CDEC FINAL RECOMMENDATION

PRUCALOPRIDE
(Resotran — Janssen Inc.)
Indication: Constipation, Chronic

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that prucalopride not be listed.

Reasons for the Recommendation:
1. The Committee considered the clinical effectiveness of prucalopride in the relevant patient population to be uncertain due to the fact that the reviewed trials included a proportion of patients who had not previously failed laxative therapy.

2. Given the uncertain clinical effectiveness in patients who had previously failed laxative therapy, the Committee noted that there was uncertainty regarding the cost-effectiveness of prucalopride.

3. At the recommended daily doses, the cost of prucalopride ranges from $2.15 (1 mg for adults > 65 years) to $3.30 (2 mg daily for adults ≤ 65 years). Most oral laxatives cost < $1 a day.

Background:
Prucalopride has a Health Canada indication for the treatment of chronic idiopathic constipation in adult female patients in whom laxatives failed to provide adequate relief. Prucalopride is a 5-hydroxytryptamine-4 receptor agonist. It is available as 1 mg and 2 mg oral tablets and the dose recommended by Health Canada is 2 mg once daily; for patients > 65 years the recommended dose is 1 mg once daily, with an increase to 2 mg once daily if needed.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind randomized controlled trials (RCTs) of prucalopride, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials

The systematic review included four double-blind, placebo-controlled RCTs of adult men and women with chronic idiopathic constipation.

All trials included a two-week run-in period during which constipation was confirmed, followed by a 12-week, double-blind treatment period. In three trials, (PRU-INT-6, N = 720; PRU-USA-11, N = 628; and PRU-USA-13, N = 651), patients were randomized to prucalopride 2 mg, prucalopride 4 mg, or placebo. In one trial (PRU-CRC-3001, hereafter referred to as study 3001; N = 507) patients were randomized to prucalopride 2 mg or placebo.

PRU-USA-11 and PRU-USA-13 were conducted exclusively in the United States, PRU-INT-6 was conducted in Europe, North America, Australia, and South Africa; study 3001 was conducted in an Asian-Pacific population. In all trials, the majority of patients were women (> 85%) and the mean age ranged from 42 to 47 years across the trials. The mean duration of constipation at baseline was approximately 13 years in study 3001 and ranged from approximately 17 to 22 years in the remaining studies. Patients older than 65 years accounted for less than 15% of the study population in PRU-INT-6, PRU-USA-11, and PRU-USA-13. Patients older than 65 years were not included in study 3001.

In all trials, the use of laxative-type medications was not permitted. However, patients failing to have a bowel movement for three or more consecutive days received bisacodyl rescue treatment, followed by an enema if needed.

Among patients randomized to either placebo or prucalopride 2 mg, the frequency of study withdrawal was < 15% in all trials; the frequency of withdrawal was similar between treatment groups, with the largest between-group difference observed in PRU-USA-11 (17% versus 13% for prucalopride 2 mg and placebo respectively).

In PRU-INT-6, PRU-USA-11, and PRU-USA-13, the proportion of patients reporting laxative or enema use in the last six months prior to study entry was 80% to 89%, and 80% to 84% of patients reported that these agents had not provided adequate relief. In study 3001, prior to study entry approximately 70% of patients reported previous laxative or enema use. Of those patients who reported prior use, 77% reported inadequate therapeutic effect.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: proportion of patients with three or more complete spontaneous bowel movements per week, bowel movement symptoms, patient global assessment, quality of life, and adverse events.

For all four RCTs, the primary outcome was the proportion of patients with an average of three or more complete spontaneous bowel movements per week.

Quality of life was assessed using the Patient Assessment of Constipation – Quality of Life (PAC-QOL) and the 36-item Short-Form Health Survey (SF-36). The PAC-QOL is a reliable, valid, and responsive measure of constipation. The minimal clinically important difference for the PAC-QOL ranges between 0.19 and 0.72, depending on the method of estimation.

Results

Based on the Health Canada-recommended dosing, the Committee focused their discussion on the results of patients randomized to prucalopride 2 mg, as described below.

Efficacy or Effectiveness

- In all trials, the percentage of patients reporting an average of three or more complete spontaneous bowel movements per week, during week one to 12, was statistically significantly greater for prucalopride groups (range 18% to 31%) compared with placebo groups (range 9% to 13%).
- In all trials, improvements in the PAC-QOL scores were statistically significantly greater for prucalopride compared with placebo at both weeks four and 12. Statistically significant differences in SF-36 scores favouring prucalopride were reported only for the physical component, and in only two of four trials.
- Compared with placebo, prucalopride-treated patients reported statistically significant improvements in straining, stool consistency, and sensation of complete evacuation in studies PRU-INT-6, PRU-USA-11, and PRU-USA-13, and improvement in sensation of complete evacuation in study 3001. In all trials, improvements from baseline in Patient Global Assessment of Severity of Constipation scores were statistically significantly greater for prucalopride compared with placebo. The clinical importance of these differences is uncertain.

Harms (Safety and Tolerability)

- There were no deaths reported in the trials nor were there any cardiovascular safety concerns. Adverse events were mostly associated with the gastrointestinal tract.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing prucalopride plus rescue medications (bisacodyl or an enema) with placebo plus rescue medications for the treatment of chronic idiopathic constipation in adult females in whom laxatives failed to provide adequate relief over a one-year time horizon. The model was based on patients transitioning between two health states, responder (≥ 3 complete spontaneous bowel movements per week) and non-responder, based on the results from PRU-INT-6, PRU-USA-11, and PRU-USA-13 for the female subpopulation. Utility scores were obtained by mapping PAC-QOL scores from the RCTs to EuroQol 5-Dimension values. The manufacturer reported that treatment with prucalopride is associated with an incremental cost per quality-adjusted life-year of $30,501 compared with placebo.

CDR noted the following limitations with the manufacturer's analysis: the clinical data used by the manufacturer did not fully represent the population modelled (in the pivotal RCTs, 22.6% of patients had not previously failed laxatives); results from the SF-36 captured in the clinical trials generally did not show improvements for prucalopride compared with placebo, suggesting quality of life may not be substantially improved; insufficient data sources and calculations were provided for CDR to verify the clinical inputs; the 1 mg dose of prucalopride was not included in the manufacturer's economic evaluation to reflect the treatment of patients > 65 years; and, the manufacturer assigned utility values that were treatment specific rather than reflective of the health states alone (i.e., responder, non-responder) in the base case. CDR was unable to evaluate the implications of some of these limitations on the model results.

At the recommended daily doses, the cost of prucalopride ranges from $2.15 (1 mg for adults > 65 years) to $3.30 (2 mg daily for adults ≤ 65 years). Most oral laxatives cost < $1 a day.

Patient Input Information:
The following is a summary of information provided by one patient group who responded to the CDR Call for Patient Input.

- Patients reported that chronic constipation is associated with constant discomfort, which may adversely affect a patient's quality of life.
- Patients suggested that current treatments may be insufficient for chronic constipation, have adverse events, or are not appropriate for long-term use. Patients are forced to alternate between various treatments with limited effectiveness.

Other Discussion Points:

- The Committee considered the clinical importance of the between-treatment differences in the PAC-QOL to be uncertain.

CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

June 20, 2012 Meeting

Regrets:
None

Conflicts of Interest:
None

About this Document:
CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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