PUBLIC SUMMARY DOCUMENT
Product: Prucalopride, tablets, 1 mg and 2 mg (as succinate), Resotrans®
Sponsor: Janssen-Cilag Pty Ltd
Date of PBAC Consideration: July 2012

1. Purpose of Application

The re-submission requested a Restricted Benefit listing for the treatment of chronic functional constipation in adults in whom laxatives fail to provide adequate relief.

2. Background

At the November 2011 meeting, the PBAC rejected a submission seeking 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 on the basis of uncertain clinical effectiveness in the requested PBS population and uncertain cost-effectiveness.

3. Registration Status

Prucalopride was TGA registered on 18 November 2011 for the indication:

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 initial treatment of chronic functional constipation in adults in whom laxatives fail to provide adequate relief. Before Resotrans is considered patients must have tried at least three different types of laxatives from different classes (such as bulk forming agents, osmotic laxatives and stimulant laxatives at the highest tolerated recommended doses) for at least six months, but have not had adequate relief from constipation.

Note:
If the intake of 2mg Resotrans once daily is not effective after 4 weeks of treatment, the patient should cease treatment with prucalopride.

RESOTRANS is not indicated for the treatment of opioid induced constipation.

Restricted Benefit

For the continuing treatment of chronic functional constipation in adults in whom laxatives fail to provide adequate relief and who have achieved an adequate response to treatment with prucalopride. Before Resotrans is considered patients must have tried at least three different types of laxatives from different classes (such as bulk forming agents, osmotic laxatives and stimulant laxatives at the highest tolerated recommended doses) for at least six months, but have not had adequate relief from constipation.

Note:

RESOTRANS is not indicated for the treatment of opioid induced constipation.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Chronic functional (also called primary or idiopathic) 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.

Patients use a variety of descriptive terms to define constipation, while physicians tend to think in terms of bowel movement frequency. 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 self managed by most patients using dietary (increase fibre, adequate non caffeinated fluid) and lifestyle changes (e.g. exercise, adjusting bowel habits), over the counter laxatives (bulk forming laxatives, osmotic laxatives, stimulant laxatives) and herbal remedies.

The submission proposed that the place in therapy of prucalopride is for the last line pharmacological treatment of chronic functional constipation after all types of conventional laxative therapies (i.e. bulk forming agents, osmotic laxatives and stimulant laxatives) have been trialled and failed to provide adequate relief.

6. Comparator

The submission nominated a new definition of best supportive care (BSC) as the comparator. BSC was defined as stimulant laxatives in patients who had failed to achieve adequate relief with bulk forming agents, osmotic laxatives and stimulant laxatives.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission included all trials presented in the previous submission. The basis of the re-submission was a meta-analysis of four randomised placebo controlled trials over 4 and 12 weeks comparing prucalopride + BSC with placebo + BSC (PRU-INT-6, PRU-USA-11, PRU-USA-13 and PRUCRC3001), and a supportive 4-week randomised trial of 1mg prucalopride in elderly patients (PRU-INT-12). The meta-analyses were updated to include an additional trial PRUCRC3001, a recently completed randomised placebo control trial of prucalopride.

The safety results of the 4-week trial conducted in a nursing home (PRU-USA-26) were presented to provide additional evidence of the cardiovascular safety of prucalopride.

The table below details the published trials and associated reports presented in the submission:

Trial ID / First author	Protocol title / Publication title	Publication citation
Direct randomised trials- Pivotal 12-week trials		

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 NCT00488137 05 September 2007 – Final
Tack J et al.(2009)	Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives.	Gut. 2009 Mar; 58(3):357-65
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 NCT00483886 02 April 1998.
Camilleri M et al. (2008)	A Placebo-Controlled Trial of Prucalopride for Severe Chronic Constipation.	N Engl J Med 2008;358:2344-54.
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 04 October 2007 – Final NCT00485940
Quigley E 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.
PRUCRC3001	A Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Prucalopride (Resolor®) Tablets in Subjects With Chronic Constipation.	Clinical Study Report 06 July 2011
Direct randomised trial- Supportive 4-week trial		
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 NCT 00487422 5 October 2007.
Müller-Lissner S et al. (2010)	A double-blind, placebo-controlled study of prucalopride in elderly patients with chronic constipation.	Neurogastroenterol Motil. 2010 Sep;22(9):991-8.
Additional 4 week safety trial		
PRU-USA-26	A double-blind, placebo-controlled study to evaluate the safety and tolerability of oral once-daily prucalopride solution in constipated elderly patients living in a nursing facility.	Clinical Study Report: NCT 00627692 21 Feb 2008.
Camilleri M et al. (2009)	Safety assessment of prucalopride in elderly patients with constipation: A double-blind, placebo-controlled study.	Neurogastroenterology and Motility (2009) 21:12 (1256-263+e117) (References)

8. Results of Trials

All pivotal trials allowed "best supportive care" (i.e. use of rescue agents bisacodyl and enemas) 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 analyses of efficacy.

