Drugs (2016) 76:99–110
DOI 10.1007/s40265-015-0518-3

ADIS DRUG EVALUATION

Prucalopride: A Review in Chronic Idiopathic Constipation

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Published online: 1 December 2015

Abstract Prucalopride (Resolor®), a highly selective serotonin 5-HT_4 receptor agonist, is indicated in the European Economic Area for the treatment of adults with chronic idiopathic constipation (CIC) in whom laxatives have failed to provide adequate relief. This article reviews the pharmacological properties of prucalopride and its clinical efficacy and tolerability in patients with CIC. In five well-designed, 12-week trials in patients with CIC, oral prucalopride 2 mg/day was significantly more effective than placebo at improving bowel function, including the number of bowel movements and a range of other constipation symptoms, as well as health-related quality of life and patient satisfaction; however, no significant differences in bowel function measures were observed between prucalopride and placebo in a 24-week trial. Oral PEG-3350 + electrolytes reconstituted powder was found to be noninferior but not superior to prucalopride according to primary endpoint data from a 4-week, controlled-environment trial. Prucalopride was generally well tolerated in clinical trials; the most common adverse events were headache, diarrhoea, nausea and abdominal pain. No cardiovascular safety issues have arisen with prucalopride treatment. Although further long-term and comparative data would be beneficial, prucalopride provides an additional treatment option for patients with CIC.

Prucalopride in chronic idiopathic constipation: a summary
Highly selective serotonin 5-HT_4 receptor agonist
Improves bowel function, constipation-related symptoms, patient satisfaction and health-related quality of life in patients with chronic idiopathic constipation, according to 12-week trials
Generally well tolerated; adverse events were mostly transient, occurring on the first day of treatment
No cardiovascular safety issues have arisen

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1 Introduction

Chronic idiopathic constipation (CIC), also known as functional constipation, presents as persistently difficult, infrequent or seemingly incomplete defecation that is not consistent with irritable bowel syndrome-constipation (IBS-C) criteria [1]. Constipation is more common in women [1, 2], the elderly, and those of lower socioeconomic status [2]. CIC is associated with impaired health-related quality of life (HR-QOL), especially in elderly patients [2]. CIC is generally divided into two categories:

slow-transit constipation (colonic inertia; manifests as infrequent stools) and 'outlet-type' constipation (defecatory dysfunction or anismus; manifests as difficulty associated with the act of defecation, such as straining or incomplete evacuation) [3].

Traditionally, treatment options for CIC include lifestyle and dietary changes, as well as the use of osmotic [e.g. polyethylene glycol (PEG)] or stimulant (e.g. bisacodyl or sodium picosulfate) laxatives [1, 2]. More recently, prucalopride [Resolor®, a selective, high-affinity serotonin (5-HT_4) receptor agonist with gastrointestinal prokinetic properties [2]] and prosecretory agents (e.g. linaclotide, lubiprostone) have been investigated; the availability of these newer drugs differs between markets.

Oral prucalopride 1–2 mg/day is indicated in the European Economic Area (EEA) for the symptomatic treatment of CIC in adults in whom laxatives have failed to provide adequate relief [4, 5]. The approval of prucalopride was initially restricted to women, as there were limited data in men (most patients in the pivotal clinical trials were female) [6]; however, the indication has now been extended to include men [4, 6]. This article reviews the pharmacological properties of prucalopride and its clinical efficacy and tolerability in patients with CIC.

2 Pharmacodynamic Properties of Prucalopride

Prucalopride is a dihydrobenzofurancarboxamide derivative that stimulates colonic motility by selectively binding to and activating 5-HT_4 receptors in the gut [4, 7]. It has a high affinity for 5-HT_{4a} and 5-HT_{4b} receptors [inhibition constant (K_i) values of 2.5 and 8 nmol/L, respectively] [7]. Selectivity for other receptors (including 5-HT receptor subtypes other than 5-HT_4; monoamine, opioid and peptide receptors; ion channels; and transporters) was either not measurable (K_i of >10,000 nmol/L) or at least ≈290-fold lower (human dopamine D_4 receptor K_i of 2350 nmol/L; human σ1 receptor K_i of 3680 nmol/L; mouse 5-HT_3 receptor K_i of 3822 nmol/L) [7].

