NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Prucalopride for the treatment of chronic constipation in women

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Movetis	*Section 1.1*:We welcome the committee's recommendation for the use of prucalopride, and for clarity ask that the committee amend their recommendation for prucalopride to; 'an option for the **symptomatic** treatment of chronic constipation in women for whom laxatives fail to provide adequate relief'	Comment noted. The Committee considered that the recommendations in the FAD reflect the intended usage of prucalopride for women with laxative-refractory chronic constipation.
	*Section 1.2:*The following amendment to the text of the committee's recommendation may be considered helpful; Prucalopride should only be considered in women who have been managed by a clinician with experience of treating chronic constipation. During a period of at least six months the female patient should have tried at least two different types of laxatives, and have received advice on lifestyle modification but have failed to achieve adequate relief from constipation	Comment noted. Section 1 of the FAD has been amended to reflect the population in whom treatment with prucalopride is considered to be most clinically effective and cost-effective.
	Section 2.1:We recommend the following amendment: Prucalopride (Resolor, Movetis) is a selective serotonin (5HT4) receptor agonist that predominantly stimulates colonic motility. Prucalopride belongs to the therapeutic and pharmacological WHO ATC subgroup class (AO3AE04) of drugs for the treatment of functional bowel disorders that are acting on serotonin receptors. Prucalopride has a UK marketing authorization for the 'symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief'	Comment noted. The FAD provides a summary of the mechanism of action and does not address technical details in depth. Readers are referred to the SPC for more complete information about prucalopride. No changes have been made to the FAD.
	Section 3.6: We request that for clarity the description of PRU INT 12 is amended to: In PRU INT 12, (a study in elderly (>65 years) patients, the proportion of patients treated	Comment noted. The details of the PRU-INT-12 trial are provided in section 3.1 of the FAD and are not included in section 3.5 to avoid repetition. No changes have been made to the FAD.

Consultee	Comment	Response
Movetis	*Section 3.8*: We suggest that the following clarification may be considered helpful, SF36 data was collected from patients in fewer clinical trials compared to the disease specific PAC QOL data, for this reason alone it was decided by Movetis to use the more abundant PAC QOL for analysis of the quality of life changes associated with treatment with prucalopride.	Comment noted.
	The committee's comment regarding outcomes measured using SF36 data; 'that no trials showed statistically significant greater improvements in SF36 for prucalopride compared with placebo at week 12' is correct, however only so when all patients are considered irrespective of response to treatment. Further analysis shows when the cohort of patients who responded to treatment are compared to placebo a statistically significant difference between prucalopride and placebo exists, with an average QALY gain of 0.04 and a cost per QALY gained of £15,300. This outcome based on SF36 data only shows prucalopride to be cost effective in patients who respond to treatment.	Comment noted. Section 3.7 of the FAD has been amended to include a description of the SF-36 data when only patients who responded to treatment with prucalopride are compared with placebo. The analysis informing the revised ICER of £15,300 was not made available to the Committee by the manufacturer.
	Sensitivity analysis of these SF36 based outcomes show that treating all patients irrespective of response produces an average QALY gain of 0.019 and a cost per QALY gained £32,100 whereas treating the responder cohort only, produces a QALY gain of 0.040 at a cost per QALY gained of £15,300. Further sensitivity analysis has been conducted varying the acquisition cost by changing the number of days on treatment. The outcome is consistent with work conducted by the ERG.	Comment noted. The Committee heard from the manufacturer during the 2nd Committee meeting that further SF-36 data (not in the submission) for people whose constipation responded to treatment showed statistically significant improvement for prucalopride compared with placebo. The Committee concluded that changing the mapping equation to include SF-36 instead of PAC-QoL would unlikely alter the results of the model substantially. Please refer to FAD section 4.8.

Consultee	Comment	Response
Movetis	*Section 3.9*: We welcome the opportunity to offer further clarification regarding withdrawal and continuation in the long-term open label extension study. All patients who completed the 12 week double blind phase were invited to take part in the extension; approximately 80% of these participants choose to join the open label extension. Therefore the patients who continued in the open label extension study were a mix of responders and none responders, patients on active treatment or placebo. All of the patients in the extension study were put on to active treatment. Approximately 45% of the total patients enrolled in the extension study dropped out as a consequence of the sponsor stopping the studies. Of the remaining patients, the main reasons for drop out were: insufficient response (18%) withdrawal of consent (15%) adverse events (9%). Post hoc analysis shows that 90% of patients who dropped out of the extension due to insufficient response were already non-responders in the previous double blind phase. This confirms that patients who do not respond early in treatment will not respond with continued treatment and patients who do respond will show a sustained response with no loss of efficacy over time	Comment noted. The Committee heard from the manufacturer that 90% of the people whose constipation did not respond to treatment in the extension studies also had no response in the randomised trial period (that is, were already non-responders). Please refer to section 4.5 of the FAD.
	Section 3.10: We concur with the committee's opinion that the incidence of serious adverse events is low and comparable between treatment and placebo. With regard to the specific adverse events of diarrhoea, nausea, abdominal pain, and headache we agree with the committee that the incidence of these adverse events in the treatment arm is higher than in the placebo arm for the first two days of treatment then afterwards are comparable. These adverse events are mainly mild transient and do not require medical intervention	Comment noted. No action required. For more information on the Committee's consideration of the adverse event profile of prucalopride please refer to Section 4.7 of the FAD.

Consultee	Comment	Response
Movetis	*Section 3.11*: We would like to clarify a very minor point in the consultation document regarding male data in the HE model. All data from the included trials is incorporated into the model, however the model is run using female data only, in accordance with the licensed indication.	Comment noted. The FAD has been amended. Please refer to section 3.10 of the FAD.
	Section 3.11: We request that for the purpose of clarity the text of 3.11 is amended to include: …The model compared prucalopride with placebo. In both arms, bisacodyl as rescue medication was allowed, if bisacodyl was used by a patient any bowel movement in the following 48 hours were not included as these were not counted as spontaneous complete bowel movements.	Comment noted. The FAD has been amended. Please refer to section 3.10 of the FAD.
	Section 3.14: Please refine the text regarding the description of PAC QOL as follows… …PACQOL is a measure from 1 (mild symptoms) to 4 (severe symptoms). This should read; from 0 (no symptoms) to 4 (VERY severe symptoms) and in fact should not refer to symptoms but to impact of symptoms on HRQOL	Comment noted. The description of the PAC-QoL is no longer included in the FAD. Readers are encouraged to refer to the manufacturer's submission and the ERG report for more information regarding the PAC-QoL or other instruments used to obtain utility values for this appraisal.
	Section 3.14: We would like to clarify the purpose of including the various studies in the HE model; The three pivotal studies, PRU-INT-6, PRU-USA-11, PRU-USA-13 the two elderly studies PRU-INT-12 and PRU-USA-26 and the extension studies were used to provide outcomes data and patient characteristics to inform the starting population and disease state in the HE model. Further patient characteristic data was also obtained from other prucalopride trials in chronic constipation – PRU-INT-1, PRU-INT-2, PRU-USA-3, PRU-GBR-4 and PRU-FRA-1.	Comment noted. The FAD has been amended to clarify the reason why these trials were included in the model. Please see section 3.13 of the FAD.