The submission presented the outcome of the proportions of patients achieving at least three spontaneous complete bowel motions (SCBM) per week, prucalopride versus placebo.

The results showed that the efficacy of prucalopride was modest, with around 30% of subjects achieving greater than or equal to 3 SCBMs per week compared to around 10% in the placebo group. The results for benefits in the new trial PRUCRC3001 were slightly higher, than in previous trials (response rate 33.3% for weeks 1-12 but an overall difference of 12-20% compared to placebo). Trial PRUCRC3001 was conducted predominantly in Asian population and recruited less severe patients at baseline. The differences between the prucalopride and placebo were small and statistically significant in all four 12-week trials (rates 10%-23%) and in the meta-analysis (RD15%; 95%CI 9%, 21%).

There was a statistically significant larger proportion of patients treated with prucalopride 1mg per day in PRU-INT-12 (elderly subjects) who achieved greater than or equal to 3 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 2mg/day dose in elderly patients.

Overall the PBAC considered that, while modest, the trials showed a benefit of prucalopride in a small number of patients with chronic functional constipation who have received little benefit from other classes of oral laxatives.

The submission presented the results for the secondary efficacy outcome of an average increase of greater than or equal to one SCBMs per week. The placebo response rates for this outcome were also higher (RD 19% for weeks 1-12, 95%CI 13%, 24%).

The submission also presented the results of the updated meta-analysis of Patient Assessment of Constipation Symptom (PAC-SYM) for prucalopride versus placebo. The proportions of patients with an improvement of at least 1 point in PAC-SYM score (moderate improvement) were less than 40% across trials. There was no statistically significant benefit over placebo in PAC-SYM score for both 1mg and 2mg dosage.

The re-submission also presented an updated meta-analysis of quality of life measures to include the results from Trial PRUCRC3001. As in the previous submission, two quality of life measures, PAC-QOL (Patient Assessment of Constipation Quality of Life) and SF-36 (Short Form (36) Dimension Health Survey), were assessed. The proportion of patients who reported clinically relevant improvements in PAC-QOL scores were around 40% in prucalopride patients and 20% in placebo. Elderly patients treated with 1mg prucalopride had better response rate in comparison to 2mg group, however did not achieve statistical significance versus placebo.

The re-submission further presented results for SF-36 scores of 2 mg prucalopride and placebo at baseline, 4 week and 12 weeks.

In trials PRU-USA-11 and PRU-USA-13, there was no significant difference between prucalopride and placebo at all time points. At week 4, the statistically significant changes in SF-36 scores associated with prucalopride therapy were in the physical component in trials PRU-INT-6 and PRUCRC3001. The only significant difference between treatments at week 12 was in the physical component summary score in Trial PRUCRC3001. However, the magnitude of the differences between prucalopride and placebo were limited.

The overall incidence of treatment emergent adverse events was statistically significantly more frequent in patients treated with prucalopride (72%) compared to patients taking placebo (59%) (RR 1.21; 95%CI: 1.06, 1.38). The adverse events most frequently reported by patients treated with prucalopride were headache, nausea, diarrhoea, flatulence, dizziness and upper respiratory tract infections. The event rates in Trial PRUCRC3001 were lower than other trials and the re-submission claimed that this was due to the different coding methods used for adverse events in the trials. The adverse events most frequently reported in elderly patients (≥65 years of age) were similar to those reported in the 12-week pivotal trials.

The re-submission included PRU-USA-26, a 4-week study to evaluate the safety/tolerability of prucalopride 0.5mg, 1mg, 2mg and 4mg in elderly patients living in a nursing home. No consistent or clinically relevant treatment related differences were noted in ECG parameters (including heart rate, non-corrected QT intervals, corrected QT intervals (QTcB and QTcF), PR interval and QRS width). The study population was too small (N=89) to detect rare events and a 4-week duration is not long enough to provide evidence of the safety outcomes of the long-term use of prucalopride. There were no data provided to support the long-term safety profile of prucalopride in regards to the rare events, however it was noted that the short duration of studies and small numbers of patients enrolled in the trials would not provide this data.

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

9. Clinical Claim

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

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The resubmission presented a stepped modelled evaluation based on the proportion of responders to prucalopride at 4 and 12 weeks, extrapolated to 5 years (compared with 1 year in the previous submission) using the variables reported in the pre modelling studies.

The re-submission selected the utility AQoL (item) values for constipation severity for the basecase mapped from the SF36.

The only cost included in the economic evaluation was drug costs. Special populations including residents in aged care facilities, dosing aids users and patients receiving 7-day sample packs were considered in the sensitivity analysis and a weighted ICER is calculated based on the assumption of the proportion of populations.

The stepped economic evaluation produced an incremental cost per quality adjusted life year (QALY) gained between $15,000- $45,000, which was lower, though in the same range as the previous submission.

Prucalopride usage in aged care facilities or with dose aids was shown to reduce the ICER per QALY though it remained in the range $15,000- $45,000, however the PBAC considered that the basis for most of the assumptions in this sensitivity analysis were unlikely to apply.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients/year was estimated to be in the range 50,000 – 100,000 in Year 5 which is less, though in the same range as the previous submission.

