EXPERT REVIEWS

Prucalopride: a new drug for the treatment of chronic constipation

Expert Rev. Gastroenterol. Hepatol. 3(4), 337–343 (2009)

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Prucalopride belongs to a novel class of 5-hydroxytryptamine-4 receptor agonists, and has been evaluated extensively for the treatment of chronic constipation. Prucalopride has a stimulatory effect on gastrointestinal motility and transit, as established by *in vivo* and *in vitro* studies in animals and humans. Its therapeutic efficacy, tolerability and safety have been evaluated in Phase II and Phase III studies in chronic constipation. The cardiovascular safety profile of the drug was studied *in vitro* and *in vivo* in animal studies, in clinical studies in chronic constipation patients, as well as in specific additional clinical cardiovascular studies. Phase II studies identified a dose-dependent effect of prucalopride on bowel pattern and associated symptoms in chronic constipation. The Phase III studies mainly recruited patients with insufficient response to laxatives, and showed consistent efficacy and excellent tolerability for prucalopride.

Keywords: 5-hydroxytryptamine-4 • chronic constipation • efficacy • enterokinetic • prucalopride • receptor agonist • safety

Chronic constipation is a common disorder on a worldwide scale. Estimates of population prevalence range from 8.75% in the Asian Pacific region to 27% in Western countries [1,2]. Typical symptoms of constipation include infrequent bowel movements, hard stools and straining when passing stools. In addition, abdominal discomfort, bloating, cramps and pain are often associated, and complications, such as hemorrhoids and anal fissures, may occur [1,2]. According to the Rome III consensus, chronic constipation is defined as the presence of two or more diagnostic symptoms for at least 3 months, with symptom onset at least 6 months prior to diagnosis [3]. Chronic constipation is associated with an important impact on patients' quality of life [4,5]. A variety of treatment options are available for patients with chronic constipation, ranging from older over-the-counter laxatives to more recently developed prescription drugs [6,7]. In spite of these different treatment approaches, there remains a substantial unmet need in the treatment of chronic constipation [8].

A number of drugs targeting 5-hydroxytryptamine-4 (5-HT_4) receptors have been evaluated in the treatment of chronic constipation and irritable bowel syndrome with constipation [9–14]. However, none of these drugs are currently widely available, and some are withdrawn due to concerns regarding the risk–benefit profile. This review focuses on the pharmacology, efficacy and safety profile of prucalopride, a 5-HT_4 receptor agonist, which is currently under development for the treatment of chronic constipation.

Basic pharmacology

Prucalopride (R093877/R108512) is a 5-HT_4 receptor agonist that was developed by Janssen Pharmaceutica in the 1990s. Prucalopride is a dihydrobenzofurancarboxamide derivative and, therefore, belongs to a different chemical class than other 5-HT_4 receptor agonists, such as renzapride, mosapride, ATI-7505 and cisapride (substituted benzamides) or tegaserod (an aminoguanidine indole) [15].

Pharmacokinetics

Prucalopride is well absorbed from the GI tract, with an absolute bioavailability of 90% after oral administration. Doses up to 6 mg show dose-proportional linear pharmacokinetics. After repeated oral dosing of a 2-mg dose, a C_{max} of approximately 7.5 ng/ml is reached and the AUC 0–24 h is 109 ng•h/ml. The plasma terminal half-life is estimated to be 30 κ. The main route of elimination is via the urine (60–70% excreted

 10.1586/EGH.09.38 ISSN 1747-4124

unchanged in the urine) and the feces (10%). Prucalopride does not appear to inhibit liver enzymes in man and no cytochrome P450 3A4 drug interactions are anticipated [15].

Pharmacodynamics

Prucalopride is selective for 5-HT_4 receptors and, unlike previously marketed 5-HT_4 receptor agonists, has no affinity for other receptors or channels, except at concentrations far exceeding the plasma levels obtained at the therapeutic dose [15].

Preclinical motility studies

The pharmacokinetic and enterokinetic profile of prucalopride from animal studies provided support for the subsequent clinical development of the compound in patients with chronic constipation. Studies in the guinea-pig small intestine established that 5-HT_4 receptor agonists stimulate gastrointestinal motility through enhanced release of acetylcholine [16,17].

