National Institute for Health and Clinical Excellence
Health Technology Appraisal

Prucalopride for the treatment of chronic constipation in women

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Movetis	Movetis entirely welcomes the opportunity to prove its case for clinical and cost-effectiveness in this NICE review. It enables this important but regularly overlooked therapeutic area to emphasise the contribution that it can make to improvements in public health, patient wellbeing and the reduction in health inequalities. In this manner, we strongly believe that NICE guidance will add value by emphasising the health benefits that can be generated by patients in this underserved, stigmatized and unfashionable therapeutic area.	Comment noted.
		However, one issue that must be clarified in the scope is to specify that prucalopride should normally replace rather than be used in conjunction with laxatives. Thus it is important to evaluate prucalopride in the manner in which it will be incorporated into the treatment regimen for chronic constipation in normal clinical practice which is for adult and elderly female patients in whom laxatives fail to provide adequate relief.	Comment noted. The use of prucalopride will be considered in line with its licensed treatment regimen.
		It is important to emphasize that the clinical trials of prucalopride employed a far more stringent diagnostic criteria than the Rome III standards. The patient group treated in the prucalopride trials had experienced an average 20 years duration of chronic constipation. Further the trial population contained over 80% of patients who assessed their previous treatment as being inadequate. In order to optimize the benefit and cost effectiveness of the drug the sponsor has voluntarily restricted the indication to patients in which laxatives do not provide adequate relief.	Comment noted. All relevant clinical evidence will be considered when assessing the clinical and cost-effectiveness of prucalopride.
	Norgine	Yes, it is appropriate, as this is a new technology which needs to be compared to the existing ones in term of cost effectiveness, efficacy and safety.	Comment noted.

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Wording	Movetis	It is vital that the draft remit/appraisal objective accurately reflects the CHMP proposed indication (see comment 4) for prucalopride in the UK to ensure that the NICE evaluation reflects the population that is likely to be served by prucalopride in normal clinical practice.	Comment noted. The use of prucalopride will be considered in line with its licensed indication.
	Norgine	No, we do not agree. According to the licensed indication - as per 23 July 2009 CHMP communication, the population should be restricted to adult women.	Comment noted. The use of prucalopride will be considered in line with its licensed indication.
Timing Issues	Movetis	The timing of the evaluation is optimal given the recent (July 23rd) positive CHMP opinion of prucalopride. A total of 82 clinical trials have already been undertaken in a range of sub-populations and hence a significant amount of evidence is currently available in a range of patient populations in support of prucalopride.	Comment noted.
	Norgine	The review should be conducted and the appraisal completed prior to the launch in the UK.	Comment noted.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Movetis	A step up approach to the treatment of chronic constipation is employed by clinicians in the UK. The first step in treatment is likely to be through the use of diet and lifestyle modifications. As symptoms progress, laxatives of various kinds will be introduced but will provide diminished effectiveness over time. The most difficult problem relates to patients who have been suffering for a significant length of time and have exhausted the available therapeutic options. Only these patients who are considered to have 'failed' on laxatives will be considered for treatment with prucalopride. As such the NICE evaluation must acknowledge that prucalopride is not just another laxative but represents a new and innovative technology that is entirely targeted upon patients who have been suffering significant symptoms and quality of life deficits for an extended period of time.	Comment noted. The population which should be treated with prucalopride will be considered in line with the marketing authorisation.

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	Norgine	We do not consider that the background information is complete. In particular, it is important to stress the differences between the different laxatives available on the UK market. A recent literature review by Ramkumar and Rao suggest that certain classes of laxatives show a greater level of evidence than others (Amer Journ of Gastro 2005;100: 936-971) and in particular good evidence, (grade A) was found to support the use of only two laxatives agents, Polyethylene glycol (PEG) and Tegaserod (the latter is not available in the UK).	Comment noted. As prucalopride is intended for use by people who are laxative-refractory, only a brief description of the laxative market in the UK has been included in the scope.
The technology/ intervention	Movetis	The clinical trials of prucalopride used laxatives solely as short term rescue medication usually in non-responders who would be withdrawn from treatment in normal clinical practice. In patients who responded to treatment prucalopride almost entirely replaced the need for laxatives. The scoping document must emphasise the innovative nature of the technology being evaluated. Simply because the technical development has not been introduced in a high profile therapeutic area it should not be allowed to downgrade the cutting edge nature and the significant benefits that will be provided to patients as a consequence of this therapeutic development. Prucalopride has been accepted by WHO as distinctly different from laxatives and is the first of a new class of entero-kinetic interventions that effectively treats a previously underserved patient population. Prucalopride is not a laxative but introduces a new and effective technological approach to the treatment of a group of patients suffering from chronic constipation of exceptionally long duration.	Comment noted. The scope is meant for information only and need not contain such detail Comment noted.
	Norgine	No. In most cases of functional idiopathic constipation, there is no colon motility impairment and therefore it is not appropriate to mention that Prucalopride … "restores the slow movement of the bowels". Suggested alternative wording: "Prucalopride… is an "enterokinetic 5HT4 receptor agonist which increases intestinal motilty and transit " as per Camilleri, NEJM 358 (2), 2344-54, 2008 May 29	Comment noted. The description of prucalopride in the scope has been amended.