Consultee	Comment	Response
Movetis	*Section 3.18*: We would like to confirm that the rationale for using the studies PRU-INT 6 PRU – USA 11 and PRU USA 13 was that these 3 trials are our pivotal trials, with the largest number of patients and 12 weeks treatment duration. All three studies were of identical design so pooling the data was appropriate. Please refer to 3.9 for clarification regarding how patients were enrolled for follow-up studies. As these patients were rolled over immediately from the double blind pivotal trials their original baseline (start of double blind trial) remained unchanged. (Please see 3.20 and 4.3 with regard to comments on refractory to laxative treatment and inadequate relief). The inclusion of PRU INT 17 (Opioid Induced Trial) does not effect the overall result as the numbers were small (96 out of approximately 2500 patients) and the nature of OIC would if any effect be noticed, reduce the utility gain as these are more challenging with a high level of co-morbidity. Please also see 3.9 for further clarification regarding withdrawal.	Comment noted. The ERG reviewed all of the evidence submitted by the manufacturer on the clinical and cost-effectiveness of prucalopride. No changes have been made to the FAD.

Consultee	Comment	Response
Movetis	*Section 3.20*: The following clarification may be helpful; The patient population in the trials does not completely reflect the patient population covered by the marketing authorization; 'symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief', whereas the trial population was approximately 12% male. Further, to clarify understanding around the use of the term laxative refractory with regard to the licensed indication for prucalopride. Laxative refractory is metric based on bowel movement frequency alone, if a patient on laxatives has fewer than 3 bowel movements per week they are considered to be laxative refractory. The majority of patients in whom laxatives fail to provide adequate relief report: lack of efficacy on a cohort of symptoms, intolerable adverse events, intolerable dosage regimen and, lack of predictability. It was stated by the clinical experts at the committee meeting that some patients may achieve an increased frequency of bowel movement through the use of laxatives; however they cannot tolerate the laxative or find the unpredictability of the effect of the laxative unacceptable.	Comment noted. The Committee heard from the manufacturer that the intended positioning of prucalopride in the treatment pathway for chronic constipation is after failure of oral laxatives due to inadequate efficacy or intolerance. The Committee considered that prucalopride may be a useful treatment option for people with laxative-refractory chronic constipation who are considering invasive treatments. Please see sections 4.2 and 4.11 of the FAD.
	Section 3.22: We would like to refer the Committee to the comments made by Professor Whorwell with regard to the choice of comparator for trials of this nature, he advised the committee that trials of this nature are required to use placebo as a comparator, and that the use of an internationally available rescue medication is essential, hence the choice of biscodyl as the rescue medication.	Comment noted. No changes to the FAD have been made. Please refer to section 4.4 for the FAD for more information on the Committee's discussion regarding comparators for this appraisal.

Consultee	Comment	Response
Movetis	*Section 3.24*: Movetis acknowledge the committee's comments concerning the use of PAC-QOL and PAC-SYM to elicit quality of life data to produce EQ5D scores through mapping, and that SF36 scores did not directly contribute to the EQ5D scores. We welcome the opportunity offer further explanation of our decision: PAC-QOL and PAC-SYM are validated disease specific tools which were used in many of the prucalopride clinical trials whereas SF36 was used in few of the trials. Movetis acknowledge that from the perspective of expedience and simplicity we could have modeled the cost effectiveness of prucalopride on the available SF36 data. However having established an empirical relationship between the PAC data with SF36 and EQ5D it was appropriate to use the mapping process to translate PAC data to EQ5D directly, this producing a more robust cost effectiveness model drawn from a an abundant pool of individual patient data.	Comment noted. No action required.
	Section 3.26: We accept the criticism that adverse events were not directly accounted for in the HE model, however PAC QOL does account for the effect of any adverse events on the quality of life of the patients on treatment, and that PAC QOL outcomes were mapped to EQ5D in which case the effect of AEs on QoL were accounted for. It may also be helpful to refer the committee to comments made by the clinical experts that it is often difficult to differentiate between the AEs caused by the treatment and symptoms of chronic constipation. We would like to assure the committee that data from the trials shows that the vast majority of Adverse Events are mild to moderate, transient and do not require medical intervention	Comment noted. The Committee considered the adverse effects of prucalopride and heard from the clinical specialists that these side effects are often symptoms of chronic constipation and may not always be caused by prucalopride. Please refer to section 4.7 of the FAD for further information.
	Section 3.27: We welcome and support the finding of the ERG in their conclusion that the results from their sensitivity analysis did not differ significantly from those provided by the manufacturer	Comment noted. No action required.

Consultee	Comment	Response
Movetis	*Section 4.3*: We agree with the committee that the definition of adequate relief requires refinement; the challenge of defining adequate relief is complicated by individual patient preference and circumstance. Expert clinicians suggest that adequate relief is a matter for the patient to decide together with their treating clinician. Setting rigorous criteria for the definition of adequate relief may result in patients being treated unnecessarily or patients who would benefit from prucalopride being excluded from treatment.	Comment noted. Based on advice from clinical specialists the Committee concluded that inadequate relief from previous laxative treatments could be defined by duration of follow-up and be the number of laxatives previously used. Please refer to section 4.3 of the FAD for more information.
	Section 4.5: Movetis accept and support the conclusion of the committee that it would be difficult to define a standard laxative regimen as a comparator for patients with chronic constipation. We also feel that we must point out that the pivotal trials were placebo controlled with rescue medication available, and not comparator trials.	Comment noted. No action required. Further information regarding the comparators for this appraisal is provided in section 4.4 of the FAD.
	Section 4.6: We concur with the committee; the available data demonstrates that prucalopride is clinically effective in providing relief to patients with chronic constipation, consistently from multiple trials.	Comment noted. No action required.
	Section 4.7: We concur with the committees comments and further follow-up is planned. The submission of prucalopride to the EMEA went into considerable detail in evaluating cardio-vascular effects specifically QT prolongation. A thorough QTC study showed that prucalopride had no effect on QTC prolongation in contrast to the positive control (moxifloxacin).	Comment noted. No action required.