Preclinical studies indicate that prucalopride, as a 5-HT_4 receptor agonist, increases GI motility by promoting the contraction of longitudinal smooth muscle and the suppression of circular smooth muscle contraction (which is associated with a resistance to propulsion) [8, 9]. A study in conscious, fasted dogs showed that prucalopride has a dose-dependent, coordinated and region-specific effect on GI motility [10]. It stimulated high-amplitude clustered contractions in the proximal colon and inhibited contractions in the distal colon, as well as inducing colonic giant migrating contractions (which propagate along the entire length of the colon) [10]; these contractions were blocked by selective 5-HT_4 receptor antagonists [4].

While GI transit time data varied between trials, oral prucalopride was generally associated with a decrease in GI transit time in patients with constipation [11–14]; variable findings have also been seen with prucalopride in healthy volunteers [15–17]. For example, significant ($p < 0.05$) decreases from baseline in colonic transit time were observed in recipients of prucalopride 1 and 2 mg/day after 4 weeks' treatment in one study [13] and in recipients of prucalopride 2 and 4 mg/day in a pooled analysis of three randomized, placebo-controlled, phase II, 4- or 12-week trials [14], and colonic transit was significantly ($p = 0.04$) improved with prucalopride 4 mg/day versus placebo in a 1-week study [11]; however, prucalopride 1 [18] and 2 mg/day [11, 18] showed no significant difference from placebo in colonic transit in that same 1-week study [11] or after 2 weeks in another study [18].

Prucalopride 1 and 2 mg/day had no effect on anorectal function in one study [18]; however, a second study demonstrated a significantly ($p = 0.001$) increased rectal distension sensitivity with prucalopride 1 mg/day versus placebo [12]. In a study comparing a single dose of prucalopride 2 mg with PEG-3350, prucalopride increased the number of high-amplitude propagating contractions relative to that observed with PEG-3350 ($p = 0.012$); this endpoint is associated with increased bowel motion frequency [19].

Results from large, phase III and IV clinical trials investigating the effect of prucalopride on bowel function in patients with CIC are discussed in Sect. 4.

In vitro studies generally indicate that prucalopride does not have clinically relevant cardiovascular effects [20–25], which have been observed with the nonselective 5-HT_4 agonists cisapride and tegaserod [26]. While prucalopride blocks human ether à-go-go related gene (hERG) cardiac potassium channels, it is unlikely to be significant at clinically relevant concentrations, as the 50 % inhibitory concentration is relatively high (4.1 [24] and 5.7 μmol/L [25]); binding affinity is ≈2–3 orders of magnitude lower for hERG channels than for 5-HT_4 receptors [27]. In human atrial cells, prucalopride (at 1000-fold higher concentrations than those used therapeutically) was associated with partial agonist of the L-type calcium current and prolongation of the early phase of action potential repolarization (but not late repolarization); it was not associated with arrhythmic activity [23]. Prucalopride was an inotropic, chronotropic and lusitropic partial agonist in the heart [20–22]; however, these effects were of small magnitude [21].

A thorough QT study demonstrated that prucalopride at therapeutic (2 mg/day) and supratherapeutic (10 mg/day) dosages had no effect on cardiac repolarization in healthy volunteers [28]. Prucalopride at both dosages was noninferior to placebo with regard to effects on corrected QT (QTc) interval [28]. Small increases in heart rate were observed with prucalopride (maximum increase of

5.8 beats/min) [28]. In general, prucalopride recipients with CIC in large clinical trials did not experience QTc interval prolongation (Sect. 5).

3 Pharmacokinetic Properties of Prucalopride

Oral prucalopride has dose-proportional pharmacokinetics [4]. It is rapidly absorbed, with a time to maximum concentration (3.79 ng/mL) of 2–3 h following a single 2-mg dose [4, 29], and its absolute oral bioavailability is >90 % [4]. The oral bioavailability of prucalopride is not significantly affected by the concomitant intake of food [4]. Steady state was reached within 3–4 days with once-daily administration, with an accumulation ratio of 1.9–2.3 [4]. The drug is extensively distributed, with a steady-state volume of distribution of 567 L [4]. Prucalopride plasma protein binding is low, at ≈30 % [4].

In vitro studies indicate that human liver metabolism of prucalopride is very slow [4]. In an oral radiolabelled prucalopride dose study, unchanged active substance made up ≈92 to 95 % of the total radioactivity in plasma, most of the administered dose was recovered in the urine (84 %; 13 % was recovered in the faeces), and the majority of the dose was excreted unchanged (60–65 % in urine and ≈5 % in faeces) [4, 29]. Small amounts of seven metabolites were recovered in urine and faeces; the most common metabolite was R107504, which accounted for 3.2 and 3.1 % of the total radioactivity in the urine and faeces, respectively [4]. Other metabolites identified were formed by *N*-dealkylation (e.g. R084536, accounting for 3 % of the dose), *O*-demethylation (e.g. R104065), hydroxylation (3 % of the dose) and *N*-oxidation (2 % of the dose) [4, 29].

