Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

prucalopride 1mg and 2mg tablet (Resolor) SMC No. (653/10)

Shire/Movetis

10 June 2011

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

prucalopride (Resolor) is not recommended for use within NHS Scotland.

Indication under review: for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief.

Overall the manufacturer did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 11 July 2011

Indication

For symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief.

Dosing Information

2mg daily for adult women; 1mg daily, increasing if needed to 2mg daily for elderly women (>65 years).

If the intake of once daily prucalopride is not effective after 4 weeks of treatment, the patient should be re-examined and the benefit of continuing treatment reconsidered. The efficacy of prucalopride has been established in double blind placebo controlled studies for up to 3 months. In the case of prolonged treatment the benefit should be reassessed at regular intervals.

Product availability date

23 March 2010

Summary of evidence on comparative efficacy

Prucalopride is a serotonin 5-HT_4 receptor agonist with enterokinetic effects, stimulating colonic motility. It is the first drug in this pharmacological class to be marketed for treatment of chronic constipation. The company has requested that the Scottish Medicines Consortium (SMC) consider the use of prucalopride when positioned for use in women with chronic constipation after lifestyle interventions then a therapeutic trial of two or more laxatives from different classes have failed to provide adequate relief.

Three pivotal double-blind studies, of similar design, recruited adults who had, on average, no more than two spontaneous complete bowel movements (SCBM) per week, and for at least six months experienced hard stools, sensation of incomplete evacuation or straining at defaecation with at least a quarter of spontaneous bowel movements. After a two-week placebo run-in patients were randomised equally to double-blind treatment with placebo, prucalopride 2mg or 4mg daily for 12 weeks. Use of laxatives was not permitted. However, bisacodyl up to 15mg could be taken as rescue medication by patients with no bowel movement for three consecutive days and an enema could be administered after unsuccessful bisacodyl treatment. The primary outcome, proportion of patients with an average of at least three SCBM per week over the 12-week treatment phase, was assessed within the intention-to-treat (ITT) population comprising patients who received at least one dose of study drug and provided follow-up data for at least one key efficacy variable. Post-hoc analyses were performed on data from subgroups of women who considered the overall therapeutic effect of treatment measures for constipation in the previous six months to be inadequate. Results are summarised in the table, with data for the unlicensed prucalopride 4mg dose omitted. Compared to placebo, prucalopride 2mg was associated with significantly more responders in all three studies, the pooled data from these and in the post-hoc subgroup analysis of pooled data.

Table 1: primary outcome (patients with average of ≥3 SCBM per week over weeks 1 to 12)

	Study A	Study B	Study C	Pooled
ITT population				
Prucalopride 2mg	46/236 (20%)	55/190 (29%)	50/209 (24%)	151/640 (24%)
Placebo	23/240 (9.6%)	25/193 (13%)	25/207 (12%)	73/645 (11%)
Post-hoc subgroup analysis*				
Prucalopride 2mg	32/159 (20%)	40/144 (28%)	37/149 (25%)	109/452 (24%)
Placebo	14/181 (7.7%)	17/140 (12%)	13/147 (8.8%)	44/468 (9.4%)

*women who considered the overall therapeutic effect of treatment measures for constipation in the previous six months to be inadequate

The main secondary outcome was the proportion of patients with an average increase of at least one SCBM per week during the 12-week double-blind treatment phase. It was significantly greater with prucalopride 2mg, compared to placebo, within the ITT analyses of all three studies and pooled data from these and in the post-hoc subgroup analysis of pooled data.

Table 2: patients with average increase of ≥1 SCBM per week over weeks 1 to 12

	Study A	Study B	Study C	Pooled
ITT population				
Prucalopride 2mg	86/226 (38%)	89/177 (50%)	89/209 (43%)	264/612 (43%)
Placebo	49/234 (21%)	49/189 (26%)	57/207 (28%)	155/630 (25%)
Post-hoc subgroup analysis*				
Prucalopride 2mg	60/153 (39%)	64/134 (48%)	66/146 (45%)	190/433 (44%)
Placebo	36/175 (21%)	32/137 (23%)	33/143 (23%)	101/455 (22%)

*women who considered the overall therapeutic effect of treatment measures for constipation in the previous six months to be inadequate

Over the study period in the ITT population the mean SCBM per week was significantly increased with prucalopride 2mg compared to placebo. The between group difference was approximately one SCBM per week.