Consultee	Comment	Response
Movetis	*Section 4.8*: We agree with the committee's comments that the SF36 data taken directly from the trials does not show a statistically significant improvement for prucalopride compared with placebo when all patients are included in the analysis. The mean of all SF36 patient data shows that the average qaly gained is 0.014 which would produce a cost per qaly of £33,400. However this is an unrealistic scenario as this includes continued treatment for all patients irrespective of effect. If the qaly is based on continued treatment for responders only, with the cost of none responder carried by the responder, using SF36 data the qaly gained by the under 65 cohort is 0.04 with a cost per qaly of £15,300.	Comment noted. Section 3.7 of the FAD has been amended to include a description of the SF-36 data when only patients who responded to treatment with prucalopride are compared with placebo. The analysis informing the revised ICER of £15,300 was not made available to the Committee by the manufacturer.
	Section 4.9: We support the conclusion of the committee that the use of prucalopride could conceivably reduce the secondary care costs of treating chronic constipation; this opinion is also supported by clinical experts. We would like to bring to the attention of the committee that in 2008/09 in England and Wales in excess of £60 million cost were incurred by the NHS treating patients admitted as emergencies for treatment for fecal impaction associated with chronic constipation. We anticipate that a significant proportion of these patients, if treated with prucalopride would not attend at accident and emergency to be admitted.	Comment noted. The Committee agreed that the costs of chronic constipation presented by the manufacturer in its economic model were probably conservative and if the true resource costs associated with treating chronic constipation when laxatives failed to provide adequate relief were included, it was likely that the ICERs presented by the manufacturer would be reduced (that is, prucalopride would be considered to be more cost-effective). Please refer to section 4.10 of the FAD.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
PromoCon	PromoCon welcomes the committee's recommendations regarding the option to be able to offer women an alternative oral treatment for intractable constipation. Currently the only other options are rectal preparations (which many do not find acceptable) or surgery.	Comment noted. Further information on the Committee's consideration of the current treatment options for intractable constipation in the UK is provided in section 4.4 of the FAD.
	Would like some clarification on any drug interactions - particularly anticholinergics.	Comment noted. Please refer to the SPC for further information on the drug interactions associated with prucalopride.
	We think it is important to take into account not only the cost of the prucalopride treatment but to balance that with the potential savings of hospital admissions and the reduced need for any invasive surgical procedures etc.	Comment noted. The Committee agreed that the costs of chronic constipation presented by the manufacturer in its economic model were probably conservative and if the true resource costs associated with treating chronic constipation where laxatives had failed to provide adequate relief were included, it was likely that the ICERs presented by the manufacturer would be reduced. See section 4.10 of the FAD.

Nominating organisation	Comment	Response
PromoCon	The 2nd paragraph under key conclusions perhaps needs clarification as it could be misinterpreted in 2 different ways. Is the recommendation saying that after 6 mths of trying at least 2 different laxatives prucalopride can be tried or is it saying that each course of different laxative treatment needs to be at least 6 mths meaning that a period of 12 months needs to pass prior to prucalopride being considered?	Comment noted. The FAD states that prucalopride is recommended as an option for the treatment of chronic constipation in women for whom treatment with at least two laxatives from different classes at the highest tolerated recommended doses for at least 6 months has failed to provide adequate relief and invasive treatment for constipation is being considered. Please refer to section 1.1 of the FAD.
	In recent discussions with Primary Care based Continence Services it is envisaged that prucalopride is a treatment that could ultimately be instigated and prescribed in primary care.	Comment noted. The Committee recommended that prucalopride should only be prescribed by a clinician with experience of treating chronic constipation, who has supervised the woman's previous courses of laxative treatments. Please refer to section 1.3 of the FAD.
	Many of the women also suffer to some greater or lesser degree with faecal soiling/incontinence. It may be beneficial to link in to the NICE clinical guideline - Faecal incontinence (CG49)	Comment noted. Clinicians are encouraged to consider all NICE guidance related to this topic.

Nominating organisation	Comment	Response
Royal College of Physicians/British Society of Gastroenterology	In reading through the detail of this report I believe that all the relevant published literature has been reviewed. Who will receive the drug? Although the population prevalence of chronic constipation is high, the population who will be suitable for consideration of prucalopride is low. The ACD recommendation that lifestyle modification followed by trial of two different laxative regimes be tried will improve care for these individuals, as their current management is often rather piecemeal. As such, I believe, the numbers of patients who improve, without need for prucalopride, should not be excessive. By defining these steps of treatment, and specifying also the population with *chronic* constipation I believe the key conclusion is a sound one.	Comment noted. No action required.
	Who should prescribe the drug? Of course gastroenterologists and colorectal surgeons have “experience of treating chronic constipation”. Other specialists who manage significant numbers of patients who develop constipation will not necessarily use the drug: for example gerontologists and rehabilitation specialists should implement the lifestyle and structured laxative approach first. Post-surgical constipation does not fall into the description of chronic constipation, so again the drug will not be used in that setting. The remaining issue is within primary care: there are some GPs with a special interest in gastroenterology who may see a disproportionate number of constipated patients within their practice, and the introduction of a stepped approach to care should help patient management. I do not believe the majority of GPs will prescribe the drug above the currently available laxatives with which they have greater familiarity.	Comment noted. No action required.

Nominating organisation	Comment	Response
Royal College of Physicians/British Society of Gastroenterology	Could the drug reduce costs to the NHS? I do not believe that there would be significant numbers of patients prescribed the drug in primary care to reduce referrals, and I believe patients will still have rationalisation of laxatives as a first specialist intervention. Only in refractory patients will prucalopride be considered, and here it would, I believe, be a cheaper and less invasive option than alternatives like irrigation and surgery.	Comment noted. The Committee considered the true resource costs of treating chronic constipation when laxatives fail to provide adequate relief such as referrals to secondary care, rectal irrigation and surgery. It agreed that these costs could be reduced by using prucalopride. Please refer to section 4.10 of the FAD.

Comments received from commentators

Commentator	Comment	Response
Norgine Pharmaceuticals	The ICER for prucalopride of around £15,000 to £17,000 per QALY gained, whilst probably acceptable for an innovative medicine for a serious or life-threatening condition, is far in excess of what should be considered as acceptable for a laxative. As far as providing value for the NHS is concerned the ICER for Norgine's macrogol laxative Movicol is estimated at £250 per QALY gained, which clearly provides much better value for money. Norgine would therefore question whether prucalopride should be recommended at all by NICE for use in the NHS in England and Wales.	Comment noted. The remit of this appraisal is to consider the clinical and cost-effectiveness of prucalopride for the treatment of women with chronic constipation in whom laxatives have failed to provide adequate relief. As such, this appraisal considers the use of prucalopride in laxative-refractory patients and therefore a comparison with laxatives such as macrogol has not been made. In addition, the Committee has not considered the cost-effectiveness of macrogol (suggested to be £250 per QALY gained) as part of this appraisal. Section 5.12 of the guide to methods of technology appraisals states that an additional QALY has the same weight regardless of the other

Commentator	Comment	Response
		characteristics of the individuals receiving the health benefit. As such, a QALY gain by a patient with constipation is considered equal under these assumptions to a QALY gain in a patient with a life threatening condition. The Committee agreed that prucalopride would be an appropriate use of NHS resources and recommended that it should be considered as an option for the treatment of chronic constipation in women for whom laxatives fail to provide adequate relief. Please refer to section 4.11 of the FAD.
Norgine Pharmaceuticals	1. If it is considered that prucalopride is cost-effective for use in the NHS in England and Wales, then the preliminary recommendations of the Advisory Committee are not sufficiently precise to avoid doubt as to what the guidance is intended to recommend. For example: (i) It is not clear what is meant by "a clinician with experience of treating chronic constipation." Many clinicians treat chronic constipation and in numerical terms, nurses probably are involved to a greater extent in managing this condition in primary care than are doctors, and as a result probably have more experience in treating chronic constipation than do primary care physicians. Not all gastroenterologists in secondary care would necessarily qualify as experienced in treating chronic constipation, unless	Comment noted. The Committee considered that women who would be suitable for treatment with prucalopride should be treated by a clinician with experience in the management of chronic constipation who has supervised the use of previous courses of laxatives in the same women. Please refer to section 4.11 of the FAD. Comment noted. This is a single technology appraisal of prucalopride in patients with laxative-refractory chronic constipation. Recommendations on the sequential use of laxative therapies are outside the scope of the appraisal.

