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REVIEW

Role of prucalopride, a serotonin (5-HT$_4$) receptor agonist, for the treatment of chronic constipation

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Abstract: Constipation affects up to a quarter of the population in developed countries and is associated with poor quality of life and significant economic burden. Many patients with chronic constipation are dissatisfied with current therapy due to lack of long-term efficacy or side effects. Previous nonselective 5-hydroxytryptamine receptor 4 (5-HT$_4$) agonists have been associated with significant interactions with other receptors (5-HT$_{1B}$, 5-HT$_{1D}$, and 5-HT$_{2B}$ for tegaserod; hERG for cisapride), leading to adverse cardiovascular events resulting in withdrawal of these drugs from the market. Prucalopride is a novel gastrointestinal prokinetic agent. It acts as a high affinity, highly-selective 5-HT$_4$ agonist. Its efficacy in patients with chronic constipation has been demonstrated in several phase II and phase III clinical trials showing significant improvements in bowel transit, bowel function, gastrointestinal symptoms, and quality of life, with benefit maintained for up to 24 months in open label, multicenter, follow-up studies. Prucalopride's high selectivity for the 5-HT$_4$ receptor may explain its favorable safety and tolerability profiles, even in elderly subjects with stable cardiovascular disease. Prucalopride is a well tolerated and efficacious prokinetic medication that should enhance the treatment of chronic constipation unresponsive to first-line treatments.

Keywords: prucalopride, 5-HT$_4$ agonist, serotonin agonist, efficacy, prokinetic

Introduction

Constipation is a common, often chronic, gastrointestinal disorder with higher prevalence in women and the elderly.[1] The Rome III Committee on Functional GI Disorders[2] set criteria for the diagnosis of chronic constipation which include a description of chronicity (for the last 3 months with symptoms and an onset at least 6 months prior) and symptoms (2 or more of which must be present at least 25% of defecations). These symptoms include: fewer than 3 bowel movements per week, hard or lumpy stools, straining with defecation, a sensation of incomplete evacuation, a sensation of anorectal obstruction or blockage, and use of maneuvers to assist defecation.[2] It affects 10% to 15% of the population in developed countries,[3,4] and up to 27% of North Americans.[5] In a survey of almost 14,000 persons, of whom 12% reported constipation, over half experienced symptoms for three or more years.[4] In the United States (US), constipation results in 92,000 hospitalizations and more than 2.5 million physician visits per year; these figures may be rising with time.[1,6]

Chronic constipation compromises health-related quality of life (HR-QOL) proportionately to symptom severity.[3,7,8] It is also associated with significant economic impact, directly from medical evaluation and treatment including the problem of self medication and adherence to therapy, as well as indirectly from absenteeism. Thus, chronic constipation is a significant public health problem.[3,9]

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Constipation can be classified by three major categories based on pathophysiology: normal transit constipation, slow transit constipation, and defecatory disorder.[10]

Overview of standard therapies, development of new agents

Treatment for constipation is often guided by the severity of symptoms and the underlying pathophysiology. Lifestyle changes such as increasing oral fluid intake and regular exercise do not appear efficacious in alleviating chronic constipation, except in cases of dehydration.[11,12] Other therapeutic approaches for chronic constipation include fiber intake (20 to 25 g daily via diet or with fiber supplements), osmotic laxatives (such as polyethylene glycol, milk of magnesia, lactulose, or sorbitol), stimulant laxatives (such as bisacodyl or senna derivatives), secretory agents (such as lubiprostone),[13,14] and prokinetic drugs (such as cisapride and tegaserod, which are no longer easily available in most countries).

The nonselective 5-hydroxytryptamine receptor 4 (5-HT_4) receptor agonists, cisapride and tegaserod, promote intestinal motility and relieve constipation,[15–17] but their lack of selectivity for the 5-HT_4 receptor may account for adverse cardiovascular events, resulting in their restricted availability.[18] Tegaserod is an agonist at 5-HT_{1B} and 5-HT_{1D} receptors and an antagonist at 5-HT_{2B} receptors within the range of concentrations used for treatment of constipation. These nonselective interactions may explain the association of tegaserod with rare instances of ischemic adverse events, including stroke and angina.[18] Cisapride inhibits the human ether-à-go-go related gene (hERG) potassium channel at therapeutic concentrations. This can lead to cardiac electrophysiologic derangements including QT prolongation, torsade de pointes, ventricular tachycardia, and ventricular fibrillation, particularly in patients with underlying cardiovascular diseases or the concurrent use of a medication that inhibits metabolism of cisapride.[18,19]