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Population	Movetis	It is vital that the target population in the NICE evaluation accurately reflects the anticipated licensed indication to ensure that prucalopride is evaluated within the population that will present in normal clinical practice. The efficacy of treatment with prucalopride has been demonstrated in several sub-groups. Clinical trial evidence is available to support the efficacy of prucalopride in opioid-induced constipation, post-operative ileus, spinal cord injury, and multiple sclerosis. It is likely that the burden imposed on patients will grow in the future and will continue to be unequally imposed on the oldest and poorest sections of society.	Comment noted. The target population has been amended to reflect the licensed indication
	Norgine	No, the population should be restricted to women for whom laxatives have failed to provide adequate relief and should exclude sub-populations not included in phase 3 RCTs such as patients with severe cardiovascular disease. CHMP, on 23rd July 2009, restricted the use of prucalopride to women with chronic constipation for whom laxatives have failed to provide adequate relief.	Comment noted. The target population has been amended to reflect the licensed indication

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Comparators	Movetis	Determining the 'gold standard' treatment currently provided by the NHS to the target population for prucalopride is difficult given that by definition such patients are laxative refractory. However, some form of clinical support will be provided to patients either in the form of switching, combining and/or increasing the dose of different laxatives (with limited efficacy) or rectal interventions such as manual evacuation, suppositories and enemas to provide short term relief. Given the limited efficacy of laxatives in the target population for prucalopride the comparator should incorporate the frequency and effectiveness of non-laxative interventions (rectal interventions and bowel surgery). The NICE scope specifically emphasises that when oral laxative therapy is ineffective, a suppository or enema may be appropriate. As such it is important for the NICE evaluation to acknowledge that in this target population laxative therapy is of unproven benefit. This lack of proven efficacy underpins the assumption made in the clinical trials that in this target population the efficacy of laxatives can be appropriately equated with the placebo response in the clinical trial. Such an approach equating placebo response as a proxy for standard care is justifiable when an entirely new therapeutic option becomes available for treatment provision in a therapeutic area where no effective therapy currently exists. This is the case with prucalopride where a new and effective treatment is being made available to patients with no existing effective therapy. In the absence of such effective treatment patients end up as 'revolving door' patients, frequently seeking advice from GPs and specialists who are frustrated by the limited therapeutic options available to them. The scope must therefore emphasize the innovative nature of prucalopride as a first in class highly selective entero-kinetic 5-HT4 receptor agonist. Equally the exceptional nature of the target population and the extremely limited therapeutic options currently available to treat this patient group needs to be emphasised in the NICE scoping framework.	Comment noted. The scope has been amended to include invasive procedures such as direct rectal interventions and bowel surgery as comparator technologies. Comment noted. Comment noted. The description of prucalopride in the scope has been updated. The target population has been amended to reflect the licensed indication

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	Norgine	It is important that 'standard therapy' is carefully defined. A recent review of the literature highlights that the evidence available for laxatives vary widely. The only available 'grade A' laxative in the UK highlighted in Ramkumar & Rao are Polyethylene Glycol based laxatives.	Comment noted. The scope has been amended to include invasive procedures such as direct rectal interventions and bowel surgery as comparator technologies.

