3 or/1-2
4 limit 3 to "therapy (sensitivity)"

Database: EMBASE (Ovid) 1980 to 2010 Week 19
Search Strategy:

1 prucalopride.mp. or exp prucalopride/
2 resolor.mp.
3 or/1-2
4 limit 3 to "treatment (2 or more terms high sensitivity)"
5 chronic constipation.mp. or chronic constipation/
6 4 and 5

Database: MEDLINE (Ovid) 1950 to May Week 2 2010
Search Strategy:

1 prucalopride.mp. or exp prucalopride/
2 resolor.mp.
3 or/1-2
4 limit 3 to “costs” (sensitivity)
5 chronic constipation.mp.
6 limit 5 to "costs (sensitivity)"
7 4 or 6

Database: MEDLINE (Ovid) 1950 to May Week 2 2010
Search Strategy:

1 prucalopride.mp. or exp prucalopride/
2 resolor.mp.
3 or/1-2
4 limit 3 to "economics (sensitivity)"

Database: EMBASE (Ovid) 1980 to 2010 Week 19
Search Strategy:

1 prucalopride.mp. or exp prucalopride/
2 resolor.mp.
3 or/1-2
4 limit 3 to "economics (2 or more terms high sensitivity)"

Database: MEDLINE (Ovid) 1950 to May Week 2 2010
Search Strategy:

1 prucalopride.mp. or exp prucalopride/
2 resolor.mp.
3 or/1-2
4 limit 3 to "therapy (sensitivity)"
5 from 4 keep 1-44
6 chronic constipation.mp.
7 decision support techniques/
8 markov.mp.
9 exp models economic/
10 decision analysis.mp.
11 cost benefit analysis/
12 or/7-11
13 6 and 12
14 3 and 12
15 13 or 14

Database: MEDLINE (Ovid) 1950 to May Week 2 2010
Search Strategy:

1 prucalopride.mp. or exp prucalopride/
2 resolor.mp.
3 or/1-2
4 chronic constipation.mp.
5 3 or 4
6 quality of life/
7 life style/
8 health status/
9 health status indicators/
10 or/6-9
11 5 and 10

Appendix 2: Quality Assessment using ScHARR-TAG economic modelling checklist

Factor	Appraisal
Title	Prucalopride (Resolor®) for the treatment of women with chronic constipation in whom standard laxative regimens have failed to provide adequate relief
A statement of the problem	What is the incremental cost-effectiveness of Prucalopride compared to standard care for treating chronic constipated patients?
A discussion of the need for modelling	Modelling is required for the following reasons: • To calculate the probability that the treatment is cost-effective at different ICER thresholds • To extrapolate changes in outcomes over the year during the follow-up period of the clinical trials. • To obtain comparable outcomes in the population treated with prucalopride and not treated, in terms of generic quality of life (QALYs) measures. • To test the robustness of conclusions to changes in primary end point (reaching ≥3 SCBM per week) and secondary end point (reaching ≥1 improvement in SCBM per week). **Assessment by ERG**: The decision to use modelling was appropriate given the data constraints.
A description of the relevant factors and outcomes	Relevant factors and outcomes are the following: • Two groups of patient level data are used: adult (<65 years, 2mg tablet daily-dosage) and elderly (>65 years 1mg tablet daily-dosage). • The EQ-5D baseline of these two groups of patients is the result of the extension of a gamma distribution (carried out for a list of clinical trials incorporated into the model) on a larger (synthetic) sample of 38650 patients. • Responders are considered to be those who reach the primary end point of ≥3SCBM (spontaneous complete bowel movements) per week, or, in an alternative analysis, the secondary end point of ≥1SCBM improvement. • The variables used in the model to calculate the EQ-5D

	gained at each time point are the result of the regression analysis carried out applying different assumption to the clinical trial data from clinical trials incorporated in the model. • A responding patient at each time point, with a certain age and EQ-5D baseline, will have EQ-5D gain considering essentially three factors: response of the patient, dosage-treatment and baseline adjustment. List of trials incorporated in the model are: FRA-1, GBR-4, INT-1, INT-12, INT-2, INT-6, USA-11, USA-13, USA-26, USA-3. **Assessment by ERG:** The prucalopride trials did not collect data using the EQ-5D questionnaire. The SF-36 had been directly measured in the prucalopride trials alongside the patient assessment of constipation questionnaires (PAC-QOL and PAC-SYM). The relationship, established between SF-36 and the PAC questionnaires, has been extrapolated to EQ-5D. Following further clarification by telephone, two charts have been provided representing the EQ-5D baseline distribution of both adult and elderly groups. The distributions of individual patient baseline EQ-5D used in the model were a good match to these charts.
A description of model including: type of model; time frame; perspective; and setting	The economic model is designed to evaluate the cost-effectiveness of treatment with prucalopride in two separate populations; adults (18-65 years) and elderly (65+ years) 1 year time horizon. NHS perspective. UK care setting. **Assessment by ERG:** The general modelling used was appropriate considering the fact that it has used patient level data, but the cost-effectiveness acceptability curves, being based on variability between individual patients and not uncertainty around the parameters, are not appropriate and cannot summarise the evidence in support of prucalopride being cost-effective for all potential values of the decision rule.
A description of data	Data sources used to model the effectiveness: • A regression analysis was carried out on data from a list of clinical trials. As result of this analysis a table is provided in

