Pharmacotherapeutic report, summary

Prucalopride (Resolor®) for the indication symptomatic treatment of chronic constipation in women who obtain insufficient relief with laxatives

Approved on 26 November 2012 by the Medicinal Products Reimbursement Committee (CFH)

Medicine. Prucalopride (Resolor®) 1 and 2 mg.

Registered indication. "The symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief".

Posology. 2 mg once daily.

Mechanism of action. Prucalopride is a selective serotonin-5-HT4-receptor agonist (dihydrobenzofurancarboxamide) with gastrointestinal prokinetic activity. Prucalopride stimulates proximal colonic motility enhances gastroduodenal motility and accelerates delayed gastric emptying. Furthermore, giant migrating contractions are induced by prucalopride.

Specific details. The safety and efficacy of prucalopride for use in men has not been established in controlled clinical studies.

The phase 3 studies with prucalopride were performed in 1998 and 1999. The delay in publishing the study results relates to prucalopride being transferred to a different pharmaceutical company (2003-2006) and to the extensive safety programme between 1999 and 2003. This extensive safety programme was probably necessary due to experience with the older 5-HT4-receptor agonist, cisapride. Cisapride (as well as tegaserod) is known for its ability to induce QT prolongation (see Unintended effects).

Summary of the therapeutic value

Intended effects. In three double-blind, randomised, placebo-controlled phase 3 studies of patients with chronic constipation, a significantly higher percentage of women treated with 2 mg prucalopride achieved the primary endpoint ≥3 SCBM/week (spontaneous complete bowel movement) in comparison with placebo (resp. 23.6% vs 11.3%; $p<0.001$). The most important secondary endpoint (increase of ≥1 SCBM/week) was also significantly improved in the 2 mg prucalopride group in comparison with placebo (resp. 43.1% vs 24.6%; $p<0.001$). Furthermore, the use of rescue medication was significantly reduced in patients treated with prucalopride. However, at baseline 15% of the patients had not used any laxatives and 17% were satisfied with their constipation therapy. These patients did not fulfil the registered indication. It is not clear whether the remaining patients (ca. 70%), who were constipated despite using laxatives, had received optimum treatment with the standard laxatives as cited in the NHG standard.

Unintended effects. The most frequently reported adverse reactions associated with treatment with prucalopride were headache, abdominal pain, nausea and diarrhoea. The side effects occur predominantly at the start of the treatment. The phase 3 studies with prucalopride indicate that the effect on the QT interval is negligible and that an increase in adverse reactions related to the secretion of prolactin has not been proven. However, there are insufficient long-term data to be able to detect these rare adverse reactions.

Experience. Experience with prucalopride is limited.

Applicability. Due to the lack of sufficient data involving men, prucalopride can only be used by women. Women of childbearing potential should use effective contraception during treatment with prucalopride.

Ease of use. The recommended dose of 2 mg prucalopride is administered orally once daily. The recommended dose for the elderly is 1 mg. Treatment should be reconsidered after 4 weeks.

Final conclusion. The data from the phase 3 studies indicate that, in chronically constipated patients, prucalopride normalises the frequency of defecation (≥3 spontaneous complete bowel movements/week) during 12 weeks. However, the use of prucalopride is registered for women in whom laxatives fail to provide adequate relief. It is not clear whether the patients included in the studies are refractory to optimum doses of the standard laxatives. For example, no data are available on the laxatives used, it is not clear whether different laxatives were used and/or whether the maximum doses of laxatives were given. On these grounds is concluded that the therapeutic value of prucalopride is lower for women in whom laxatives fail to provide adequate relief due to insufficient data on this group of patients. This conclusion is based in part on the observation that it is not clear whether the patients included in the phase 3 studies are refractory to optimum doses of the standard laxatives.