PUBLIC SUMMARY DOCUMENT
Product: Prucalopride, tablets (film-coated), 1 mg and 2 mg (as succinate), Resotrans®
Sponsor: Janssen-Cilag Pty Ltd
Date of PBAC Consideration: November 2011

1. Purpose of Application

The submission requested a Restricted Benefit listing for the treatment of moderate to severe chronic constipation in adults who are intolerant to or are not adequately controlled with both bulk forming agents and osmotic laxatives.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Prucalopride tablets were registered by the TGA on 18 November 2011 for:
Treatment of chronic functional constipation in adults in whom laxatives fail to provide adequate relief.

- Before prucalopride is considered patients must have tried at least two different types of laxatives from different classes (at the highest tolerated recommended doses) for at least 6 months, but have not had adequate relief from constipation.
- If treatment with prucalopride is not effective within 4 weeks, the benefit of continuing treatment should be reconsidered.

4. Listing Requested and PBAC's View

Restricted Benefit

For the treatment of moderate to severe chronic constipation in adults who are intolerant to or are not adequately controlled with both:

- bulk forming agents, and
- osmotic laxatives

Note:
If the intake of 2 mg RESOTRANS once daily is not effective after 4 weeks of treatment, the patient should be re-examined and the benefit of continuing treatment with prucalopride reconsidered.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Chronic constipation is a common condition in the Australian population. The prevalence of chronic constipation is higher in women, the elderly and in individuals of lower socioeconomic class. Complications of chronic constipation are infrequent, but if poorly managed, constipation can lead to serious and severe complications such as faecal impaction, bowel perforation and ulceration, intestinal obstruction and bleeding.

Chronic constipation is largely self managed by most patients using over the counter laxatives and herbal remedies.

The submission proposed that the place in therapy of prucalopride is third line therapy after bulk forming agents and osmotic laxatives in patients who are not adequately controlled by or are unable to tolerate bulk forming agents and osmotic laxatives.

6. Comparator

The submission nominated best supportive care as the comparator (BSC). BSC constituted stimulant laxatives and/or enemas as rescue interventions in those patients who had failed or were intolerant to bulk forming and osmotic laxatives.

The PBAC did not agree that best supportive care (BSC) was the appropriate comparator. The PBAC considered that bisacodyl or possibly docusate sodium would be a more appropriate choice of comparator, as they are likely to be used after bulk forming agents and osmotic laxatives have failed.

7. Clinical Trials

The submission presented a meta-analysis of four randomised placebo controlled trials (over 4 and 12 weeks) comparing prucalopride plus best supportive care with placebo plus best supportive care (PRU-INT-6, PRU-USA-11, PRU-USA-13 and PRU-INT-12), two related extension safety studies (PRU-INT-10 and PRU-USA-22) and four supportive randomised phase II dosing trials.

The submission also presented a post-hoc pooled subgroup analysis of female and male patients in the pivotal 12 week trials with baseline bowel function of at least one complete bowel motion (CBM) per week. The proportion of male patients enrolled in the four randomised placebo controlled studies was low (14%). Details of the studies published at the time of submission are shown in the table below:

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
PRU-INT-6 Tack et al 2009	Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives.	Gut. 2009, 58(3):357-65.
PRU-USA-11 Camilleri et al 2008	A placebo-controlled trial of prucalopride for severe chronic constipation.	N Engl J Med 2008, 358:2344-54.
PRU-USA-13 Quigley et al 2009	Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation – a 12-week, randomised, double-blind, placebo-controlled study.	Aliment Pharmacol Ther. 2009, 29;315–328.
PRU-INT-12 Müller-Lissner et al 2010	A double-blind, placebo-controlled study of prucalopride in elderly patients with chronic constipation.	Neurogastroenterol Motil. 2010, 22(9):991-8.

8. Results of Trials

In all four pivotal trials "best supportive care" (i.e. use of rescue agents bisacodyl and enemas) was allowed in both the prucalopride and placebo trial arms after patients failed to experience a bowel motion for three consecutive days. Bowel motions reported within 24 hours of the use of a rescue agent were not included in the primary analyses of efficacy.

Efficacy was measured using data derived from patient diaries. However, there were concerns regarding missing data as the primary analyses were based on weekly frequencies and scores. Patients with missing diary entries had their data inputed using the last 7 days of data recorded after week 1 (at least 14 days of data required).

The primary efficacy measure was the proportion of patients with three or more spontaneous complete bowel motions (SCBM) per week over 1-12 weeks. A bowel movement was defined as spontaneous if no laxatives were taken in the 24 hours preceding that bowel movement.

The PBAC noted that the results of the trials for the primary outcome suggested that the response to prucalopride was modest, with fewer than 30% of prucalopride treated patients in Trials PRU-INT-6, PRU-USA-11 and PRU-USA-13 achieving relief of symptoms. The differences between the prucalopride and placebo arms were small and statistically significant in all three 12 week trials (rates 10%-16%) and in the meta-analysis (12%).

