Prucalopride (Resolor): new treatment for chronic constipation

Steve Chaplin MSc, MRPharmS, *Paul Blaker* BSc, MRCP and *Mark Wilkinson* BSc, MD, FRCP

KEY POINTS

- prucalopride (Resolor) is a selective $5HT_4$ agonist licensed for the symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief
- available as 1 and 2mg tablets; 28=£38.69 (1mg), £59.52 (2mg)
- the recommended dose is 1-2mg once daily
- in clinical trials involving mostly women with chronic constipation, prucalopride approximately doubled the proportion averaging at least 3 complete spontaneous bowel movements per week over 12 weeks from 11 per cent with placebo to 24 per cent
- more patients rated prucalopride quite or extremely effective (33-39 per cent) than placebo (17-20 per cent)
- prucalopride was also associated with improvements in other objective measures of bowel function, patients' assessments of bowel function and constipation-related quality of life
- nonblinded extension studies suggest there may be no loss of efficacy after up to 18 months of treatment
- the commonest adverse events reported with prucalopride were headache, nausea, abdominal pain and diarrhoea
- prucalopride is a new therapeutic option in patients with constipation who have not responded to conventional treatment

Prucalopride (Resolor) is a new treatment for women with chronic constipation who have not responded to conventional laxatives. In our New products review, Steve Chaplin presents the data relating to its efficacy and adverse effects and Drs Paul Blaker and Mark Wilkinson comment on its place in the treatment of constipation.

Chronic constipation is associated with a diversity of long-term conditions and drug therapies, or it may be idiopathic.[1] Functionally, constipation may be attributed to difficulty in passing stools despite a normal colon transit time, abnormal anal sphincter or pelvic floor function, or slow colonic transit time associated with a reduction in high-amplitude peristaltic contractions.[1]

Management in adults is based on consensus opinion and clinical experience and involves relieving impaction, attention to diet and hydration and treatment with a laxative. The initial choice of laxative is a bulk-forming agent; this may be supplemented or replaced by an osmotic and/or a stimulant laxative.[2]

Chronic constipation is associated with some cases of irritable bowel syndrome, though diagnostic criteria distinguish between them.[3] National Institute for Health and Clinical Excellence (NICE) guidance recommends adjustment of lifestyle and diet, followed if necessary by treatment with a laxative other than lactulose.[4]

The technology

Prucalopride (Resolor) is a selective $5HT_4$ agonist licensed for the symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief. At the recommended dose of 1-2mg once daily, it increases intestinal motility and reduces colonic transit time; higher doses also accelerate stomach emptying and small intestine transit time.[5,6]

It is not licensed for use in men because 90 per cent of the participants in key clinical trials were women and there was evidence that

efficacy at the licensed dose was greater among women.[5]

Treatment should be initiated at a dose of 2mg per day (1mg per day in older patients); the maximum dose for patients with severe renal or hepatic impairment is 1mg per day. If there is no evidence of benefit after four weeks, treatment should be stopped.

Prucalopride is contraindicated in patients with intestinal obstruction, ileus or inflammatory bowel disease and should be use with caution in patients taking drugs that may prolong the QTc interval, *eg* erythromycin.

End-point	Number (%) of patients achieving end point		
	Placebo	2mg	4mg
≥3 SCBM*/week	73 (11.3)	151 (23.6)	158 (24.7)
≥1 SCBM*/week	155 (24.6)	264 (43.1)	279 (47.0)
≥1 PAC-QOL†	137 (22.2)	273 (44.0)	261 (43.3)

*spontaneous complete bowel movement
†patient assessment of constipation – quality of life scale

Table 1. Summary of intent-to-treat pooled analysis of 12-week end-points[5]

Clinical trials

Evidence for the efficacy of prucalopride comes from three clinical trials with identical design (n=620, 641, 713).[7-9] The eligibility criteria were age over 18 with a history of chronic constipation, defined as two or less spontaneous complete bowel movements per week for at least six months plus hard or very hard stools and, for at least 25 per cent of bowel movements, a sensation of incomplete evacuation or straining during bowel movements.

Patients were excluded if their constipation was secondary to drugs, endocrine, metabolic or neurological disorder, surgery or organic disorders of the large intestine.

Mean frequency of spontaneous complete bowel movements during a two-week run-in period was 0.4-0.5 per week.

All trials were placebo controlled and double blind. Patients (mean age 44-48) were randomised to 12 weeks' treatment with prucalopride 2 or 4mg per day or placebo. Rescue medication (bisacodyl followed by an enema if necessary) was allowed if a bowel movement did not occur for three consecutive days; no other laxative use was permitted.

There were no significant differences in efficacy between the 2mg and 4mg doses; only data for the 2mg dose are detailed. The proportions of patients discontinuing the trials were 11-16 per cent: this was due to adverse effects in 4-10 per cent with prucalopride 2mg and 2-7 per cent with placebo.