Commentator	Comment	Response
	they specialise in the functional bowel disorders. Therefore we would suggest that initially at least the guidance should state that prucalopride therapy should only be initiated by a secondary care physician specialising in the treatment of the functional bowel disorders. (ii) The recommendation "The woman must have tried at least two different types of laxative, and lifestyle modification for at least 6 months, but have not had relief from constipation" is reasonable but practitioners need interpretation of what the clinical evidence shows in order to guide them as to the best choice of laxative(s). It is reasonable to suggest lifestyle modification including increased fibre in the diet, increased fluid intake and increasing exercise prior to considering prescription of a laxative As there is clear evidence that macrogol is superior to lactulose and ispaghula husk[4] we would suggest that the evidence is clear that macrogol should be used as first-line choice. At the very least if another class of laxative has failed to provide adequate relief, prucalopride should not be considered unless a macrogol laxative has been used for a reasonable period of time at optimal dosing. We would agree that 6 months is a reasonable period to assess if there is inadequate response to these interventions.	
Norgine Pharmaceuticals	The improvement in stool frequency seen in clinical trials with macrogol laxatives is superior to that seen in any clinical trials involving prucalopride. Therefore there is indirect evidence that	Comment noted. This is a single technology appraisal of prucalopride. Evidence on the comparative effectiveness

Commentator	Comment	Response
	the macrogol laxatives are more effective than prucalopride, and they are certainly much less expensive. Therefore, at the very least it should be stated in the final guidance that prucalopride should only be used if inadequate response has been seen with at least two other types of laxatives, one of which should be a macrogol laxative. Furthermore it should be specified that the macrogol should have been continued for not less than one month and that the dose of the macrogol should have been titrated under the supervision of a doctor or nurse in order to achieve the optimal result.	of prucalopride and macrogol was not presented to the Committee. The Committee can only make a decision based on evidence available at the time of the appraisal. In addition, prucalopride is recommended as a treatment option for chronic constipation when other laxatives fail to provide adequate relief and therefore is not at the same position as macrogol in the treatment pathway for chronic constipation.
Norgine Pharmaceuticals	The efficacy of prucalopride has only been assessed in comparison to placebo. In contrast, the efficacy of macrogol laxatives has been assessed in comparison to placebo, lactulose and ispaghula husk. In these trials, macrogol laxatives have come out as superior in efficacy to all comparative agents. Consequently, it is equally true that macrogol is effective in patients who have not responded to other laxatives and there is absolutely no evidence that prucalopride is effective in patients who have properly used macrogol. We are therefore surprised and disappointed that NICE should see fit to issue the draft recommendation as it stands in the absence of any direct comparative data between prucalopride and other laxatives.	Comment noted. Prucalopride is recommended as a treatment option for women with chronic constipation after laxatives fail to provide adequate relief. Evidence on the comparative effectiveness of prucalopride and oral laxatives was not presented to the Committee as laxatives were not included as comparators in the decision problem for this appraisal.
Norgine Pharmaceuticals	The wording of the recommendation as it stands will mean that prucalopride can be considered for use in the NHS in patients with an inadequate response to another laxative or laxatives, yet there is no direct comparative evidence whatsoever that prucalopride is likely to be more effective than say senna, lactulose, ispaghula husk or macrogol. Therefore an expensive treatment will be approved for use in the NHS when there is no direct evidence that it is likely to work at all for its NICE-	Comment noted. Evidence on the comparative effectiveness of prucalopride and oral laxatives was not presented to the Committee as laxatives were not included as comparators in the decision problem for this appraisal. In view of the different classes of laxatives used in clinical practice and the fact that many of these are often

Commentator	Comment	Response
	approved recommendation.	rotated to avoid tolerance, the Committee agreed that it would be difficult to define a standard laxative regimen as a comparator for patients with chronic constipation. Please refer to section 4.4 of the FAD.
Norgine Pharmaceuticals	Commercial in Confidence information removed	Comment noted. No action required.
Norgine Pharmaceuticals	2. We are confused by some points made about the clinical effectiveness of laxatives in the Appraisal Consultation Document. "The Committee heard from clinical specialists that many patients' lives are impaired by laxative treatment with unpredictable and uncontrolled bowel movements." Whilst it is true that laxatives may produce unpredictable and uncontrolled bowel movements, prucalopride is no better than other laxatives in this respect. The SmPC for Resolor classifies nausea, vomiting and diarrhoea as 'very common' (>1:10 patients) undesirable effects. "The Committee also heard that the primary aim of treatment is to enable patients to have predictable bowel movements rather than sporadic relief in response to rescue medication." This is also true, but that aim of therapy is not an aim that prucalopride is in any way unique in being able to fulfil. The macrogol-based laxatives in particular can be titrated in dose to allow the patient with chronic constipation to have regular, predictable bowel movements with normal stool form.	Comment noted. Clinical trial evidence for prucalopride showed that the side effects are transient and often subside within a few days of treatment onset. Information on the nature of the adverse effects of treatment with prucalopride is in sections 2.3 and 4.7 of the FAD. Comment noted. This is a single technology appraisal of prucalopride in laxative-refractory patients. Evidence on the comparative effectiveness of prucalopride and oral laxatives was not presented to the Committee as laxatives were not included as comparators in the decision problem for this appraisal.
Norgine Pharmaceuticals	There seems to be an assumption persisting throughout the appraisal that the mode of action of prucalopride is in some way unique in that its mechanism of action is on the gut muscle	Comment noted. The SPC for prucalopride states that Prucalopride (Resolo) is a selective serotonin (5-HT4) receptor

Commentator	Comment	Response
	rather than the gut mucosa. This is simply not true. Laxatives have some differences in their mode of action, but in the case of the stimulant laxatives like senna and bisacodyl it is generally understood that their mode of action is one of direct stimulation of the muscle wall of the bowel which results in more rapid transit of faecal material in the large bowel. Osmotic laxatives like Movicol also stimulate gut muscle, the pharmacodynamic properties for Movicol as listed in its SmPC state: *Macrogol 3350 acts by virtue of its osmotic action in the gut, which induces a laxative effect. Macrogol 3350 increases the stool volume, which triggers colon motility via neuromuscular pathways. The physiological consequence is an improved propulsive colonic transportation of the softened stools and a facilitation of the defecation.*	agonist that predominantly stimulates colonic motility. The Committee heard from the clinical specialists that prucalopride's mechanism of action is on the gut muscle rather than the mucosa and that this mechanism of action means that efficacy could be sustained in the long term. The Committee also acknowledged that some consultees argued that the mechanism of action of prucalopride is not unique. Please refer to section 4.5 of the FAD.
Norgine Pharmaceuticals	This assumption about a unique mode of action is then extrapolated to mean that efficacy could be sustained in the long term. This may also be a false assumption. In the case of the stimulant laxatives which also act to stimulate the colonic muscles, the development of tolerance is well established and there is no logical reason why this should not also apply to agents stimulating the colonic muscles by acting on serotonin receptors. In fact in study PRU-INT 10 there is evidence of the possible development of tolerance as the report states that the for the first 11 weeks of the study 2mg was the more frequent pattern of use, from week 15 onwards 4mg became more common. The development of tolerance may be a problem in clinical use, especially as although the 4mg dose was used in clinical trials, only the 1mg or 2mg dose is recommended for the licensed product as the dose for the elderly and adults respectively. In contrast, long term trials of macrogol have shown a steady decline in the required dose over time with persistence of a healthy bowel habit.	Comment noted. The Committee heard from the clinical specialists that prucalopride's mechanism of action is on the gut muscle rather than the mucosa and that this mechanism of action means that efficacy could be sustained in the long term. The Committee also acknowledged that some consultees argued that the mechanism of action of prucalopride is not unique. However, the Committee was persuaded that the stopping rule in the SPC for prucalopride, which restricts treatment after 28 days to women who gained normal bowel movements while on treatment would be followed by prescribing clinicians. Please refer to section 4.5 of the FAD.