Table 3: SCBM within the ITT population mean at baseline and over weeks 1 to 12 and mean change

	Study A	Study B	Study C	Pooled
Baseline mean SCBM				
Prucalopride 2mg	0.4	0.5	0.4	Not reported
Placebo	0.4	0.4	0.4	Not reported
Mean over weeks 1-12 (mean change)				
Prucalopride 2mg	1.6 (1.2)	2.3 (1.9)	1.9 (1.5)	1.89 (1.49)
Placebo	1.0 (0.5)	1.3 (0.8)	1.2 (0.8)	1.11 (0.69)

In the ITT population the average number of days with laxative or enema use was significantly reduced over the 12 weeks with prucalopride compared to placebo. The between group difference was less than half a day. Also the mean number of bisacodyl tablets per week was significantly reduced with prucalopride compared to placebo. The between group difference was less than one tablet per week.

Table 4: laxative use in ITT population over weeks 1 to 12

	Study A	Study B	Study C	Pooled
Average number of days with bisacodyl or enema per week, mean (mean change)				
Prucalopride 2mg	0.4 (-0.4)	0.5 (-0.5)	0.6 (-0.3)	0.49 (-0.39)
Placebo	0.8 (-0.2)	0.9 (0.0)	0.7 (-0.1)	0.82 (-0.10)
Number of bisacodyl tablets per week, mean (mean change)				
Prucalopride 2mg	1.1 (-0.8)	0.9 (-1.1)	1.4 (-0.7)	1.1 (-0.9)
Placebo	2.1 (-0.2)	2.0 (0.0)	1.7 (-0.1)	1.9 (-0.1)

A similar double-blind study randomised 300 patients with chronic constipation aged at least 65 years to placebo, prucalopride 1mg, 2mg or 4mg once daily for four weeks after a two-week placebo run-in. The primary outcome, proportion of patients with an average of at least three SCBM per week in the ITT population over 4 weeks, was 40% (30/76), 32% (24/75) and 32% (25/79) with the respective prucalopride doses and 20% (14/70) with placebo. In the post-hoc subgroup, as defined for the pivotal studies, these outcomes were 44% (22/50), 18% (6/33), 34% (14/41) and 16% (6/37), respectively, and comparisons to placebo were not significant.

Within the ITT populations in the three pivotal studies at week 12, mean changes from baseline with prucalopride 2mg compared to placebo were not significant for short-form (SF-36) scores but were significantly improved for patient assessment of constipation quality of life (PAC-QOL) and patient assessment of constipation symptoms (PAC-SYM) questionnaires. In the study in elderly patients mean improvements in PAC-SYM and PAC-QOL at week 4 were significant compared to placebo with prucalopride 1mg, but not 2mg.

Patients completing the three 12-week phase III studies could continue open-label prucalopride treatment in two follow-up studies: one planned for 24 months and the other for 36 months with pooled published efficacy results. However both studies were prematurely stopped when the clinical development of prucalopride was discontinued by the previous sponsor. Eighty-six percent (1455/1691) of patients chose to continue open-label treatment, 494 treated with placebo and 961 with prucalopride during the double-blind phases. Forty-four percent of patients discontinued when the studies terminated and 20% discontinued treatment due to insufficient response. The median duration of open-label prucalopride was 308 days (10 months) with 30% of patients mainly using 2mg and 52% mainly using 4mg. Efficacy results demonstrate that improvements in PAC-QOL satisfaction score were maintained from 3 to 18 months. During the open-label follow-up, laxatives were not used in 41 to 50% of patients.

Summary of evidence on comparative safety

In the double-blind placebo-controlled studies described previously the most common adverse events were headache, abdominal pain, nausea and diarrhoea. These generally occurred within the first few days of treatment and thereafter the incidence of these symptoms was similar to placebo. These were also the main causes of the higher rates of discontinuations due to adverse events in the prucalopride groups compared to placebo.