In addition the PBAC noted that a statistically significantly larger proportion of patients treated with prucalopride 1 mg per day in PRU-INT-12 (elderly subjects) achieved three or more SCBMs per week in weeks 1-4; however response rates were less than 40% in prucalopride treated patients. There was no evidence of additional benefit from a 2 mg/day dose in elderly patients.

The submission also presented results for the less stringent secondary outcome of proportion of patients with an average increase of one or more SCBMs per week over 1-12 weeks. The results showed higher proportions of patients achieving this secondary outcome, but response rates in prucalopride treated patients were generally less than 50%.

The PBAC noted that the pivotal trials only included small proportions of men (8-15%). However, the submission presented a pooled subgroup analysis of the pivotal trials by gender for the less stringent secondary outcome of one or more SCBMs per week (weeks 1-12).

The small number of male patients in the trials showed lower rates of response to prucalopride at doses up to and including 2 mg per day for the secondary outcome. A larger proportion of males taking the higher dose of 4 mg per day achieved one or more SCBMs per week, however the 4 mg dose was not included in the requested listing. The PBAC noted that the requested PBS listing was for both males and females and that the European Medicines Agency approved use of prucalopride is for women only.

A post-hoc subgroup analysis of male and female patients reporting greater than nil complete bowel motions (CBMs) per week at baseline and achieving the outcome at least one or more SCBMs per week in the pivotal trials suggested that response rates were higher in males than females for both placebo and the two dose regimens of prucalopride. However the clinical relevance of this analysis was unclear as patients with CBM greater than nil at baseline will be patients with the least severe symptoms and may not reflect the population for whom PBS listing is requested.

The four studies included in the meta-analysis assessed two quality of life measures: PAC-QOL, a disease based measure, and SF-36. PAC-QOL scores were averaged to a score between 0 and 4, where a change of 1 point represented the MCID (minimum clinically important difference, Dubois et al., 2010). Over weeks 1-12, around 40% of prucalopride-treated patients and 20% of placebo-treated patients reported clinically relevant improvements in PAC-QOL scores. The one statistically significant change in SF-36 scores associated with prucalopride therapy was in the summary score for the physical health component at week 4 in study PRU-INT-6. There were no statistically significant differences between treatments at week 12.

The submission also presented the results of a post hoc analysis of individual patient assessment of constipation severity, with response defined as an improvement in constipation severity. The submission claimed that improvement in a patient's global assessment of constipation severity was likely to be indicative of their willingness to continue therapy. The results of the post-hoc analysis of responders (improved severity of constipation) suggested more positive outcomes with prucalopride treatment than implied in the PAC-QOL and SF-36 results.

For PBAC's view of these results, see Recommendation and Reasons.

The results for the meta-analysis of adverse events in the randomised controlled trials showed statistically significantly larger proportions of patients treated with prucalopride reported events compared to patients taking placebo, but noted that these events were generally transient and occurred mainly on the first day of dosing. Also, a larger proportion of patients treated with prucalopride reported severe adverse events compared to patients taking placebo.

The adverse events most frequently reported by patients treated with prucalopride were headache, nausea, diarrhoea, flatulence, dizziness and upper respiratory tract infections.

The Post Marketing Safety Update (14 October 2010), reporting on the post-marketing exposure of prucalopride in the European Union identified no change in the character or frequency of reported adverse events.

There are limited long-term safety data for prucalopride. The submission suggested that the selectivity of prucalopride differentiated it from the older systemically acting 5-HT_4 inhibitors cisapride and tegaserod. Supportive pharmacokinetic studies (PRU-GBR-9, PRU-GBR-10 and M0001-C102) which found no evidence of clinically relevant QT interval prolongation in healthy individuals taking prucalopride at doses up to 10 times those included in the requested listing.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described prucalopride plus best supportive care as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo plus best supportive care.

The PBAC considered that the submission's claim of superiority of prucalopride plus BSC in

terms of comparative effectiveness over placebo plus BSC was probably reasonable based on the clinical trials, but the Committee considered that the population included in the pivotal trials was not sufficiently representative of the population in the requested PBS listing. The PBAC accepted that prucalopride plus BSC was inferior in terms of comparative safety over placebo plus BSC.

10. Economic Analysis

The submission presented a stepped modelled evaluation based on the proportion of responders to prucalopride at 4 and 12 weeks, extrapolated to 52 weeks. The only cost included in the model was the cost of prucalopride; there were no costs included for adverse events, complications of chronic constipation or investigations.

Three algorithms to map the SF-36 individual patient data from the pivotal trials to the AQoL were investigated. The utilities derived using the AQoL (Item) model were used in the base case evaluation.