Commentator	Comment	Response
Norgine Pharmaceuticals	There is a statement from the British Society of Gastroenterology which states that “The quality of clinical trials for the vast majority of laxatives is poor”. Whilst this might be true for most laxatives, it is not true for the macrogol-based laxatives. A systematic review of the all clinical trial data available for all laxatives, and gave a 1A rating to the clinical evidence in support of the macrogol (PEG) laxatives, higher than for other laxatives.	Comment noted. No action required.
	The quality of the clinical evidence for macrogol laxatives has been confirmed by a recently published Cochrane systematic review which aimed to review all relevant data in order to determine whether lactulose or polyethylene glycol is more effective in treating chronic constipation and faecal impaction. Their findings indicated that polyethylene glycol is superior to lactulose in outcomes of stool frequency per week, form of stool, relief of abdominal pain and the need for additional products. Their conclusion was that “polyethylene glycol should be used in preference to lactulose for the treatment of chronic constipation.” This is a particularly strong conclusion for a Cochrane systematic review, and indicates the strength of the evidence in support of macrogol laxatives.	Comment noted. No action required.
	It is stated in the Appraisal Consultation Document that “The Committee heard that there have not been any new laxative treatments available in the UK for over 25 years.” The Committee were misled on this point. Movicol (macrogol 3350 + electrolytes) was a novel laxative when it was first licensed in the UK in 1996 (ie 14 years ago).	Comment noted. This statement was made by a clinical expert at the first committee meeting in relation to there not being a new agent for laxative refractory patients for over 25 years. The FAD has been amended to remove this comment to avoid any further confusion.
	Section 4.9 of the Appraisal Consultation document refers to the cost of possible comparators in the treatment of chronic	Comment noted. Prucalopride is recommended as an option for the

Commentator	Comment	Response
Norgine Pharmaceuticals	constipation. The statements made to the Committee by 'clinical specialists' do seem to be unrepresentative of the situation of treating constipation in clinical practice where there is an inadequate response to laxatives. It is not true to say that the interventions used after inadequate response to laxatives would be bowel irrigation or colonoscopy. These comments perhaps reflect the perception of the clinical specialists who see the rarer but more severe presentations of constipation which may not have been managed optimally by supervised use of laxatives in primary or residential care. The normal presentation of constipation in primary care is different and can in the vast majority of cases be managed with careful dietary history and judicious compliant use of laxatives and dietary adjustment after ruling out serious underlying complications through careful history taking. It is ironic that the committee considers that one of the consequences of failed laxative treatment is faecal impaction when Movicol, a far less expensive laxative composed of macrogol and electrolytes, is the only oral product indicated for the treatment of faecal impaction. Far from being an expensive consequence of the failure of macrogol therapy, faecal impaction is a wholly unnecessary condition which could be prevented through the consistent use of macrogol and which, if it does occur, can be inexpensively treated on an out-patient basis through the use of a macrogol product.	treatment of chronic constipation in women for whom laxatives fail to provide adequate relief and invasive treatment is being considered. The relative effectiveness of prucalopride compared to oral laxatives such as macrogol was not considered in this appraisal, as the decision problem was only targeted to laxative-refractory patients.
Norgine Pharmaceuticals	When looking at what interventions are used to treat constipation, it is necessary to look at the typical patient population that the intervention that is the subject of this appraisal is targeted towards. Prucalopride is indicated for women with chronic constipation who have failed to respond to previous laxative use. We note	Comment noted. Based on advice from clinical specialists, the Committee concluded that inadequate relief from previous laxative treatments could be defined by duration of follow-up and by the number of laxatives previously used. Please refer to section 4.3 of the FAD.

Commentator	Comment	Response
	the committee's concerns about the number of patients in the clinical studies who could objectively be considered to have failed their previous laxative use and wonder if those patients were excluded from the clinical trials if the cost effectiveness would still be positive and whether the degree of efficacy seen would still be significant. A subset analysis of these 'true failures' should be conducted. In reality, a very high proportion of younger and middle aged women with chronic constipation will be suffering from constipation related to underlying irritable bowel syndrome (IBS-C), in older women the constipation will tend to be idiopathic or secondary to other medical conditions or occurring as a result of drug treatment	
Norgine Pharmaceuticals	The vast majority of women with IBS-C will respond to an appropriate orally administered laxative in the right dose, it is very unusual for these patients to need further interventions. Indeed, Norgine has recently successfully concluded a placebo controlled study of macrogol in the treatment of constipation associated with IBS-C. In any event, if patients did require further interventions, then the next step would probably be the regular use of suppositories administered at home, or if this was unsuccessful, the home administration of micro-enemas. Bowel irrigation would certainly not be the next step in therapy, and colonoscopy is purely a diagnostic procedure and not a therapeutic procedure.	Comment noted. The pivotal trials for prucalopride excluded patients who met the criteria for irritable bowel syndrome (IBS). As such, patients with IBS are not included in the marketing authorisation for prucalopride and are also not considered in this appraisal.
Norgine Pharmaceuticals	It is highly unusual for female patients with IBS-C to require any intervention for their constipation which requires management in secondary care. Patients who may require management in secondary care would be those with intractable constipation, such as patients suffering from idiopathic slow-transit constipation. The fact is that macrogol laxatives will provide an adequate	Comment noted. This appraisal considered the use of prucalopride for women with laxative-refractory chronic constipation in whom invasive procedures are being considered.