In the placebo-controlled studies, palpitations that occurred in the prucalopride groups were generally observed in the first few days of treatment. The European Medicines Agency (EMA) notes that definite conclusions cannot be made about the mechanism of these. However the first day of treatment is accompanied by a small increase in heart rate and this, in combination

with gastrointestinal symptoms and/or headache may contribute to palpitations in certain patients. The potential risk of an association with more significant cardiovascular events is difficult to ascertain and available data provide no evidence of this. In double-blind studies cardiovascular ischaemic-related event rates were low and comparable with placebo. The available clinical trial data cannot exclude the possibility of a causal relationship with prucalopride and given the limitations of these to detect such rare events this class of events is to be monitored in post-authorisation surveillance.

The EMA notes that certain 5-HT_4 agonists such as cisapride induce QT interval prolongation, which in some instances leads to ventricular arrhythmias and sudden death. Short-term clinical trial data indicate prucalopride has a negligible influence on the QT interval. A randomised double-blind active (moxifloxacin) and placebo-controlled study in 120 healthy adults also indicated that QT intervals were not prolonged by therapeutic (2 mg) or supra-therapeutic (10 mg) doses of prucalopride.

Summary of clinical effectiveness issues

In the pivotal studies the majority of patients failed to achieve the primary outcome (normalisation of bowel function: average of at least three SCBM per week: 76% with prucalopride 2mg and 89% with placebo) or the key secondary outcome (average increase of at least one SCBM per week: 57% with prucalopride 2mg and 75% with placebo). However it has been suggested that an improvement of 10% over placebo may be considered clinically meaningful. The therapeutic effect of prucalopride at four weeks was comparable to that at 12 weeks, therefore, it is possible to identify patients who will not benefit from prucalopride at four weeks and discontinue it then.

Inadequate relief from previous laxative treatment was not an inclusion criterion for the pivotal trials. These studies also permitted the inclusion of male patients. Efficacy data for the primary outcome and key secondary outcome that are most relevant to the licensed indication are derived from post-hoc subgroup analyses in women who considered the overall therapeutic effect of their treatment measures for constipation in the previous six months to be inadequate. Over the three pivotal studies 71% of ITT population was included in this subgroup. Previous measures included a laxative for 88% of patients, with a further 9% having used bulking agents and only 3% having tried diet changes only. However, it is unclear if previous treatment measures included regular laxative use, how many different laxatives were tried and also how the subjective component “inadequate relief” was defined. No quality of life or long-term data were presented for these subgroups.

In the pivotal studies, patients were not receiving a regular laxative, but used rescue medication with a stimulant laxative and, if required, an enema. In practice many patients may continue to use a regular laxative in addition to prucalopride and the size of the treatment effect in this population is unknown.

The long-term studies did not record data on bowel movement frequency, only subjective data on PAC-QOL satisfaction subscale for patients remaining on treatment and data were not provided for the subgroup of women in whom laxatives fail to provide adequate relief. In addition, large proportions of patients received doses of prucalopride above the licensed dose for the majority of the open-label phases. However, these studies provide data on the proportion of patients requiring additional treatment with a laxative which was slightly greater

than 50%. The studies were stopped before completion due to the halting of the clinical development programme and this limits data on rates of discontinuation due to lack of efficacy (20%). However, only 10% (26/252) of patients who responded during double-blind prucalopride treatment, withdrew due to lack of efficacy in the long-term open-label phases. This suggests low rates of discontinuation due to lack of efficacy on long-term treatment within patients who experienced an initial response and in practice would be permitted to continue treatment after the four-week review.

For many patients with chronic constipation, this symptom is secondary to organic disease or drug therapy. These patients were excluded from the three pivotal trials. Efficacy data are limited to a small four-week phase II study in 196 patients with opioid-induced constipation. The primary outcome, proportion of patients with an increase of at least one SCBM per week was greater with prucalpride 2mg (36%) and 4mg (40%) compared to placebo (23%) with differences compared to placebo only significant at week one but not during subsequent weeks or over the four week study period.