The *in vitro* pharmacological profile of prucalopride is consistent with selective 5-HT_4 receptor agonistic properties [18]. Binding studies show high affinity for the human 5-HT_4 receptor, with an affinity in the nanomolar range. Unlike previously marketed 5-HT_4 receptor agonists, affinities of prucalopride for other receptors, ion channels or transporters are low, yielding a 200-fold selectivity for the 5-HT_4 receptor [15,18]. The 5-HT_4 agonistic properties of prucalopride were confirmed in two classical *in vitro* preparations: prucalopride-induced contractions in the guinea-pig proximal colon (pEC_{50} = 7.5) and relaxation of the rat esophagus tunica muscularis preparation (pEC_{50} = 7.8), in a 5-HT_4 receptor antagonist-sensitive manner [18]. Electrophysiological studies of the myenteric plexus in the guinea-pig ileum confirmed enhancement by prucalopride of fast cholinergic neurotransmission [19].

Using canine and human colonic tissue, prucalopride has been shown to activate 5-HT_4 receptors on nerve and muscle cells in the colonic wall. In circular muscle strips from the dog rectum *in vitro*, prucalopride was found to induce a relaxation of the circular muscle through activation of 5-HT_4 receptors on smooth muscle cells [20]. Similar results were found for human colonic muscle strips *in vitro*, where 5-HT and prucalopride were shown to relax potassium chloride-precontracted circular muscle via a tetrodotoxin-resistant 5-HT_4 receptor-mediated pathway [21]. In circular muscle strips from the human colon, prucalopride enhanced acetylcholine release and contractions evoked by electrical stimulation, via a 5-HT_4 receptor on cholinergic nerves [22]. In longitudinal muscle strips from both the human and canine colon, prucalopride enhanced contractions evoked by electrical stimulation, through 5-HT_4 receptor-mediated enhancement of acetylcholine release from cholinergic nerves [23]. Taken together, these *in vitro* studies suggest that 5-HT_4 receptor agonism may facilitate colonic propulsion through a combination of inhibition of circumferential resistance and enhancement of circular muscle contractility. In keeping with this hypothesis, an extensive study of the influence of 5-HT_4 agonists, including prucalopride, on electrical field stimulation-induced responses in the human isolated colon found evidence for activation of both cholinergic and nitrergic pathways [24].

The effects of prucalopride on contractility of the upper GI tract have also been investigated. Prucalopride was found to enhance contractions evoked by electrical stimulation in the proximal and distal canine stomach *in vitro* through activation of 5-HT_4 receptors on cholinergic nerves [25]. Similar findings were made in longitudinal muscle strips from the proximal porcine stomach [26]. In studies with human proximal stomach circular-muscle strips, prucalopride significantly enhanced electrical stimulation-evoked contractions through 5-HT_4 receptor-mediated enhancement of acetylcholine release from cholinergic nerves [27].

In rats *in vivo*, administration of prucalopride dose-dependently enhanced the migration of charcoal, which was instilled intragastrically [28]. In a rat model of postoperative ileus, prucalopride was only able to enhance transit when combined with a 5-HT_4 receptor antagonist [29]. In an awake dog, administration of prucalopride stimulated high-amplitude clustered contractions in the proximal colon and inhibited contractile activity in the distal colon, both after oral or intravenous administration [30]. Prucalopride also induced giant migrating contractions, the motor pattern that precedes defecation. All effects were prevented by administration of a 5-HT_4 receptor antagonist [30].

Human motility studies

The effects of prucalopride on gastrointestinal motility were evaluated in a number of studies in healthy volunteers. In 17 male healthy subjects, a crossover study compared the effects of 1-week treatments of placebo, prucalopride 1 and 2 mg on orocecal transit evaluated by breath hydrogen, whole-gut transit evaluated by radio-opaque markers and anorectal function [31]. Prucalopride significantly increased the number of stools per week and the percentage of loose or watery stools. Both doses decreased orocecal and whole-gut transit times. Anorectal manometry and sensitivity to distention were not altered by prucalopride [31]. Transient headache occurred in seven of the subjects on prucalopride.

The effect of a 7-day treatment with different doses of prucalopride (0.5, 1, 2 or 4 mg) on gastrointestinal transit was studied by means of scintigraphy in 50 healthy volunteers [32]. Prucalopride did not significantly alter gastric emptying rate or small-bowel transit, but overall colonic transit was significantly and similarly enhanced by doses of 0.5, 2 and 4 mg. The 0.5- and 2-mg doses induced significant accelerations in overall colonic transit and proximal colon emptying half-time compared with placebo, while the 4-mg dose did not seem to provide significant incremental benefit [32].