Commentator	Comment	Response
	treatment for the vast majority of chronically constipated patients irrespective of aetiology and severity. Movicol (macrogol + electrolytes) is effective in treating all levels of severity of constipation, up to and including faecal impaction in adults and children. There is no evidence at all that prucalopride can successfully treat patients who are unresponsive to macrogol laxatives, and by doing so potentially save the costs of secondary referrals.	
Norgine Pharmaceuticals	The budget impact analysis contains some critical assumptions that are probably at considerable variance to the actual reality. The critical assumption made in the prucalopride patient population estimate is that proportion of patients in whom laxative fail to provide adequate relief is 10% of the total population. This is greatly at variance to what may be the actual situation, ie macrogol laxatives are effective; i) prucalopride adds nothing at great cost per patient; ii) consequently if the treatment protocol suggested is applied rigorously and macrogol is used before prucalopride then there would be very little if any use of prucalopride. In their own corporate material for Resolor, Movetis state that the total market for Resolor in Europe (EEA) is 70 million patients. Therefore the patient population that Movetis see as available for their product is greatly in excess of the 10% of the total of patients with chronic constipation that is assumed for the budget impact assessment. Their estimate for the NICE appraisal states that about 160,000 women in the UK would be eligible for prucalopride treatment, but their own assessment of the potential UK market would give that figure as being nearer 1,400,000 women, as the UK population is around ⅛ of the total population of the EEA.	Comment noted. The Committee considers the clinical and cost-effectiveness of a technology relative to current NHS practice. Budget impact does not affect their decision.

Commentator	Comment	Response
	Therefore their estimation of the market size for prucalopride differs by almost a factor of 10 depending on whether the audience for such an estimate is investors and potential partners, or NICE. Therefore, they have either: (i) Greatly exaggerated the market potential of Resolor to investors and potential partners, or (ii) Greatly played down the market potential of Resolor to NICE	
Norgine Pharmaceuticals	There are a number of serious concerns regarding the evaluation process and the provisional recommendations made by the Appraisal Committee. This report is structured using the central tenents of the NICE process which we do not believe have been adequately demonstrated within this particular appraisal. The three specific issues to be considered are: 1. Completeness 2. Transparency 3. Robustness/Validity	Comment noted.
Norgine Pharmaceuticals	Deficiencies in both the completeness and transparency of key aspects of the evaluation and appraisal process mean that that the validity of the cost-effectiveness results informing the Committee's provisional recommendations cannot be concluded to have been robustly demonstrated. Furthermore, the economic model submitted by the manufacturer appears to have serious limitations since it fails to produce results that are consistent with the trial data itself (i.e. the model appears to have poor internal validity) or those which could have been derived by applying a more logical 'common sense' approach If these issues are not adequately addressed before the	Comment noted. The Committee considered that the available data demonstrated that prucalopride was clinically effective in providing relief to patients with chronic constipation. Although the Committee had concerns about the generalisability of the populations who were selected for the clinical trials to the decision problem and about the extrapolation of benefits beyond the trials, the Committee concluded that the ERG

Commentator	Comment	Response
	Committee makes its final recommendations, there would appear to be a strong case for appeal based on: *Ground Two: The Institute has formulated guidance, which cannot reasonably be justified in the light of evidence submitted.*	had shown the manufacturer's cost-effectiveness estimates to be reasonably stable under varied assumptions. Please refer to section 4.9 of the FAD.
Norgine Pharmaceuticals	The manufacturer submission fails to adequately address the relevant decision problem and does not provide an appropriate basis for cost-effectiveness considerations. There are significant differences in the decision problem addressed by the manufacturer submission and the final scope agreed with NICE and this has serious implications on the validity and utility of the draft guidance.	Comment noted.
	The Committee's recommendations are based on an inappropriate comparator and there appears to have been no formal (or informal) consideration by the Appraisal Committee of the most likely ICER of prucalopride against an appropriate standard of care (including an option of continued use of different laxatives). Furthermore, it could be argued that the cost-effectiveness of prucalopride compared to an appropriate standard of care cannot reasonably be inferred from the results presented given the limited data considered by the manufacturer and deficiencies in the model	Comment noted. In view of the different classes of laxatives used in clinical practice and the fact that many of these are often rotated to avoid tolerance, the Committee considered that it would be difficult to define a standard laxative regimen as a comparator for patients with chronic constipation. Please refer to section 4.4 of the FAD.
	Section 4.11 of the ACD states that: *"The Committee was therefore persuaded that the most plausible ICER compared with placebo plus rescue medication was likely to be below £20,000 per QALY gained".* However, clearly a comparison with placebo plus rescue medication does not provide an adequate basis for informing cost-effectiveness considerations for prucalopride in the context of current NHS practice. Furthermore, including this as the only comparator in a cost-effectiveness analysis contradicts	Comment noted. The Committee considered the use of prucalopride for chronic constipation when laxatives fail to provide adequate relief and invasive procedures are being considered.

Commentator	Comment	Response
Norgine Pharmaceuticals	existing NICE methods guidance which states: *"Relevant comparators are identified, with consideration given specifically to routine and best practice in the NHS (including existing NICE guidance) and to the natural history of the condition without suitable treatment" Ref: Section 2.2.4 of the 'Guide to methods of technology appraisal'.* ICER of prucalopride compared to an appropriate standard of care. In the absence of these ICER estimates, it is not possible to conclude using the current evidence submitted to the Committee that prucalopride represents an efficient use of NHS resources.	
Norgine Pharmaceuticals	Despite these concerns, and lack of accordance with the Institute's methods guide, the Committee's conclusions were clearly based on an inappropriate comparator since reference is only made to the ICER against a placebo comparator. While the Committee appear to have discussed the use of placebo controls in undertaking regulatory trials and the difficulties in defining a standard laxative regimen as a comparator, neither of these issues should lead to a conclusion that a comparison with placebo in the context of reimbursement decisions is appropriate or that some attempt to formally compare against a relevant standard of care is not possible. Indeed, one of the advantages of the decision-analytic framework underpinning the NICE evaluation process is that these difficulties can be explicitly considered using different assumptions and scenarios. These assumptions and scenarios could have been presented to the Committee and discussed with expert clinical input in determining the most likely ICER of prucalopride compared to an appropriate standard of care. In the absence of these ICER estimates, it is not possible to conclude using the current evidence submitted to the Committee that prucalopride represents an efficient use of NHS resources.	Comment noted. The Committee considered the use of prucalopride for chronic constipation when laxatives fail to provide adequate relief and invasive procedures are being considered. . The Committee noted that the comparator used in clinical trials was placebo plus rescue medication with bisacodyl, which did not reflect current practice for chronic constipation in the NHS. It heard from the clinical specialists that generally people whose constipation has not responded adequately to laxatives would usually be encouraged to stop all current treatments, and then restart their laxative regimen in a stepwise manner. The Committee agreed that it would be difficult to define a standard laxative regimen as a comparator for people with laxative-refractory chronic constipation. Please refer to section 4.4 of the FAD.