A recently published systematic review and meta-analysis on the use of laxatives and pharmacological therapies in chronic idiopathic constipation included 21 placebo-controlled studies. Seven of these compared prucalopride with placebo in a total of 2,639 patients and included the three pivotal studies and the study in elderly patients described above. The meta-analysis found that 72% (1,288/1,796) prucalopride patients failed to respond compared to 87% (731/843) placebo patients, corresponding to a relative risk of failure to respond of 0.82 (95% confidence interval [CI]: 0.76 to 0.88) and a number needed to treat of 6 (95% CI: 5 to 9). The meta-analysis did not take into account the assessment of response at 4 weeks, which is a requirement of the marketing authorisation, and there was also significant heterogeneity between studies.

The manufacturer's proposed positioning for prucalopride was inconsistently presented throughout the submission and in their subsequent correspondence. This led to a lack of clarity regarding the group to be treated and the size of that group in the Scottish population.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing prucalopride to treatment with rescue medication alone in women with chronic constipation in whom laxatives fail to provide adequate relief. The manufacturer proposed a positioning where prucalopride would be used after lifestyle modification and therapeutic trial of two laxatives. Sensitivity analysis was presented separately for adult women aged 18 to 64 who were treated with a dose of 2mg per day and elderly women aged over 65 who were treated with prucalopride 1mg per day. The time horizon for the analysis was one year and the base case model assumed that patients would be treated for 220 days per year. A stopping rule was incorporated in to the model whereby only patients who responded at week four continued treatment. Response was defined as achievement of normalised bowel habit or ≥3 SCBM per week.

The model used individual patient-level data from the pivotal clinical trials to derive the results. The key outcome in the economic analysis was improvement in quality of life. This was estimated used a mapping algorithm to convert disease-specific quality of life measures from the trial (PAC-QOL and PAC-SYM) into EQ-5D scores, via a direct relationship between PAC and SF-36. While SF-36 data were collected in the trial and can be transformed into utility

values directly using existing, validated methodology, the manufacturer did not use them to calculate quality adjusted life years (QALYs); however the method that has been used has been published in a peer-reviewed journal. Individual utility scores were then calculated using regression equations. Patient-level data from the trials provided quality of life data for the first 12 weeks of the model. Thereafter it was assumed that the quality of life values remained stable for the duration of the model. The only resource use in the model related to the costs of prucalopride; no costs were assumed in the comparator arm of the model.

The results of the model indicated an overall cost per QALY of £13,709 (incremental costs of £501 and incremental QALYs of 0.037). In terms of the sensitivity analysis by age, for elderly women, the cost per QALY was £11,686 (incremental costs of £403 and incremental QALYs of 0.034) and for adult women £15,473 per QALY (incremental costs of £622 and incremental QALYs of 0.04). Probabilistic sensitivity analysis indicated that there was a 56% chance that prucalopride would be cost-effective at a willingness to pay for a QALY of £20,000.

There were a number of issues with the analysis:

- There were some limitations associated with the clinical data and the positioning proposed by the company which fed into the economic model.
- The analysis assumes that the drug is used intermittently over the course of the year and thus the cost reduced proportionately. It is assumed however that the quality of life value is maintained throughout. To the extent that this does not hold, the QALY gain will fall and the ICER rise; an ICER of £16,841 was reported if treatment was assumed to be continuous.
- No resource use other than prucalopride was included in the analysis but this may have been conservative given the potential for additional treatment or investigation costs in patients who do not achieve adequate symptom relief.

Given these issues, the economic case has not been demonstrated.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- The Gut Trust
- PromoCon Disabled Living

Additional information: comparators

Many patients with chronic constipation not adequately relieved by laxatives will continue to take these medicines. Prucalopride may replace laxatives for some patients or be used in addition to them in an attempt to reduce dose or dose frequency of laxatives. In practice bulk-forming laxatives (ispaghula husk, sterculia and methylcellulose) and osmotic laxatives (lactulose and macrogols) may be used regularly over long periods, with stimulant laxatives (bisacodyl, senna, docusate and sodium picosulfate) used in shorter courses on an as required basis.