The likely number of prescriptions/year was estimated by the submission to be greater than 200,000 in Year 5, compared to 100,000 – 200,000 in Year 5 in the previous submission.

The net PBS costs per year were estimated by the submission to be in the range $10-$30 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC considered that the revised definition of best supportive care (BSC, stimulant laxatives in patients who have failed to achieve adequate relief with bulk forming agents, osmotic laxatives and stimulant laxatives) was a reasonable comparator for the proposed PBS population. However, the PBAC noted that this definition of BSC only accounts for oral treatments and excludes enemas.

The PBAC noted that the resubmission proposed a Restricted Benefit listing with a restriction which limits use of prucalopride to patients with functional constipation who have failed to achieve adequate relief from at least 3 different classes of laxatives, and includes a continuation rule to restrict ongoing use to those patients who have achieved an adequate response with prucalopride.

The PBAC considered that the inclusion of trial PRUCRC3001 in a meta-analysis with trials PRU-INT-6, PRU-USA-11 and PRU-USA-13 did not substantially change the basis for the PBAC's conclusion from the November 2011 submission. For the primary outcome of proportion of patients achieving at least 3 spontaneous complete bowel movements (SCBMs) per week, the differences between prucalopride and placebo were small and statistically significant in all four 12-week trials (rates 10% - 23%) and in the meta- analysis (15%). More patients achieved the less stringent secondary outcome of average increase of at least 1 SCBM per week compared to the primary outcome. The PBAC considered that an improvement of 1 SCBM per week may be significant for patients and lead to lower rates of discontinuation than expected in the re-submission. Results of trial PRU-INT-12 in elderly patients (> 65 years) were unchanged from the previous submission.

The PBAC noted the resubmission updated the meta-analysis of quality of life measures (PAC-QOL and SF-36) to include the results from PRUCRC3001. PAC-QOL scores improved by a clinically relevant difference in around 40% of patients treated with prucalopride + BSC compared with 20% in patients treated with placebo + BSC. The results for SF-36 were inconsistent across the trials and difficult to interpret. In trials PRU-USA-11 and PRU-USA-13, there was no significant difference between prucalopride and placebo at all time points. At week 4, the statistically significant changes in SF-36 scores for the physical component of the scale were observed for prucalopride therapy in trials PRU-INT-6 and PRUCRC3001. The only significant difference between treatments at week 12 was in

the physical component summary score in PRUCRC3001. The magnitude of the differences between prucalopride and placebo were limited. The PBAC noted that the SF-36 scores showed little impact of prucalopride treatment on overall quality of life because chronic functional constipation, particularly if severe and poorly managed, has the potential to substantially impact on a patient's quality of life. No clear justification for the lack of substantial benefit on SF-36 scores was provided in the resubmission.

The PBAC considered that the updated meta-analysis of safety measures which included PRUCRC3001 did not alter its previous conclusion that prucalopride is inferior in terms of safety compared to placebo.

The resubmission presented a stepped modelled evaluation based on the proportion of responders to prucalopride at 4 and 12 weeks, extrapolated to 5 years (compared with 1 year in the previous submission). The incremental cost per quality adjusted life year gained was in the range $15,000- $45,000, less though in the same range compared with the previous submission.

The PBAC recalled its previous concern with the different mapping techniques used to derive utility scores from the SF-36 data to AQoL in the previous submission and noted that no change had been made to the derivation of utilities in the resubmission. The PBAC noted that the results of the economic evaluation were most sensitive to the different utility mapping methods.

The PBAC considered there were a number of other issues with the economic model which contributed to uncertainty in the ICER including the assumption that partial responders will discontinue treatment, and the assumption that non-adherence to (intermittent use) prucalopride therapy will reduce the costs of prucalopride to 66.4% whereas the impact of intermittent prucalopride use on quality of life is assumed to be 90%.

The PBAC considered that the submission's estimates of utilisation and financial implications are likely to be underestimates. The PBAC considered that there was considerable potential for use beyond the intended population as no definition of 'adequate response' was included in the restriction and it was likely that patients who experience a partial benefit (but less than 3 SCBMs per week) will continue therapy. The resubmission did not consider the financial implications of the use of prucalopride in residents of aged care facilities and patients using dose administration aids, in whom extensive use is likely. In addition, the PBAC considered that the prevalence of chronic moderate to severe functional constipation is uncertain as diagnosis is largely based on patient self-reporting. The PBAC noted that the sponsor attempted to address these issues in its pre-PBAC response by proposing an Authority Required restriction where diagnosis and initiation of prucalopride is limited to gastroenterologists and initial assessment of response (at week 4) for continuing treatment be made by, or in consultation with a gastroenterologist.

The PBAC rejected the resubmission on the basis of uncertain magnitude of clinical benefit and uncertain cost-effectiveness.

The PBAC also acknowledged and noted the consumer comments on this item.

Recommendation:

Reject

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 has no comments.