Commentator	Comment	Response
Norgine Pharmaceuticals	There appear to be significant problems with transparency for key assumptions and inputs applied in the model, leading to significant uncertainties regarding the validity of the model and the associated results. There appears to no systematic approach to the identification and inclusion of studies informing the model, thus increasing the likelihood of bias in the submission. Critically, ten studies are identified as relevant to the appraisal but only three form the basis of the clinical effectiveness assessment. Further, meta-analysis was not performed. This is in clear contravention to the NICE methods guide. The ERG report clearly identifies the regression equations used to determine the treatment effects (including both the clinical effectiveness and the mapping of patient outcomes to EQ-5D) applied in the model as the key input parameters. However, they also conclude that it is not possible to verify these using the evidence which has been submitted by the manufacturer. This seems to represent a fundamental challenge to demonstrating the robustness of any subsequent results. Furthermore, it could be reasonably argued that rather than simply seeing these equations as an input to the model, the patient level data and coding used for the regressions and quality of life mapping actually comprise key <u>structural</u> elements of the model itself. Indeed, the Excel model provided by the manufacturer really only represents a front-end interface, allowing a user to re-run a pre-determined set of structural assumptions and parameter estimates. Without providing appropriate access to <u>both</u> the patient level data and	Comment noted. It is stated in the manufacturer's submission that the clinical data incorporated into the model were derived from the three pivotal trials, two trials in older women and extension studies. Further patient characteristics were obtained from other trials not fully described in the manufacturer's submission. Please refer to section 3.13 of the FAD and the manufacturer's submission for more information on the clinical data informing this appraisal. Comment noted. The ERG ran the manufacturer's model using different assumptions including pooled results and varying the efficacy of prucalopride by 25-75%. It concluded that the results from these analyses were not significantly different from those provided by the manufacturer. Please refer to section 3.25 of the FAD and the ERG report for more information. In response to the ACD consultation, the manufacturer stated that further SF-36 data (not in the original submission) for people whose constipation responded to treatment showed statistically significant improvement for prucalopride compared with placebo. Sensitivity analyses of these
Norgine Pharmaceuticals		Comment noted. The Committee was aware of concerns raised by the ERG that the assumptions used in the mapping equation could not be tested and may

Commentator	Comment	Response
Norgine Pharmaceuticals	the coding used to estimate the equations/utility mapping, it is clearly not possible f to provide any adequate assessment of the validity of the model structure, the inputs or the associated results. The only justification provided by the manufacturer was that SF-36 was 'limited' and would not provide a robust mapping. However, it is unclear in what respect this data was limited, particularly since SF-36 data was collected in the 3 main studies which were also used to estimate response data. Furthermore, we would challenge anyone to be able to adequately describe or critique what has actually been done by the manufacturer in the mapping exercise based on the limited descriptions and data provided. It is peculiar that SF-36 results were used in the mapping process but did not contribute to the derived EQ-5D scores. This may be highly significant given the lack of statistical significance for the SF-36 scores save in the PRU-INT 6 study for the physical component score at week 4. In their response to the concerns expressed in the ERG report the manufacturer claims that a separate analysis was undertaken by mapping the SF-36 results contained in the trial to EQ-5D utility values. However, we can find no reference to the results of this analysis or to any discussion by the committee of these results. In the absence of these results being presented and critiqued by the ERG, it is impossible to conclude that the statements made by the manufacturer are based on empirical evidence or are simply conjecture. A key omission from the appraisal is any discussion of the appropriateness of the mapping approach to EQ-5D and the possibility of using the SF-36 results from the trial to directly	SF-36-based outcomes were considered to be consistent with work conducted by the ERG when the acquisition cost and number of days of treatment were varied. The Committee concluded that changing the mapping equation would unlikely alter the results of the model substantially. Please refer to section 4.8 of the FAD

Commentator	Comment	Response
Norgine Pharmaceuticals	estimate SF-6D utility data. It is unclear why this approach was methods used in the main analysis. While the SF-6D is not currently part of the reference case approach, it would appear not also considered given the inherent uncertainty in the to be a reasonable alternative scenario to have presented to support the robustness of the results given the methodological uncertainty surrounding existing mapping approach. Failure to consider alternative approaches and assumptions in deriving QALY estimates. As noted above, it is clear that the robustness of uncertainty surrounding the mapping process and related assumptions, applied to estimate QALY gains have not been adequately explored. Furthermore, the extrapolation of these estimates over a longer-term horizon (12-52 weeks) represents another key assumption which is subject to considerable uncertainty which we do not consider has been adequately assessed. There appear to be two important assumptions applied in the longer term extrapolation: (i) responders to prucalopride maintain their initial short-term utility gain over the longer term horizon; (ii) the initial short-term utility gain reported for the control group is considered to be a short-term 'placebo' effect which is assumed to wane over the longer-term horizon (such that at 52 weeks patients in the control group have the same utility as reported at baseline). Neither of these assumptions is supported by appropriate empirical evidence and neither assumption is subjected to sensitivity analysis by the manufacturer. The only empirical evidence in support of assumption (i) comes from long-term open label extensions measured using PAC-	

Commentator	Comment	Response
Norgine Pharmaceuticals	QOL. The actual data reported is marked AIC and has been removed from the manufacturer's response. However the absence of a control population and the lack of comparable data demonstrating that the SF-36 data remains stable, means that this assumption is clearly subject to additional uncertainty. Given the uncertainty surround the extrapolation of QALY gains, alternative scenarios should have been presented by the manufacturer as recommended in the NICE methods guide. As it stands, only the most optimistic scenario for prucalopride seems to have been considered. Furthermore, this optimism is compounded by the separate assumptions made for the long-term quality of life for the comparator group, where the 'waning' of the effect is assumed to reflect a temporary 'placebo' effect. However, it has been demonstrated that estimated cost-effectiveness and associated policy decisions may be sensitive to the assumptions regarding the mechanism underlying placebo responses and, in the absence of other evidence, additional sensitivity analysis should be undertaken. In summary, the assumptions employed by the manufacturer appear overly optimistic towards the incremental QALY gain for prucalopride and no additional sensitivity analyses are presented to the Committee. The general lack of transparency in the manufacturer's model was a key issue identified by the ERG who concluded *"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*	Comment noted. The Committee noted that the sensitivity analysis conducted by the ERG showed the model results to be stable under varied assumptions. It concluded that changes in the regression equation would not alter the results of the model substantially.

Commentator	Comment	Response
Norgine Pharmaceuticals	*effectiveness." (ERG report, p9)* Some of these concerns appear to be noted by the Committee in paragraph 4.1 of the ACD. However, despite these concerns the Committee concluded that "the ERG had shown the manufacturer's cost-effectiveness estimates to be reasonably stable under varied assumptions" (Section 4.10, ACD p21). There even seems to have been some suggestion that the Committee considered that the results may actually have been conservative since the true costs associated with treating chronic constipation were not included. We do not feel this to be a reasonable conclusion for this appraisal. We believe that the conclusions may not be robust and that a more accurate ICER estimate (i.e. with higher internal validity) could easily be in excess of £30,000 per QALY, particularly given the univariate sensitivity analyses undertaken by the ERG.	Comment noted. The ERG ran the manufacturer's model using different assumptions including pooled results and varying the efficacy of prucalopride by 25-75%. It concluded that the results were not significantly different from those provided by the manufacturer.
Norgine Pharmaceuticals	We consider the Committee conclusions potentially perverse in light of: (i) The significant uncertainty inherent in key assumptions; (ii) The poor internal validity of the model; and (iii) The series of optimistic assumptions applied by the manufacturer to the QALY gain estimates Indeed, it is evident from the sensitivity analyses undertaken by the ERG that the assumptions for the QALY gain of prucalopride are a key driver of cost-effectiveness and, importantly, that the cost-effectiveness conclusions <u>do not</u> appear robust to the alternative assumptions considered by the ERG (e.g. QALY gain reduced by 50% to 75%). These findings are important since the manufacturer did not	Comment noted. The Committee noted that the sensitivity analysis conducted by the ERG showed the model results to be stable under varied assumptions. It concluded that changes in the regression equation would not alter the results of the model substantially. The ERG ran the manufacturer's model using different assumptions including pooled results and varying the efficacy of prucalopride by 25-75%. It concluded that the results were not significantly different from those provided by the manufacturer.