Cost of relevant comparators

Drug	Dose Regimen	Cost per day (£)	Cost per year (£)
Prucalopride	**1mg or 2mg once daily**	**1.38 to 2.13**	**503 to 774**
Macrogol 3350	1 to 3 sachets daily	0.18 to 0.53	65 to 194
Sterculia	1 to 2 sachets once or twice daily	0.08 to 0.33	30 to 121
Docusate*	100mg to 500mg daily	0.06 to 0.32	23 to 116
Bisacodyl *	5mg to 20mg once daily	0.06 to 0.25	23 to 91
Sodium picosulfate*	2 to 4 capsules daily	0.11 to 0.22	40 to 79
Lactulose	10ml to 30ml daily	0.07 to 0.20	25 to 74
Methylcellulose	1,500mg to 3,000mg twice daily	0.09 to 0.17	31 to 63
Ispaghula husk	1 sachet twice daily	0.12	45
Senna*	2 to 4 tablets daily	0.02 to 0.03	6 to 12

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 24 March 2011. Cost per day and year are provided as some laxatives are taken in short courses whereas others are used regularly for extended periods. * stimulant laxatives, which are usually used for short courses on an as required basis, therefore, cost per year may not be relevant.

Additional information: budget impact

The manufacturer estimated a gross drug budget impact of £296k in year one rising to £1.2m in year five. These estimates assumed 220 days of treatment per year in responding patients. The manufacturer also estimated a gross drug budget impact of £446k in year one rising to £2m in year five if prucalopride was given for 365 days per year in responding patients. The manufacturer suggested that there could be offsetting savings from reduced levels of GP and secondary care consultations and invasive procedures. These savings were not however captured in the economic analysis.

All estimates assumed market shares of 10% of eligible patients in year one rising to 50% by year five to give 1082 adult patients and 835 elderly patients starting treatment in year one. Estimates assumed that there was a stopping rule for non-responders at 4 weeks and that patients who respond remain on treatment from one year to the next.

References

The undernoted references were supplied with the submission. The references shaded in grey are additional to those supplied with the submission.

Movetis NV. Study PRU-INT-6. A double-blind, placebo-controlled trial to evaluate the efficacy and safety of prucalopride tablets in subjects with chronic constipation. Clinical study report. Data on file, 2007.

Tack J, van Outryve M, Beyens G et al. Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. Gut 2009; 58: 357-65.

Movetis NV. Study PRU-USA-11. A double-blind, placebo-controlled trial to evaluate the efficacy and safety of prucalopride tablets in subjects with chronic constipation. Clinical study report. Data on file, 2007.

Camilleri M, Kerstens R, Rykx A, Vandeplassche L. A placebo-controlled trial of prucalopride for severe chronic constipation. N Engl J Med 2008; 358: 2344-54.

Movetis NV. Study PRU-USA-13. A double-blind, placebo-controlled trial to evaluate the efficacy and safety of prucalopride tablets in subjects with chronic constipation. Clinical study report. Data on file, 2007.

Quigley EM, Vandeplassche L, Kerstens R, Ausma J. Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation - a 12-week, randomized, double-blind, placebo-controlled study. Aliment Pharmacol Ther 2009; 29: 315-28.

Movetis NV. Study PRU-INT-12. A double-blind, placebo-controlled study to evaluate the efficacy, safety and quality-of-life of prucalopride tablets in elderly patients with chronic constipation. Clinical study report. Data on file, 2007.

Muller-Lissner S, Rykx A, Kerstens R, Vandeplassche L. A double-blind, placebo-controlled study of prucalopride in elderly patients with chronic constipation. Neurogastroenterol Motil 2010:

Movetis NV. Study PRU-INT-10. A study to evaluate the long-term tolerability and safety of oral prucalopride administered to patients with chronic constipation. Clinical study report. Data on file, 2008.

Movetis NV. Study PRU-USA-22. A study to evaluate the long-term tolerability, safety, patient satisfaction, pharmacokinetics, and use pattern of oral prucalopride tablets in patients with chronic constipation. Clinical study report. Data on file, 2008.

European Medicines Agency. European public assessment report for Resolor.

Camillera M, Van Outryve MJ, Beyens G et al. Clinical trial: the efficacy of open-label prucalopride treatment in patients with chronic constipation – follow-up of patients from the pivotal studies. Aliment Pharmacol Ther 2010;32:1113-1123.

T. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. Gut 2011;60:209-18

This assessment is based on data submitted by the applicant company up to and including 13 May 2011.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.