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Outcomes	Movetis	The NICE review should acknowledge the breadth and depth of the clinical evidence generated in support of the efficacy of prucalopride in its' target population. The clinical trial programme specifically incorporated both 'physical' outcome measures (number of Spontaneous and Complete Bowel Movements (SCBM)) and patient reported outcomes measures (Patient Assessment of Constipation Quality of Life Questionnaire (PAC-QOL), Patient Assessment of Constipation Symptoms Questionnaire (PAC-SYM) and patient satisfaction). This variety of outcome measures was specifically utilised in an attempt to ascertain which single or range of outcome measures best capture the therapeutic gain to the target patient population for prucalopride. In this regard Movetis have a broad spectrum of evidence to support the clinical effectiveness of prucalopride irrespective of whether the analysis is undertaken for physical outcomes (number of SCBMs) or patient reported outcomes (PAC-QOL, PAC-SYM and patient satisfaction). Prucalopride therefore has a very strong evidence base utilising a wide range of outcome measures. The 'softer' but patient focussed outcome measures have been extensively validated and shown to be an effective means of capturing the patient perspective with regard to the outcomes from treatment that are of greatest value to patients. Thus the outcome measures used in the prucalopride trials contain a combination of 'outcome' measures that effectively capture the full benefits experienced by the patient population as a consequence of successful treatment in this therapeutic area. In addition in recognition of the importance of long term evidence in supporting claims of treatment effectiveness in chronic populations a 52 week analysis has been undertaken evaluating patient satisfaction with treatment. The comprehensive evidence base therefore provides strong evidence of the physical benefits arising from prucalopride in the short to medium term supported by evidence of its' impact upon patient quality of life and satisfaction over the longer term.	Comment noted.
	Norgine	The missing outcome measure is a Responder analysis (% of responders defined as patients with more than 3 SCBM-spontaneous complete bowel movements per week)	Comment noted. The scope has been amended to include this outcome.

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Economic analysis	Movetis	The development of a high quality economic model focussed on UK costs and patterns of care represents the essential bedrock of the NICE submission developed by Movetis. The QALYs estimates derived are supported by other approaches over and above the use of QALYs which may have greater relevance in assessing outcomes in chronic constipation. However the economic evaluation undertaken shows that the QALY framework is an appropriate method for capturing outcomes generated by Prucalopride in this therapeutic area. Preliminary analysis of the utility data generated from the mapping exercise between disease specific and generic utility data undertaken by Movetis has estimated an average utility gain of 0.04 QALYs for patients treated with Prucalopride. This translates into a cost per QALY which approximates to £18,000 - a figure which is within the guidelines for acceptance normally utilised by NICE. In addition our estimates of utility are generated using highly conservative assumptions and thus any changes to such assumptions would be likely to enhance the cost effectiveness ratios estimated for Prucalopride. In addition to the QALY analysis the economic model can generate a range of additional cost-effectiveness parameters such as the cost per patient achieving normality (3 SCBMs)), the cost per additional SCBM, or the cost per patient achieving satisfaction with therapy. In general we can present the economic data in whichever way is required by NICE.	Comment noted. The clinical and cost effectiveness of prucalopride will be evaluated based on available evidence for its licensed indication.
	Norgine	Without a clear indication as to what is considered “standard treatment” it will be difficult to accurately determine the efficacy and cost outcomes needed for the ICER. A time horizon of at least three months should be sufficient to provide long term outcomes data. As the proposal stands, it will evaluate an adult population; however, as the drug’s indication is in women only, an economic evaluation in adults may not give an accurate reflection of cost-effectiveness for the drug’s target population or against appropriate comparators.	Comment noted. The clinical and cost effectiveness of prucalopride will be evaluated based on available evidence for its licensed indication.

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Equality and Diversity	Movetis	Chronic constipation is a disease which is particularly prevalent in the elderly and disadvantaged social groups.	Comment noted.
	Norgine	Evidence of efficacy vs placebo has been demonstrated in a mainly female population, explaining the CHMP restriction. There is a need for more visibilty of evidence of efficacy of this new technology across both genders to avoid any discrimination.	Comment noted.
Other considerations	Norgine	The definitions of both standard therapy and failure need to be qualified; Prucalopride should only be indicated when a recognised standard and well defined therapy has been tested in compliant patients and shown to fail; compliance to standard therapy is an important element which needs to be considered. Any assessment must be primarily based upon clinical trials vs an established standard therapy such as Polyethylene Glycol.	Comment noted. The scope has been amended to reflect the intended position of prucalopride in the treatment pathway.
Questions for consultation	Norgine	1/ Definition of standard therapy should be defined and be based on a clear methodology ; please refer to the literature review by Ramkumar and Rao, cited above. 2/ Prucalopride should be restricted to female patients with demonstrated slow transit constipation. A separate analysis should be done for men 3/ Use in opioid induced bowel constipation should be based on clinical evidence (randomised clinical trials conducted with an appropriate active comparator).	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Actavis UK
Department of Health
RICE – The Research Institute for the Care of Older People
Royal College of Nursing
Royal College of Pathologists
Royal Pharmaceutical Society
Welsh Assembly Government