Commentator	Comment	Response
Norgine Pharmaceuticals	adequately justify their own assumptions in relation to a review of reasonable alternatives, nor did they present appropriate sensitivity analysis demonstrating the robustness to several key inputs/assumptions. It is particularly concerning that the current model results do not appear to match those which could have been derived by applying a more logical 'common sense' approach by the Committee. That is, given the uncertainties noted, how well does the economic model appear to predict the main trial results? Tables 2-9 of the ERG report consistently demonstrate that the mean change from baseline for measures of response, PAC-SYM, PAC-QOL and SF-36 data for weeks 1-12 with placebo was approximately half that of the group treated with prucalopride. Hence, a common sense 'mapping' approach to utility and QALY gain might reasonably conclude that the utility gain (compared to baseline) for placebo would be approximately half that of prucalopride. However, it is clear ... that this common sense approach is not matched by the predictions of the model at 4 or 12 weeks. The resulting low internal validity of these findings does not appear to have been adequately explained Faced with this inconsistency between the trial findings and the model predictions, we do not consider it appropriate to conclude that the subsequent cost-effectiveness estimates are likely to be robust. It naturally follows from the QALY gain calculations, that it is entirely plausible that the cost-effectiveness estimates reported by the manufacturer could also have been over-estimated by as much as 50%. This	

Commentator	Comment	Response
Norgine Pharmaceuticals	obviously has clear implications for the robustness of the Committee's provisional decision. Indeed, sensitivity analyses were presented in the ERG report assuming a 50% reduction in QALY gain (Table 15, p 71 of the ERG report) where the ICER estimates were reported to be either above or close to a £30,000 threshold. These specific results do not appear to be mentioned in the ACD. Faced with such uncertainty, and applying a 'common sense' logic, it seems difficult to accept either the conclusions of the Appraisal Committee, that the most likely estimate of the ICER is likely to be below £20,000, or the ERGs conclusion that while this estimate is likely to be optimistic it is not possible to establish a more accurate estimate of cost effectiveness. It would seem reasonable to conclude that the most likely estimate of the ICER is much more likely to be closer to a £30,000 threshold (or above) than it is to the £20,000 threshold.	
Norgine Pharmaceuticals	Without providing appropriate access to both the patient level data and the coding used to estimate the equations/utility mapping, it only possible to speculate on what could be causing the low internal validity of the economic model. The most likely explanation lies with the mapping function used to map PAC-QOL to EQ-5D (using SF-36 data as the link between PAC-QOL and EQ-5D). Not only is the mapping process subject to significant methodological uncertainty, it also appears subject to potential bias. Indeed, the same publication cited by the manufacturer to support the mapping process also concludes that: *"Our results suggest that approaches mapping the SF-36 onto the EQ-5D are robust across setting and medical condition but overpredict for more severe EQ-5D states. Our results raise*	Comment noted. The Committee was aware of concerns raised by the ERG that the assumptions used in the mapping equation could not be tested and may therefore not be robust. In light of the additional sensitivity analyses conducted by the manufacturer in response to the ACD consultation, the Committee concluded that changing the mapping equation would unlikely alter the results of the model substantially. Please refer to section 4.8 of the FAD.

Commentator	Comment	Response
Norgine Pharmaceuticals	*doubts over the suitability of mapping for patient datasets which have a proportion of subjects with poorer health or where dimensions are not represented in the target measure. Potential policy implications are that mapping the SF-36 onto the EQ-5D can be useful, but may not be suitable for all populations.* The risk to validity of this methodology is highlighted by the ERG group who note that the utility value derived from the mapping algorithm for the severe chronic constipation groups of 0.585 differs from the distributions of baseline score provided by the manufacturer in their clarification document. These data are highly skewed towards better quality of life and may not represent individuals with severe chronic constipation.	
Norgine Pharmaceuticals	Given the poor quality of life of the population under consideration, the use of the current mapping approach appears questionable and should be subject to additional investigation before any final recommendations are made. Furthermore, results should also be made available to the Committee using the SF-36 trial data to generate SF-6D utility values.	Comment noted. The Committee was aware of concerns raised by the ERG that the assumptions used in the mapping equation could not be tested and may therefore not be robust. In light of the additional sensitivity analyses conducted by the manufacturer in response to the ACD consultation, the Committee concluded that changing the mapping equation would unlikely alter the results of the model substantially. Please refer to section 4.8 of the FAD.

Summary of comments received from members of the public

Theme	Response
Definition of ‘inadequate relief from constipation’	Based on advice from clinical specialists, the Committee concluded that inadequate relief from previous laxative treatments could be defined by duration of follow-up and by the number of laxatives previously used. Please refer to section 4.3 of the FAD.
Clarification on how long prucalopride should be used for	The Committee was persuaded that the stopping rule in the SPC for prucalopride, which restricts treatment after 28 days to women who gained normal bowel movements while on treatment would be followed by prescribing clinicians. Please refer to section 4.5 of the FAD.
Long-term efficacy and safety of prucalopride	Comment noted. The Committee was aware of concerns from consultees that the short duration of the clinical trials may not adequately reflect the efficacy of a drug that treats a long term condition. The Committee considered the adverse effects of prucalopride and heard from the clinical specialists that these side effects are often symptoms of chronic constipation and may not always be caused by prucalopride. Please refer to section 4.7 of the FAD for further information.
Uncertainty surrounding cost-effectiveness estimates of prucalopride	Although the Committee had concerns about the generalisability of the populations who were selected for the clinical trials to the decision problem and about the extrapolation of benefits beyond the trials, the Committee concluded that the ERG had shown the manufacturer’s cost-effectiveness estimates to be reasonably stable under varied assumptions. Please refer to section 4.9 of the FAD.

Theme	Response
Definition of a “clinician with experience in treating chronic constipation”	The Committee recommended that prucalopride should only be prescribed by a clinician with experience of treating chronic constipation, who has supervised the woman’s previous courses of laxative treatments.
Budget impact of introducing prucalopride for chronic constipation relative to currently available oral laxatives	The Committee considers the clinical and cost-effectiveness of a technology relative to current NHS practice. Budget impact does not affect their decision.
Limitations to the quality of the clinical evidence for prucalopride	Although the Committee had concerns about the generalisability of the populations who were selected for the clinical trials to the decision problem and about the extrapolation of benefits beyond the trials, the Committee concluded that the ERG had shown the manufacturer’s cost-effectiveness estimates to be reasonably stable under varied assumptions. Please refer to section 4.9 of the FAD.
Potential for use outside of marketing authorisation (in men, children and in people who are not laxative-refractory)	The Committee can only make a recommendation for the use of a technology within the marketing authorisation. In the case of prucalopride, it is currently only licensed for use in women in the UK and therefore the Committee was unable to make recommendations for its use in men or children.