Biofeedback retraining is essential for outlet dysfunction resulting in chronic constipation. Intractable cases of severe slow transit constipation associated with colonic inertia may require colectomy with ileorectostomy.[10]

Despite their widespread use, evidence of long-term clinical efficacy for laxative medications is lacking.[20–22] Patient dissatisfaction with current laxative treatment is high, with lack of efficacy reported by 82% and concerns about side effects in 16% of constipated subjects in a US based survey.[8]

New pharmacotherapeutic approaches for treatment of chronic constipation include guanylate cyclase C agonists (eg, linaclotide),[23,24] neurotrophins (eg, NT-3),[25,26] and serotonergic agents, predominantly 5-HT_4 receptor agonists, with enterokinetic properties. This class of compounds includes prucalopride, velusetrag, and ATI-7505. Of these, the agent with the largest clinical trial evidence of efficacy is prucalopride.

Pharmacology and mode of action of prucalopride

Prucalopride (previously known as R093877 and R108512) is a dihydro-benzofurancarboxamide derivative, with a different structure relative to older serotonergic gastrointestinal prokinetics such as cisapride (a substituted benzamide derivative) and tegaserod (an aminoguanidine indole derivative). Prucalopride is a highly selective agonist and has high affinity for 5-HT_4 receptors promoting cholinergic and nonadrenergic, noncholinergic neurotransmission by enteric neurons. Prucalopride displays high affinity binding to human 5-HT_{4a} and 5-HT_{4b} receptor isoforms with pK_i values of 8.6 and 8.1, respectively.[27] Prucalopride also displays very high specificity for the 5-HT_4 receptor isoforms, with a greater than 290-fold selectivity for 5-HT_4 receptor isoforms than for the only three other receptors showing measurable affinity to prucalopride (human dopamine D_4 receptor with pK_i of 5.63, mouse 5-HT_3 receptor with pK_i of 5.41, and human σ_1 receptor with pK_i of 5.43).[27] Agonist binding to the G protein-coupled 5-HT_4 receptor activates adenylate cyclase and increases intracellular cyclic adenosine monophosphate (AMP) levels.[28]

Specific activation of the 5-HT_4 receptors that are present in the range quantities in the gastrointestinal tract promotes gastrointestinal motility and mucosal secretion.[28] Gastrointestinal motility stimulation has been demonstrated in several experimental models *in vitro* and *in vivo*. In isolated guinea pig colon, prucalopride induced dose-dependent, nonadrenergic, noncholinergic contractions ($pEC_{50} = 7.48 \pm 0.06$).[27] Selectivity for the 5-HT_4 receptor was confirmed via inhibition by a selective 5-HT_4 antagonist (GR113808), but lack of inhibition by 5-HT_{2A} (ketanserin) and 5-HT_3 antagonists (granisetron).[27] Prucalopride also stimulated contractions in the stomach (in rat and dog) and colon (in dog and human) ($pEC_{50} = 7.50 \pm 0.08$), but mediated relaxation of the esophagus (in rat) ($pEC_{50} = 7.81 \pm 0.17$) in a manner sensitive to 5-HT_4 receptor antagonism.[27]

Prucalopride stimulated contractions in colonic longitudinal smooth muscles by promoting acetylcholine release via activation of 5-HT_4 receptors on presynaptic, cholinergic enteric neurons.[29] Prucalopride also induced relaxation of human

colonic and canine rectal circular smooth muscles through local 5-HT_4 receptor activation.[29,30] Therefore, 5-HT_4 agonists facilitate gastrointestinal motility by promoting longitudinal smooth muscle contractility while suppressing the resistance to propulsion due to circular smooth muscle contraction.

Prucalopride's *in vivo* effects in the canine colon suggest a coordinated, region-specific mechanism, whereby longitudinal smooth muscles demonstrate increased contractile activity in the proximal colon, but reduced contractility in the distal colon.[31] In addition, circular smooth muscle relaxation is negligible in the proximal colon, but increasingly more pronounced towards the distal colon with prucalopride treatment.[30] In conscious, fasted dogs, prucalopride also induces colonic giant migrating contractions (GMC) that propagate along the entire length of the colon to facilitate propulsion of luminal contents.[31] GMC are the canine equivalent to human high amplitude propagated contractions (HAPC). A reduction of HAPC is observed in patients with idiopathic constipation.[32]