In another healthy volunteer study, 24 subjects received 1-week treatment periods with placebo, prucalopride 1 or 2 mg, with evaluation of bowel habits, anorectal motility, colonic transit time using radio-opaque markers and safety assessment [33]. Both doses of prucalopride induced a significant a shortening of mean colonic transit time (35 κ after placebo vs 25 κ with prucalopride 1 mg and 43 κ with placebo vs 22 κ with prucalopride 2 mg; both $p < 0.05$). With the 2-mg dose, significant increases occurred in the number of stools (11.5 stools per week vs 7.1 with placebo; $p < 0.05$) and in the percentage of loose/watery stools (48 vs 12% with placebo; $p < 0.005$). Anorectal function was not affected by prucalopride, and there were no safety or tolerance issues [33].

The effects of 1-week treatment with placebo or prucalopride 4 mg on colonic motor function, evaluated by colonic manometry, was assessed in ten healthy volunteers in a crossover design [34]. Daily diaries confirmed that prucalopride increased stool frequency and decreased stool consistency and straining. The colonic manometry analysis revealed that prucalopride stimulated the occurrence of high-amplitude propagated contractions (6.0 vs 10.3 per 24 κ; p = 0.05) and increased segmental contractile activity (AUC: 23.418 vs 15.725 kPa*s; p < 0.05), motor patterns thought to underlie the altered stool pattern [34].

The effect of prucalopride on gastrointestinal transit was also evaluated in patients with chronic constipation. In a study by Bouras *et al.*, 40 patients with chronic constipation and without rectal evacuation disorder were randomized to receive placebo or prucalopride 2 or 4 mg daily for 7 days. Gastrointestinal and colonic transit times were measured by scintigraphy [35]. Prucalopride accelerated overall gastric emptying and small-bowel transit. The 4-mg dose significantly enhanced overall colonic transit and ascending colon emptying [35]. In another mechanistic study in chronic constipation, 28 patients with chronic constipation were treated for 2 weeks with placebo or prucalopride 1 or 2 mg in a crossover design, with evaluation of bowel habits, anorectal motility, colonic transit time using radio-opaque markers and safety assessment [36]. Significant increases in the number of bowel movements were seen with the 1-mg dose. Prucalopride did not alter anorectal manometry parameters [36].

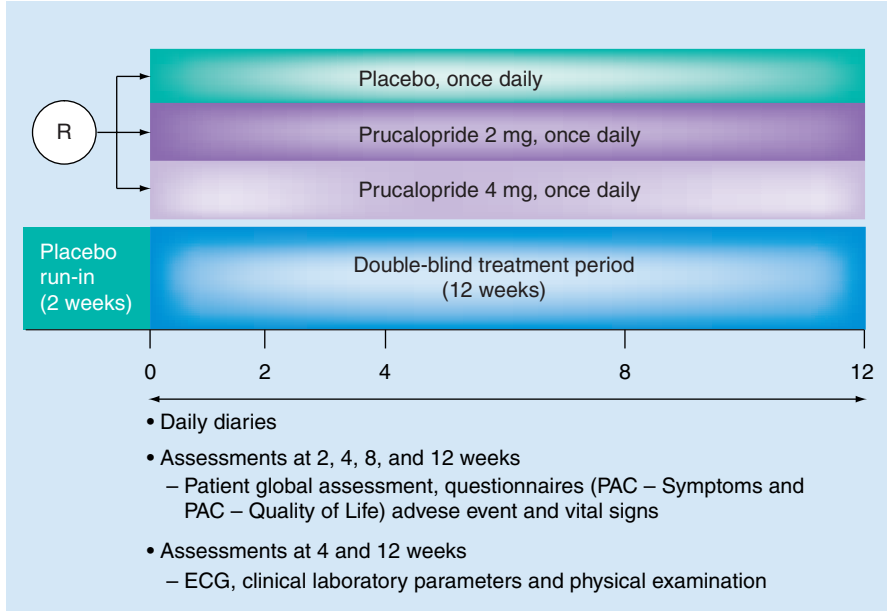

Figure 1. Outline of three pivotal clinical trials with prucalopride in chronic constipation.
PAC: Patients' Assessment of Constipation.