sources, with description of respective strengths and weaknesses	the submission, containing the variables applied in the model. • The analysis carried out was per-responder; each individual patient with a certain baseline characteristic will have a specific incremental EQ-5D depending on the variables of the model extrapolated by the clinical trials used in the regression analysis. • Only the acquisition cost of prucalopride was incorporated in the model since no other costs-resources were collected during the trials. From the list of studies included in the model only one is the pivotal trial for elderly patients (INT-12) and three of them are pivotal for adult patients (INT-6, USA-13, USA-11) **Assessment by ERG:** The clinical trials data have been pooled together and being used to run the regression analysis. No information on the pooling process has been provided; no meta-analysis has been carried out either.
Key assumptions relating to model structure and data stated	• Only the acquisition cost of prucalopride is considered in the model. It is assumed that responders take the treatment for an average of 220 days through the year and that non-responders stop the treatment after 28 days. • The EQ-5D baseline is considered to be the placebo data from the prucalopride clinical trial. This assumption was undertaken because the target patient population for prucalopride had already failed on laxatives and subsequently expressed their dissatisfaction with laxatives. • The adverse event profile of prucalopride looks quite similar to that of placebo. So adverse events are not included in the model. **Assessment by ERG:** The broad structural assumptions used in modelling were appropriate. However it does not allow for constructing any uncertainly around the mean of the cost. Data on QALYs gained were collected at 4 weeks and 12 weeks. The incremental QALYs at 4 weeks is applied across the first month of treatment and the incremental QALYs at 12 weeks is applied across the same for the 11 remaining months of the year. No explicit allowance is made for patients stopping treatment later than 4

	weeks. It has been assumed that non-responders have no QALY gain. Instead of calculating average costs and QALYs per patient treated, the average QALYs per responder have been calculated. For costs, the average cost is in effect the total cost (across all patients) divided by the number of responders. While this means that the ICER eventually calculated is the correct ICER given the assumptions in the model, the average costs and QALYs do not carry the obvious meaning.
Disease specific factors included within modelling (Items to be specified in conjunction with expert clinical input)	• Two subgroup analyses were undertaken in the model for adults and elderly patients, in order to reflect the clinical trials dosage response data. • Having not collected any resources used during the clinical trials, it was considered preferable not to add any additional GP and specialist visits for the placebo group.
Validation	The mapping analysis has been extensively reviewed by Dr Antonieta Medina Lara (senior research fellow) at the University of Liverpool, external validation process was undertaken with Professor John Brazier from ScHARR (University of Sheffield). The approach, analysis and results of the mapping process have been accepted for publication in the journal *Pharmacoeconomics*.
Results	The results reported in the submission consider all female patients responders: • Average incremental cost/year (SD) = £498.01 (108) • Average QALY gained per year (SD) = £0.0316 (0.1124) • Average cost/QALY (SD) = £15,700 (961) Two further analyses on two groups of female patients (adult and elderly) were presented; those analyses were considered for patients who achieved the primary end point (≥3SCBM per week)

	and the secondary end point (≥1SCBM)(See sensitivity analysis). In the new excel version incremental cost effectiveness ratio (ICER) was calculated for patients achieving the primary end point £13899/QALY and the secondary end point £13277/QALY. New version of the model: The ICER is calculated for all age group treated and considering all responders. **Assessment by ERG:** The results of the submission: • It is not appropriate to consider an overall result for both groups (adults and elderly) as they have got different costs, different dosage treatment and different response rate. • Average cost/QALY figures given are based on median not mean QALY gain
Sensitivity analysis results	In the submission two subgroup analyses were carried out for responders reaching the primary clinical endpoint (≥3SCBMper week) and secondary end point (≥1SCBMper week). Results of the subgroups reaching the primary end point are the followings: ADULT • Average incremental cost/year (SD) = £622.00 (0) • Average QALY gained per year (SD) = £0.0369 (0.045) • Average cost/QALY (SD) = £16,800 ELDERLY • Average incremental cost/year (SD) = £403 (0) • Average QALY gained per year (SD) = £0.0342 (0.1495) • Average cost/QALY (SD) = £11,700 The results of the secondary end point subgroup analysis are the followings: ADULT • Average incremental cost/year (SD) = £622.00 (0) • Average QALY gained per year (SD) = £0.0342 (0.043) • Average cost/QALY (SD) = £18,000 ELDERLY • Average incremental cost/year (SD) = £403 (0) • Average QALY gained per year (SD) = £0.0255 (0.1466) • Average cost/QALY (SD) = £15,815

	In the new version of excel costs and QALYs of ignoring the stopping rule are presented (i.e. aggregating responders and non responders). The scenario that describes this is scenario four (responders defined as ≥3SCBM, without baseline constipation severity related treatment effect). The average QALY gained is 0.014 at an average cost per QALY gained of £34,606.