Prucalopride for the Treatment of Chronic Constipation in Women:

Single Technology Appraisal

Response to consultation from Norgine Pharmaceuticals Ltd

Comments on clinical assessment

1. 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[1], 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.

2. 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 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[2,3] 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.

3. 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 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.

4. 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[2], lactulose[3] and ispaghula husk[4]. 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.

   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-approved recommendation.

5. 

   [The information in the above paragraph is confidential to Norgine as it is commercially sensitive]

6. We are confused by some points made about the clinical effectiveness of laxatives in the Appraisal Consultation Document.

(i) "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.

(ii) "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.

7. 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 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[5] 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.*

8. 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.

9. 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[6], and gave a 1A rating to the clinical evidence in support of the macrogol (PEG) laxatives, higher than for other laxatives.

	PEG(macrogol)	Lactulose	Psyllium/Isphagula	Stimulant laxatives (eg senna)
	LEVEL I	**LEVEL II**	**LEVEL II**	**LEVEL III**
	Good Evidence	Fair Evidence	Fair Evidence	Poor Evidence
	Consistent results from well designed, well conducted studies	Results show benefit, but strength is limited by the number, quality or consistency of the individual studies	Results show benefit, but strength is limited by the number, quality or consistency of the individual studies	Insufficient because of limited number or power of studies, flaws in their design or conduct

	PEG (macrogol)	Lactulose	Psyllium/Isphagula	Stimulant laxatives (eg senna)
	Grade A	**Grade B**	**Grade B**	**Grade C**
	Good evidence in support of the use in the treatment of constipation	Moderate evidence in support of the use in the treatment of constipation	Moderate evidence in support of the use in the treatment of constipation	Poor evidence to support a recommendation for or against the use in the treatment of constipation

In addition, the quality of the clinical evidence for macrogol laxatives has been confirmed by a recently published Cochrane systematic review[3] 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.

10. 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).

11. Section 4.9 of the Appraisal Consultation document refers to the cost of possible comparators in the treatment of chronic 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.

    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 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.

    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.

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 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.

12. 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[7], 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.

    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:

    (iii) Greatly exaggerated the market potential of Resolor to investors and potential partners, or

(iv) Greatly played down the market potential of Resolor to NICE.

Summary

1. Norgine would question whether prucalopride should be recommended at all by NICE for use in the NHS in England and Wales.

2. At an ICER of around £15,000 to £17,000 per QALY gained, it would not appear to offer value for money compared to Movicol which has an ICER of only £250 per QALY gained. In this respect the Committee might like to note that no application for the recommendation for the use of prucalopride in Scotland has been made to the Scottish Medicines Consortium *(SMC website, accessed 5th August 2010)*[8].

3. 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.

4. If it is considered that prucalopride is cost-effective for use in the NHS in England and Wales, the guidance should be very specific on the treatment pathways to be tried over the first 6 months under supervision until prucalopride can be recommended. A macrogol laxative must be part of this treatment pathway, and prucalopride should only be used in the unlikely event of failure of adequate response to a macrogol laxative given under the supervision of a health professional for not less than one month with proper titration of the dose.

5. If it is considered that prucalopride should be recommended for use in the NHS in England and Wales 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.

6. There is a considerable inconsistency in forecasts made by Movetis for the potential market for Resolor in the UK. The forecasts made to as part of their NICE assessment are less by a factor of 10 than forecasts made to investors and potential commercial partners.

References

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