Prucalopride, given intravenously at a dosage of 1 to 2 mg/kg in fasted rats, increased whole gut transit of activated charcoal, mainly by increasing colonic transit, and without affecting gastric or proximal small bowel transit.[33] On the other hand, in dogs, prucalopride dose-dependently promotes gastric contractility[34] and accelerates gastric emptying.[35]

Pharmacokinetics of prucalopride

Prucalopride is rapidly and extensively absorbed from the gastrointestinal tract after oral dosing. Peak plasma concentration of 4.34 ng/mL (mean) was achieved in 2.1 hours after a single 2 mg dose in 14 healthy adult subjects.[36] Absolute oral bioavailability of prucalopride exceeds 93% and is not affected by food intake.[36] Prucalopride displays linear pharmacokinetics with exposure to drug, increasing proportionally with increasing dosage over the dose range 1 to 20 mg daily.[36] Plasma protein binding is low at 28% to 33%.[36] Extensive distribution is reflected in a steady state volume of distribution of 567 L.[36]

Prucalopride undergoes limited metabolism in the human body. Only small amounts of its metabolites are found in the urine and feces, with the major metabolite accounting for less than 4% of the dose.[37] Unchanged prucalopride accounts for about 85% of the plasma radioactivity after administration of radiolabeled drug in an oral dose study.[37] The drug is excreted largely unchanged, with about 60% of the administered dose excreted in urine by active secretion and passive filtration and greater than 6% appearing in the feces.[36] The elimination half-life of prucalopride of between 24 and 30 hours supports once daily dosing.[37]

Age, gender, body weight, and race have no influence on pharmacokinetics. Plasma prucalopride concentrations are nearly 30% higher in the elderly due to age-related decline in renal function. Therefore, a reduction of the dosage to half the normal adult dosage is recommended for elderly patients and for patients with severe renal insufficiency (creatinine clearance less than 25 mL/min).[37] Given the relatively low level of metabolism by the liver, hepatic impairment is unlikely to alter prucalopride pharmacokinetics significantly. Halving the normal adult dosage is recommended for patients with severe liver dysfunction.[37]

Prucalopride has a low potential for drug-drug interactions due to lack of significant metabolism by the cytochrome P450 system at therapeutic concentrations and due to lack of extensive binding to plasma protein.

Efficacy studies

Pharmacodynamics in humans

In healthy volunteers, placebo-controlled pharmacodynamic studies showed that prucalopride treatment for 1 week accelerated colonic transit at 0.5, 1, 2, and 4 mg/day,[38,39] orocecal transit at 1 mg/day,[40] and whole gut transit at 1 and 2 mg/day.[40] An increase in stool frequency and a loosening of stool consistency were also documented.[38–41] There was no rebound effect on bowel function after discontinuation of drug.[40] Prucalopride's effects on gastrointestinal transit and bowel function in healthy men were comparable to those observed in healthy women in a trial that enrolled an equal number of male and female healthy volunteers.[39] In addition, a study conducted exclusively in males provided results similar to those of trials that enrolled mostly females.[40]

In patients with chronic constipation in whom an evacuation disorder was excluded (Figure 1), prucalopride therapy at 4 mg/day for 1 week[42] or at 1 mg/day for 4 weeks[43] accelerated gastric emptying half-time,[42] ascending colon emptying half-time,[42] overall colonic transit,[42] orocecal transit time,[42,43] and whole gut transit.[43] Prucalopride-induced acceleration of colonic transit was also associated with increased stool frequency and loosening of stool consistency in patients with chronic constipation.[43,45] Prucalopride exhibited dose responsiveness in effects on gastrointestinal transit and bowel functions.[43,44]

Therapeutic efficacy

Phase IIB studies

Phase IIB clinical trials assessing prucalopride's efficacy in chronic constipation were conducted for up to 4 weeks with dosage ranging from 0.5 to 4 mg/day.[45–48] The primary