Cardiovascular safety studies

Owing to the cardiovascular risk associated with cisapride, a non-selective 5-HT_4 receptor agonist, potential cardiovascular effects of prucalopride received special attention. The arrhythmogenic potential of cisapride is caused by excessive action potential prolongation through inhibition of the human ether-à-gogo (hERG) K^+ channel. In a kidney cell line expressing the hERG channel, cisapride concentration dependently inhibited the hERG current in the nanomolar range (IC_{50}s ranging from 6.5 to 240 nM), while for prucalopride this only occurred in the micromolar range [37–41]. Effects on the hERG channel, therefore, are likely to occur at plasma levels reached with the recommended therapeutic dose, while prucalopride has this effect only at concentrations exceeding more than 50-times those reached with the recommended therapeutic dose. In a study on isolated atrial myocytes from patients undergoing cardiac surgery, prucalopride prolonged the early repolarization phase of the action potential, and this was attributed to a 5-HT_4 receptor-mediated increase in the L-type Ca^{2+} current [41]. Prucalopride had no significant effect on the late repolarization or refractory period, and was devoid of arrhythmic activity; even at concentrations markedly above those used therapeutically [41]. Moreover, in *in vitro* studies, 5-HT_4 receptor-mediated effects on atrial contractility desensitized rapidly, while gastric contractility in response to 5-HT_4 agonists did not show signs of desensitization [42].

In studies in healthy volunteers and patients, prucalopride at therapeutic concentrations had no significant effect on the QT interval [34,36]. The cardiovascular safety of prucalopride was further evaluated in a dose-escalation crossover study in 24 healthy volunteers receiving 2 weeks of placebo or prucalopride 2–20 mg daily [43]. A small and transient increase in mean heart rate occurred on the first days of treatment after prucalopride. No significant differences in QT interval occurred between any of the doses of prucalopride and placebo. No increases of QT interval above 500 ms occurred in the study; increases of QT with 30–60 ms occurred with similar frequency during placebo and prucalopride treatment, and increases of QT interval length of more than 60 ms were only seen after placebo. These data demonstrate safety of prucalopride from a cardiovascular perspective, even at supertherapeutic doses [44].

Clinical studies

Chronic idiopathic constipation

Prucalopride was mainly investigated in the treatment of patients with chronic constipation. Mechanistic studies confirmed the ability of prucalopride to enhance transit times and to improve stool pattern in patients with chronic constipation [35,36]. A placebo-controlled study in 53 patients with chronic constipation in whom laxatives fail to provide adequate relief, showed that 4 weeks of treatment with prucalopride 4 mg was superior to placebo in decreasing stool consistency, straining and time to first bowel movement [45].

Three pivotal studies of similar design evaluated the efficacy of prucalopride at 2- and 4-mg doses in patients with chronic constipation (Figure 1) [46–49]. After a 2-week run-in period, patients were randomized to 12 weeks treatment with placebo or prucalopride 2 or 4 mg daily. Stool pattern was recorded in daily diaries, while questionnaires assessing constipation symptom severity and quality of life impact were filled out at baseline and at 2–4-week intervals during the studies. The daily diaries recorded the presence and number of stools, and whether or not they were spontaneous (absence of rescue therapy laxatives during the preceding 24 κ) or complete (associated with a sense of complete evacuation). Rescue therapy consisted of bisacodyl tablets to be taken after 3 days without spontaneous bowel movement. Responders were patients with three or more spontaneous complete bowel movements (SCBMs) per week, a stringent end point that restores stool pattern to within the normal range. The primary efficacy variable in the studies was the percentage of patients with three or more SCBMs per week over 12 weeks. Secondary end points included the proportion of patients with an increase of one or more SCBM per week, as well as the number of bowel movements, stool consistency and severity of straining on daily diaries. In addition, validated disease-specific questionnaires were used to assess symptom severity (using the Patient's Assessment of Constipation – Symptoms [PAC-SYM] questionnaire) and quality of life (using the PAC – Quality of Life [PAC-QOL] questionnaire) [49,50]. Patients aged older than 18 years were eligible if they had a history of chronic constipation according to a modified Rome II definition: less or equal to two SCBMs per week for a minimum of 6 months, with at least one of three symptoms (i.e., very hard or hard stools, sensation of incomplete evacuation and straining) for at least a quarter of the stools [51]. Due to the identical design, the studies can be pooled for analysis.

All three studies showed efficacy of both doses of prucalopride over placebo in achieving the primary end point (average ≥ three SCBMs per week over 12 weeks), with no significant difference between the 2- and 4-mg doses (Figure 2) [52]. Similar results were obtained for the secondary end point of increase of greater than or equal to one SCBM per week (Figure 2) [52]. Both doses of prucalopride were superior to placebo in improving PAC-SYM (all domains significantly better compared with placebo) and PAC-QOL scores (all domains significantly better compared with placebo) [46–48].