In a pooled analysis of the three trials, the proportion of patients averaging three or more spontaneous complete bowel movements per week over 12 weeks (the primary end-point) was 11.3 per cent with placebo and 23.6 per cent with prucalopride ($p<0.001$, see Table 1).[5] Long-term, uncontrolled non-blinded studies suggest there may be no reduction in efficacy for up to 18 months.[5]

The proportion of patients with an increase of at least one complete spontaneous bowel movement per week over 12 weeks was significantly increased from 25 per cent with placebo to 43 per cent with prucalopride 2mg per day (see Table 1).[5] The median number of days to first spontaneous complete bowel movement was 1.3-2.3 with prucalopride and 12-13 with placebo.

Prucalopride also significantly reduced use of rescue bisacodyl by 0.6-0.9 tablets per week, increased the proportion of bowel movements of normal consistency (by 17-23 *vs* 12-14 per cent with placebo) and reduced severe or very severe straining.[7-9]

After 12 weeks, more patients rated prucalopride quite or extremely effective (33-39 per cent) than placebo (17-20 per cent) and

reported a greater reduction in the severity of constipation.[7-9] Patient assessments favoured prucalopride for improvement in global, abdominal, rectal and stool symptoms. Scores for constipation-related quality of life were significantly improved by prucalopride (see Table 1) but there was no change in general health status.[7-9]

Adverse effects

Most patients in clinical trials of prucalopride, including those taking placebo, reported an adverse event. These were more frequently reported with prucalopride on the first day of treatment, after which differences from placebo were slight.[5]

The commonest adverse events after the first day were headache (11 per cent), nausea (9 per cent), abdominal pain (7 per cent) and diarrhoea (6 per cent).[5]

Other 5-HT agonists (such as cisapride) may prolong the QTc interval; there is no evidence that this occurs with prucalopride.[5] Palpitations may occur on the first two days of treatment but the incidence is low (1 *vs* 0.7 per cent with placebo) and more frequently associated with the (unlicensed) 4mg per day dose.

References

1. Lembo A, *et al. N Engl J Med* 2003; 349:1360-8.
2. Clinical Knowledge Summaries. *Chronic constipation in adults.* January 2008. http://cks.nhs.uk/constipation/management/detailed_answers/constipation_in_adults/treating_chronic_constipation).
3. Rome Foundation. *Rome III diagnostic criteria for functional gastrointestinal disorders.* www.romecriteria.org/assets/pdf/19_RomeIII_apA_885-898.pdf.
4. NICE. *Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care.* CG61. February 2008. www.nice.org.uk/nicemedia/pdf/CG061NICEGuideline.pdf.
5. European Medicines Agency. *Resolor European public assessment report.* November 2009. www.ema.europa.eu/humandocs/PDFs/EPAR/resolor/H-1012-en6.pdf.
6. Bouras EP, *et al. Gastroenterology* 2001;120:354-60.
7. Camilleri M, *et al. N Engl J Med* 2008;358:2344-54.
8. Quigley EM, *et al. Aliment Pharmacol Ther* 2009;29:315-28.
9. Tack J, *et al. Gut* 2009;58:357-65.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics

Place in therapy

Chronic constipation is a common disorder affecting up to 28 per cent of individuals.

In Western populations the pathophysiology is poorly understood and is likely to be multifactorial.[1] Accordingly, response to conventional laxatives is variable and often diminishes over time. Recent studies have suggested that constipation may be caused by abnormalities in the enteric nervous system, which has led to the development of novel therapeutic strategies that promote intestinal motility.[2]

Prucalopride is a selective high-affinity $5HT_4$ receptor agonist, resulting in a potent enterokinetic effect. Unlike other $5HT_4$ agonists such as cisapride and tegaserod it does not appear to have an unfavourable cardiovascular side-effect profile since it does not activate $5HT_{1B}$ receptors or the hERG channel.

Phase I and II trials have demonstrated that prucalopride significantly increases intestinal transit, improves the frequency of bowel movements and patients' satisfaction with defecatory function.[3,4]

In phase III trials mostly involving women with severe constipation, prucalopride 2-4mg once daily significantly increased the number of patients achieving at least three complete spontaneous bowel movements per week over a 12-week period in comparison to placebo and the effect was maintained for up to 24 months.[5]

It is currently licensed for the symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief of symptoms, at a recommended dose of 1-2mg daily.

While prucalopride provides a new therapeutic option in patients failing conventional treatment with osmotic and stimulant laxatives, it is not a panacea. Theoretically it is most likely to benefit those patients with normal and slow-transit constipation and prove much less effective for patients with pelvic dyssynergia.

Unfortunately, most clinical trials investigating constipation fail to discriminate between the different subtypes of constipation. Therefore further investigations are required to characterise the efficacy of prucalopride on different types of constipation, in addition to determining its long-term efficacy and safety.

References

1. Lembo A, *et al. NEJM* 2003;349: 1360-8.
2. Bassotti G, *et al. World J Gastroenterol* 2006;12:4609-13.
3. Camilleri M, *et al. NEJM* 2008;358: 2344-54.
4. Coremans G, *et al. Digestion* 2003;67:1347-56.
5. Frampton JE. *Drugs* 2009;69:2468-76.

Dr Blaker is a specialist registrar and Dr Wilkinson is consultant gastroenterologist at Guy's and St Thomas' Hospital NHS Trust, London