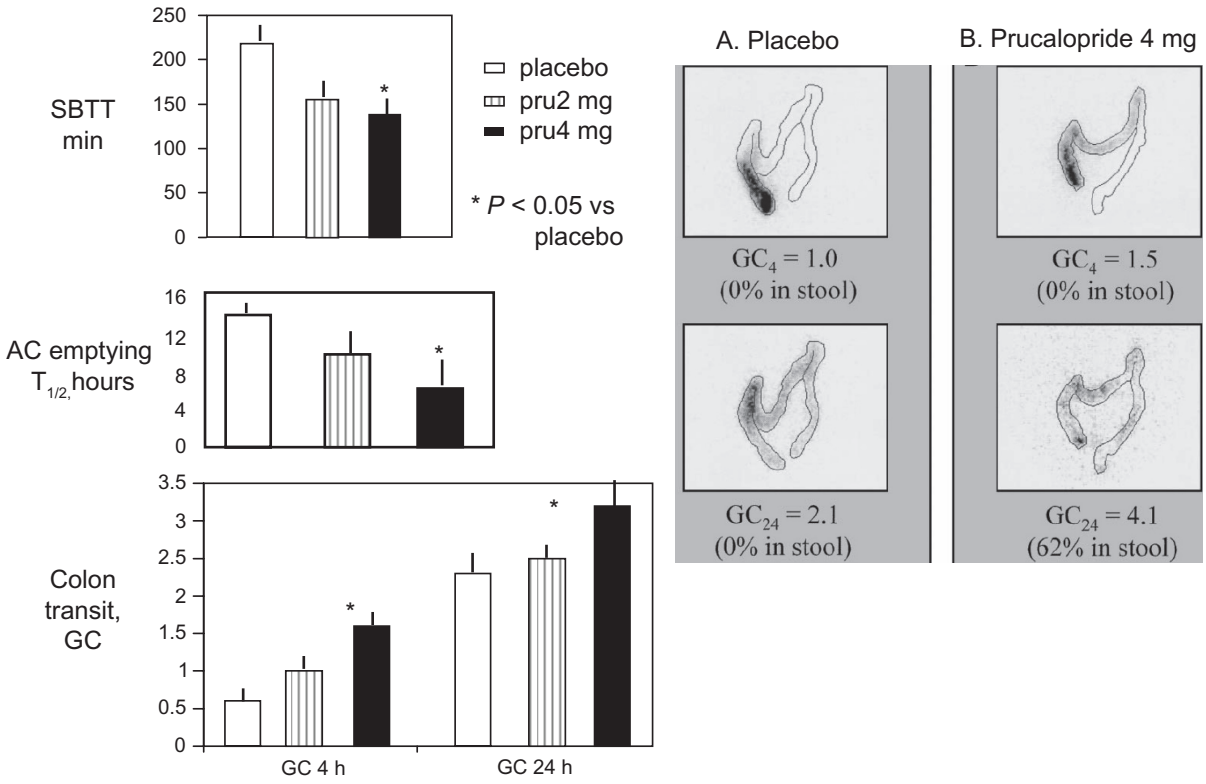

Figure 1 Effect of prucalopride on small bowel and colonic transit.

Notes: Right panel: Two sets of scintigraphic images obtained from 2 study objects: **A**) one receiving placebo and **B**) the other 4 mg of prucalopride. Top images are 4-hour scans and bottom images are 24-hour scans for each individual. Prucalopride accelerates movement of the radioisotope through the colon both at 4 and 24 hours in comparison with placebo. A higher GC value implies more rapid colonic transit, with a value of 4.1 implying that most of the isotope has already been excreted. Left panel: Summary data from groups of patients treated with placebo or prucalopride 2 or 4 mg/day. The histograms show the acceleration of small bowel and ascending colon transit.

*$P < 0.05$ vs placebo treatment..

Reprinted from Bouras EP, Camilleri M, Burton DD, et al. Prucalopride accelerates GI and colonic transit in patients with constipation without a rectal evacuation disorder. *Gastroenterology*. 2001;120:354–360.[76]

Abbreviations: GC, geometric center at 4 (GC 4 h) and 24 (GC 24 h) hours; SBTT, small bowel transit time; AC, ascending colon; pru, prucalopride.

endpoint of ≥3 spontaneous, complete bowel movements per week (SCBM/w) is thought to reflect clinical response, since consensus criteria show that healthy people have 3 bowel movements per week. This endpoint was achieved in ~32% and 55% for patients on 2 mg/day and 4 mg/day, respectively.[46,47] Another endpoint of significant clinical relevance to patients is the ability to have spontaneous bowel movements (SBM). SBM per week (SBM/w) were increased 1.8- to 3.5-fold with prucalopride relative to placebo.[44,45,49] Prucalopride also ameliorated a number of secondary endpoints: frequency of straining during bowel movements, stool consistency, subjective sense of constipation, and time to first bowel movement.[49] In children aged 4 to 12 years, prucalopride decreased number of days with hard stools or without stools and increased average number of days with bowel movements.[50]