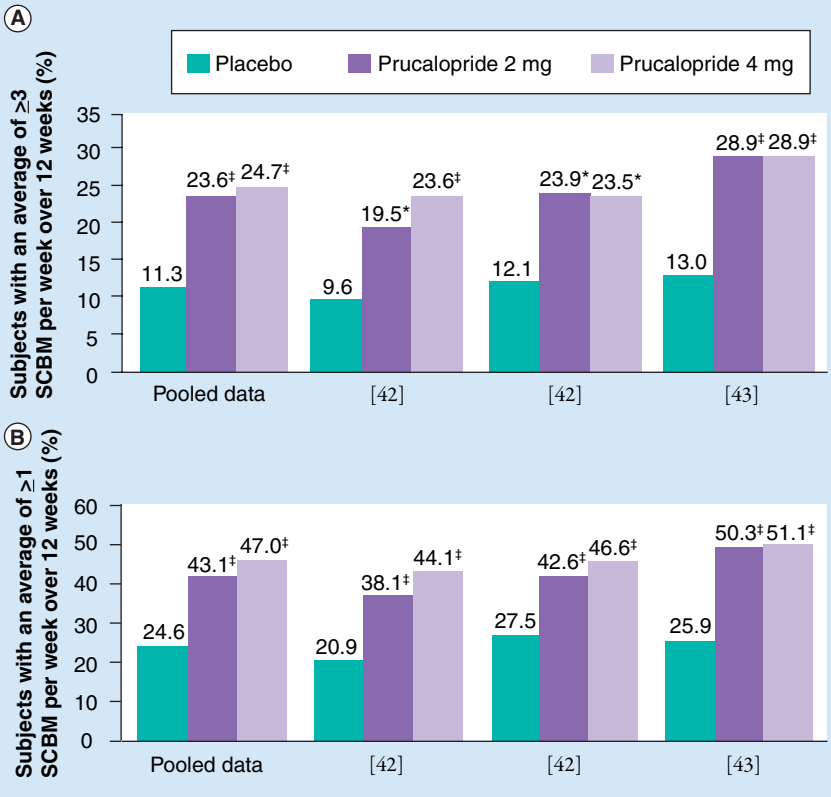

Figure 2. Summary of results of pivotal clinical trials with prucalopride in chronic constipation. (A) Responder rate for the primary end point (average ≥ three spontaneous complete bowel movements per week over 12 weeks) with placebo or prucalopride 2 or 4 mg daily in the pooled analysis and in each of the clinical trials. **(B)** Responder rate for the secondary end point (average increase of ≥ one spontaneous complete bowel movements per week over 12 weeks) with placebo or prucalopride 2 or 4 mg daily in the pooled analysis and in each of the clinical trials.
*$p < 0.01$ vs placebo.
‡$p < 0.001$ vs placebo.

The efficacy of prucalopride in chronic constipation was also studied in a cohort of elderly patients with constipation. In total, 300 patients with no more than two SCBMs per week and aged over 65 years were randomized to placebo or prucalopride 1, 2 or 4 mg daily for 4 weeks. Patients had a mean age of 76 years and a long-standing history of constipation not adequately relieved by laxatives in 80%. All doses of prucalopride were significantly more efficacious than placebo in increasing the number of SCBMs with at least one per week, or in increasing the weekly average number of SCBMs. Most PAC-QOL scores improved significantly more with prucalopride than with placebo. No changes in laboratory, cardiovascular and ECG variables occurred with prucalopride [53].

Other motility disorders

Prucalopride was also investigated in a number of conditions that are associated with constipation or intestinal hypomotility. A dose-escalation study was performed in 23 patients with constipation due to spinal cord injury [54]. Both 1- and 2-mg doses of pruclaopide significantly improved constipation severity ratings. The 2-mg dose showed

a significant improvement in the number of bowel movements and reduced colonic transit time measured by means of radio-opaque markers [54].

In two patients with scleroderma and impaired intestinal motility, treatment with prucalopride 2 mg improved symptoms of constipation and abdominal distention, and this was associated with increased intestinal motor activity as assessed by antroduodenal manometry [43]. These case observations suggest a potential for prucalopride in the treatment of generalized motor disorders.

Subcutaneous administration of prucalopride to shorten postoperative ileus was evaluated in 317 patients undergoing elective partial colectomies. Compared with placebo, subcutaneous administration of prucalopride 0.5, 2 or 4 mg for 3 days postoperatively shortened median time to first flatus or stool and tended to shorten hospital stay. The 4-mg dose was statistically significantly better than placebo in shortening time to first flatus or stool guinea-pig [55]. These observations suggest a potential for prucalopride in the treatment of postoperative ileus.