The incremental cost per quality adjusted life year (QALY) gained was between $15,000 and $45,000. Sensitivity analyses showed the ICER to be most sensitive to the utility mapping method used and moderately sensitive to the prucalopride adherence rate.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The net financial cost/year to the PBS was estimated by the submission to be between $10 million and $30 million in Year 5. The estimate was uncertain.

12. Recommendation and Reasons

The PBAC did not agree that best supportive care (BSC), consisting of stimulant laxatives and/or enemas as rescue interventions in patients who have failed or are intolerant to bulk forming and osmotic laxatives, was the appropriate comparator. The PBAC considered that bisacodyl or possibly docusate sodium would be a more appropriate choice of comparator, as they are likely to be used after bulk forming agents and osmotic laxatives have failed.

The Committee considered that the patient population included in the pivotal trials was not representative of the patient population targeted in the requested listing. Participants in the trials were primarily female, and included patients with mild constipation as well as patients who had not attempted treatment with both bulk forming agents and osmotic laxatives. In addition dose regimens of the randomised therapies in the pivotal trials are not all within those recommended in the draft PI for prucalopride. The PBAC also noted that the Advisory Committee on Prescription Medicines (ACPM) had recommended approval for prucalopride for treatment of chronic 'functional' constipation, consistent with the trial populations, and considered that the PBS restriction should specify use in patients with functional constipation.

The submission presented a meta-analysis of four randomised placebo controlled trials comparing prucalopride plus BSC with placebo plus BSC. Efficacy outcomes were measured using data derived from self-reported patient diaries. The PBAC noted that-a high rate of protocol violations were reported and had concerns regarding missing data.

The primary efficacy measure was the proportion of patients with three or more spontaneous complete bowel motions (SCBM) per week over 1-12 weeks. The PBAC noted that the results of the trials for the primary outcome suggested that the response to prucalopride was modest, with fewer than 30% of patients achieving the outcome. In addition, the PBAC noted that a statistically significantly larger proportion of patients treated with prucalopride 1 mg daily in study PRU-INT-12 (in elderly patients) achieved the primary endpoint in weeks 1-4, however response rates were less than 40%. There was no evidence of additional benefit from a daily dose of 2 mg in elderly patients.

The submission also presented results for the secondary outcome of proportion of patients with an average increase of one or more SCBMs per week over 1-12 weeks. The PBAC noted that the results showed higher proportions of patients achieving this secondary outcome, but response rates in prucalopride treated patients were generally less than 50%. The PBAC considered that the clinical importance of this outcome was uncertain. The small number of male patients in the trials showed lower rates of response to prucalopride at doses up to and including 2 mg per day for the secondary outcome.

In terms of safety, the PBAC noted the overall incidence of treatment emergent adverse events was statistically significantly higher in patients taken with prucalopride compared to placebo. The PBAC was interested in the cardiovascular safety of prucalopride, noting that no data were provided on cardiovascular outcomes with longer term exposure to prucalopride. The PBAC recalled other 5HT-4 receptor agonists, cisapride (2004) and tegaserod (2007) were withdrawn from the market as a result of cardiovascular safety concerns. The PBAC noted that the routine pharmacovigilance plan along with proposed studies to investigate relevant cardiovascular events would provide more substantial evidence relating to the potential safety issues raised.

The PBAC considered that the submission's claim of superiority of prucalopride plus BSC in terms of comparative effectiveness over placebo plus BSC was probably reasonable based on the clinical trials, but the Committee considered that the population included in the pivotal trials was not sufficiently representative of the population in the requested PBS listing. The PBAC accepted that prucalopride plus BSC was inferior in terms of comparative safety over placebo plus BSC.

The submission presented a stepped modelled evaluation based on the proportion of responders to prucalopride at 4 and 12 weeks, extrapolated to 52 weeks. The incremental cost per quality adjusted life year (QALY) gained was between $15,000 and $45,000. The PBAC noted sensitivity analyses showed the ICER to be most sensitive to the utility mapping method used (ICER increased to between $45,000 and $75,000 using SF-6D and between $105,000 and $200,000 using AQol (Rasch method)), and it was moderately sensitive to the prucalopride adherence rate (ICER increased between $15,000 and $45,000, 100% adherence rate).

The PBAC noted that three different mapping techniques to derive utility scores from the SF-36 data were investigated, in addition to using the SF-6D algorithm. The PBAC noted that the different mapping techniques gave vastly different results, which impact the results of the economic evaluation, and demonstrates considerable uncertainty deriving from the assumed utility values.

The PBAC considered that the submission's estimates of patient numbers, number of prescriptions per patient and financial implications to the PBS were likely significant underestimates. The PBAC considered there was considerable risk of use outside the population described in the restriction to those with milder disease, in place of other therapies (e.g. macrogol) or administered regularly as a chronic medication (e.g. via dose administration aids in residential aged care facilities) and use for different periods of time than proposed in the submission.

The PBAC therefore rejected the submission on the basis of uncertain clinical effectiveness in the requested PBS population and uncertain cost-effectiveness.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor had no further comment.