Studies conducted in subgroups of patients with secondary constipation suggest prucalopride is also efficacious:

a. In opioid-induced constipation, ~36% of prucalopride-treated patients had an increase of one or more SMB/w, compared to 23% for patients on placebo.[51]
b. In patients with spinal cord injury, prucalopride (2 mg/day) increased number of bowel movements per week (BM/w) and reduced colonic transit relative to placebo without affecting stool consistency.[52]
c. In patients with multiple sclerosis and constipation, prucalopride (1 to 2 mg/day) decreased time to first BM and severity of constipation, and increased number of BM/w by ≥1 in 57% of patients on prucalopride compared to 25% placebo. This led to a decrease in the need for laxatives.[53]

Phase III studies

The clinical efficacy of prucalopride is best demonstrated by the three pivotal phase III clinical trials conducted in the treatment of chronic constipation in patients not experiencing symptomatic relief with laxatives (Table 1).[54–56] The trials had virtually identical design (2-week run-in, 12 weeks on treatment), doses (placebo, prucalopride 2 and 4 mg) and primary outcome measurements (percentage of patients achieving ≥3 SCBM/w over the 12-week treatment period) in patients with chronic constipation (based on self report

Table 1 Pivotal phase III trials of prucalopride in patients with chronic constipation who are dissatisfied with current laxative treatment

Trial	N	Primary endpoint average ≥3 SCBM/w (%)			Main secondary endpoint average ↑ ≥1 SCBM/w (%)			Secondary endpoint average increase BM/w			Symptoms Δ PAC-SYM at w 12			QoL ↓ ≥1 on PAC-QoL at w 12 (%)		
		Placebo	2 mg	4 mg	Placebo	2 mg	4 mg	Placebo	2 mg	4 mg	Placebo	2 mg	4 mg	Placebo	2 mg	4 mg
Camilleri[54]	620	12.0	30.9†	28.4†	25.8	47.3†	46.6†	0.8	2.2†	2.5†	–0.4	–0.6†	–0.7†	24.1	44.9†	48.7†
Quigley [55]	641	12.1	23.9**	23.5**	27.5	42.6†	46.6†	0.8	1.5†	1.5†	–0.5	–0.8†	–0.6*	26.0	43.5†	44.4†
Tack [56]	713	9.6	19.5**	23.6†	20.9	38.1†	44.1†	0.5	1.2†	1.4†	–0.4	–0.7†	–0.7†	16.4	33.5†	29.4†

Notes: For comparison with placebo: *$P < 0.05$, **$P < 0.01$, †$P < 0.001$.

Abbreviations: SCBM/w, spontaneous, complete bowel movements per week; BM/w, bowel movements per week; PAC-SYM, patient assessment of constipation symptoms; QoL, quality of life; PAC-QoL, patient assessment of constipation quality of life.

of <2 SCBM/w for 6 or more months,[54] averaged over 12 weeks,[55] and for a minimum of 2 weeks,[56] respectively). Patients were required to have hard or lumpy stool, as well as straining on defecation and a sensation of incomplete evacuation during ≥25% of BM. Secondary constipation was excluded.

Efficacy endpoints were derived from daily diaries of bowel habits, the Patient Assessment of Constipation Symptoms (PAC-SYM),[57] and the Patient Assessment of Constipation Quality of Life (PAC-QOL).[58] Compared to 11% of the placebo group, 23.6% (2 mg/day) and 24.7% (4 mg/day) of patients achieved the primary endpoint (≥3 SCBM/w), which reflects normalization of bowel function.[54]

Prucalopride was also effective in significantly improving secondary endpoints, such as proportion of patients achieving an increase of ≥1 SCBM/w over the 12 weeks of therapy relative to baseline, the average number of SCBM/w, stool consistency, time to first SCBM, sensation of incomplete evacuation, need for rescue medication, patient-rated satisfaction, overall PAC-SYM score, and overall treatment effectiveness.[54–56]

Efficacy of prucalopride in retreatment was shown during a second 4-week treatment period compared to the first 4-week period: retreatment was associated with improved bowel function and associated patient-reported symptoms.[59]

There are no reported direct comparative studies of prucalopride with other colonic prokinetics or secretagogues. The data from clinical trials regarding the average increase in number of BM/w with prucalopride suggest that it may be more efficacious (+1.4–1.8 SCBM/w)[54] relative to the mean number of BM/w on placebo when compared to tegaserod (+1.3 BM/w) and renzapride (+0.2 BM/d), and similar to the efficacy of cisapride (+1.9 SBM/w) and bulk laxatives (+1–2 BM/w).[60–63]

In open label, long-term, follow-up studies, continuation of prucalopride for a median of about 1 year and a range of up to 24 months was associated with sustained patient satisfaction with bowel function which was documented every 3 months for up to 18 or 24 months.[64,65] There was also overall satisfaction with treatment.