Safety & tolerability

The safety and tolerability of prucalopride, as assessed in the three pivotal trials, was pooled, allowing evaluation of 1924 patients [46–48,56]. No clinically relevant differences occurred in vital signs, laboratory parameters. There was a higher incidence during prucalopride compared with placebo for headache, nausea, diarrhea and abdominal pain (2.7–4.7% for placebo vs 5.1–11.8% for 2 mg and 6.1–16% for 4 mg). However, this higher incidence was only present on the day 1 of treatment, and analysis of the whole treatment period, excluding day 1, did not show any differences in adverse event profile between prucalopride and placebo. The only serious adverse event was an abdominoplasty in two patients in the 4-mg group, unrelated to drug intake [56].

In an extension study of 693 patients who participated in one of the pivotal trials, patients received prucalopride 2-mg tablets and could use a maximum of 4 mg daily for up to 24 months. Median study duration was 14 months. The most frequent adverse events were headache, diarrhea, abdominal pain and vomiting. Serious adverse events included two deaths and surgical interventions, considered not or doubtfully drug related, and one case of abdominal pain, which was possibly drug related. No clinically relevant changes in safety parameters occurred. This long-term open-label study confirms sustained safety of prucalopride. Moreover, patient satisfaction with bowel function, assessed by the PAC-QOL scale, was maintained during the entire treatment period [57].

Conclusion

Prucalopride is effective in the treatment of chronic constipation. Mechanistic studies have shown stimulation of gastrointestinal motor activity, reduced colonic transit times, increased stool frequency, softer stools and decreased straining. The safety profile of the drug, reported from extensive clinical and cardiovascular trials to date, has been excellent. In particular, prucalopride seems devoid of cardiac side effects seen with cisapride both in animal and human studies. The drug may have potential for treatment of other gastrointestinal motility disorders.

Expert commentary

The potential of 5-HT_4 agonists to enhance colonic motility and to provide symptom relief in chronic constipation has been well established over the last decade, based on studies with tegaserod, renzapride, TD5108 and prucalopride. However, the safety profile of these drugs remains an area of controversy, mainly due to the cardiovascular side effects associated with the use of cisapride, and with a suggested increased prevalence of cardiovascular adverse events associated with the use of tegaserod. Thus, development of 5-HT_4 receptor agonists for gastrointestinal motility disorders faces a major challenge in demonstrating efficacy in the absence of clinically relevant adverse events.

The prucalopride development program pioneered this field, as studies in fact antedated the development of tegaserod and showed convincing and consisting of evidence of efficacy in chronic constipation. This is evident from the impact on primary (e.g., number of complete spontaneous bowel movements) as well as secondary (e.g., abdominal symptoms and PAC-SYM questionnaire) end points and quality of life (e.g., PAC-QOL questionnaire) in three identical Phase III trials. The delay in the development program of prucalopride is mainly attributable to transfer of commercial rights from Johnson&Johnson, the company that originally developed prucalopride, to Movetis, the company that is currently submitting the compound for review by the EMEA and Swissmedic. According to the company website, intellectual property protection is assured until 2020 [101].

The safety and tolerability profile of prucalopride has been reassuring throughout the Phase II and III study programme. This is also true for cardiovascular safety, in spite of some challenging studies, including dosing up to ten-times the therapeutic dose, and a clinical trial in elderly patients with chronic constipation.

Five-year view

The use of prucalopride for the treatment of chronic constipation is currently under evaluation by regulatory authorities. Based on the efficacy and safety profile, prucalopride has the potential to resolve a major part of the unmet needs in the treatment of chronic constipation. Additional studies to explore the potential of prucalopride in other disorders of gastrointestinal motility are warranted, given the lack of effective drugs in this therapeutic area and the motor effects of prucalopride, which are not limited to the colon.

Key issues

- Prucalopride is a selective 5-hydroxytryptamine-4 receptor agonist of a novel chemical class.
- The drug stimulates intestinal and colonic transit.
- Three Phase III studies established efficacy of prucalopride 2 mg in patients with chronic constipation.
- The majority of patients in these studies were dissatisfied with laxatives.
- Safety studies showed no effect of prucalopride on QT interval and other cardiovascular parameters.
- Prucalopride was well tolerated in short- and long-term studies.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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