Safety and tolerability

Prucalopride's high selectivity at therapeutic dosages minimizes interactions with other receptors that may lead to serious adverse events.[18] It is eliminated from the human body without extensive metabolism, thus reducing potential for drug–drug interactions with medications that affect hepatic or renal metabolism and clearance.[36]

Cardiac safety

Since the report of 341 cases of cisapride-related, serious cardiac arrhythmias in 2000,[66] extensive cardiac monitoring, in particular the duration of the QTc interval, has been mandated for development of 5-HT_4 receptor agonists, as there are 5-HT_4 receptors in the atrium and ventricle. Prucalopride has some inotropic and chronotropic effects on the heart;[67–69] however, studies with prucalopride in the porcine atrium suggest low cardiac risks,[70] consistent with the almost 300-fold difference in affinity constant for the 5-HT_4 receptor and hERG.[18] This indicates a high safety margin and low risk of cardiac side effects with prucalopride.[71,72] No arrhythmic activity was demonstrated in human atrial cells treated with prucalopride, even after pretreatment with β-adrenoceptor antagonists to increase the proarrhythmic potential.[73]

In the prucalopride clinical trial cohorts (~4000 people), there were no clinically relevant cardiac adverse events. In healthy volunteers in two phase I trials exposing healthy volunteers to up to 10 times the therapeutic dosage of prucalopride, there was higher heart rate and associated decreases in PQ and QT intervals, but not in the Fridericia-corrected QT (QTcF) interval.[74] Longer-term clinical trials exposing patients to up to 4 mg/day for a maximum of 24 months confirmed prucalopride's safety.[64] A phase II safety study in nursing home patients, of whom >85% had a history of cardiovascular disease,[75] showed no detrimental change in pulse rate, blood pressure, electrocardiographic indices, or laboratory safety parameters.[75]

General tolerability

Prucalopride is generally well tolerated; the adverse event profile after long-term treatment is similar to that of 12-week exposure. The most common adverse events (which occur in 10% or more of treated subjects) are headache, nausea, abdominal pain, and diarrhea.[45,49,54–56,76,77] Most adverse events have been mild or of moderate severity, transient, and have occurred mainly on the first day of treatment, independent of the dosage received. Treatment-related adverse events leading to discontinuation of medication occurred in <8.3% of patients.[54–57] Four patient deaths have been reported, with three unrelated to drug and treatment information unavailable for the fourth patient.[54,65]

Patient perspectives: quality of life, satisfaction, acceptability, and adherence

As illustrated above, prucalopride treatment was associated with improved quality of life (based on PAC-QOL) during placebo-controlled trials and satisfaction with bowel function was maintained during open label treatment with prucalopride for up to 24 months (less than 10% prucalopride cessation because of treatment emergent adverse events). Therefore, patients appear to tolerate and benefit from this treatment in the medium- and long-term. It is also worth noting that >80% patients entering the pivotal trials of 12 weeks' duration reported lack of satisfaction with current laxatives and there was significant improvement in QOL scores as estimated by the validated PAC-QOL assessment.

Conclusion

Prucalopride is a novel compound, stimulating 5-HT_4 receptors with high affinity. The lack of interaction of prucalopride with other receptors or channels at therapeutic doses is advantageous relative to available prokinetics. In patients with chronic constipation, prucalopride increases stool frequency and loosens stool consistency by stimulating gastrointestinal and colonic motility. The drug appears to be safe (with a safety window of ~300 between efficacy in constipation and proarrhythmic potential), is well tolerated, and adverse events are mild.

In July 2009, prucalopride was approved by the European Medicines Agency for the symptomatic treatment of chronic constipation for women in whom laxatives fail to provide satisfactory relief.[78] Prucalopride will be the first oral medication marketed for severe chronic constipation in the European Union. Recommended dosage is 2 mg by mouth once daily, except for those over 65 years of age for whom the recommended dosage is 1 mg by mouth once daily. The dose can be subsequently increased to 2 mg daily, as tolerated.

Current data suggest that, at the least, prucalopride will prove to be a valuable addition to the therapeutic arsenal in treating chronic constipation. At present, prucalopride should be regarded as a second-line treatment after supplementation of fiber, and osmotic, or over-the-counter laxatives.

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Disclosures

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