Prucalopride has a plasma clearance of 317 mL/min [4], and its terminal half-life is ≈1 day [4, 29]. The renal excretion of unchanged drug involves both passive filtration and active secretion [4]. Prucalopride apparent total clearance was correlated with creatinine clearance (CL_{CR}) in a population pharmacokinetic analysis; age, body weight, sex and race had no effect on total clearance [4].

The pharmacokinetics of prucalopride are affected by renal impairment [4, 30], and dosage adjustments are recommended for patients with severe renal impairment [4] (Sect. 6). Exposure to prucalopride was 1.3-, 1.5- and 2.3-fold higher in patients with mild (CL_{CR} 50–79 mL/min), moderate (CL_{CR} 25–49 mL/min) and severe (CL_{CR} ≤24 mL/min) renal impairment, respectively, than in subjects with normal renal function, following a single dose of prucalopride 2 mg ($p < 0.001$ for overall comparison) [30]. The exposure to prucalopride was 26–28 % higher in elderly patients than in younger patients receiving prucalopride 1 mg/day, probably as a result of diminished renal function in elderly patients [4].

Prucalopride exposure is also affected by hepatic impairment [4, 31]. Exposure to prucalopride was increased by 10–20 % in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment compared with healthy volunteers [4, 31]; this is unlikely to be of clinical relevance [31], but dosage adjustments may be necessary in patients with severe hepatic impairment [4] (Sect. 6).

As prucalopride is largely excreted as unchanged drug, it has a low pharmacokinetic interaction potential [4]. In vitro studies indicated that prucalopride does not inhibit specific cytochrome P450 (CYP) activity at therapeutically relevant concentrations. Prucalopride is a weak substrate for but not an inhibitor of P-glycoprotein, at therapeutically relevant concentrations [4].

While ketoconazole (a potent CYP3A4 and P-glycoprotein inhibitor) was associated with a small increase in systemic exposure to prucalopride, this was not considered to be clinically relevant; other potent P-glycoprotein inhibitors (e.g. verapamil, cyclosporine A and quinidine) may have a similar effect [4]. Coadministration of prucalopride with probenecid, cimetidine, paroxetine or erythromycin had no effect on prucalopride pharmacokinetics [4]. Coadministration of prucalopride and erythromycin led to a 30 % increase in plasma erythromycin concentrations [4]. Prucalopride did not have any clinically relevant effects on the pharmacokinetics of warfarin, digoxin, alcohol, paroxetine or oral contraceptives [4, 32].

4 Therapeutic Efficacy of Prucalopride

In the trials discussed in this section, CIC was defined as an average of ≤2 spontaneous, complete bowel movements (SCBMs) [13, 33–38] or spontaneous bowel movements (SBMs) [39] per week, plus at least one additional symptom (hard or very hard stools, a sensation of incomplete evacuation, straining during defecation [13, 33–39], sensation of anorectal obstruction or blockade [13, 39], and/or a need for digital manipulation to aid evacuation [13, 39]) with ≥25 % of bowel movements [13, 33–39]. To be defined as spontaneous, the bowel movement was required to occur >24 h after the last use of laxatives [33–39] or enemas [13, 33, 37–39]. To be defined as complete, the bowel movement was required to be associated with a sensation of complete evacuation [13, 33, 34, 36, 38].

Treatment response was defined as an average of ≥3 SCBMs/week [13, 33–39]. Exclusion criteria included constipation that was secondary to drugs, certain disorders/diseases or surgery [13, 33–39]. Rescue use of bisacodyl [33–39] and enemas [13, 33–37, 39] was permitted under certain circumstances. The modified intent-to-treat (mITT) population was defined in most trials as randomized patients who received at least one dose of trial

Table 1 Twelve-week efficacy of prucalopride in patients with chronic idiopathic constipation in phase III trials

Study	Treatment (mg/day)	No. of pts	Response rate (% of pts)		Mean no. of SCBMs/week [BL]	Pts with an avg. ↑ from BL of ≥ 1 SCBM/week (% of pts)	Median time to first SCBM (days)
			weeks 1–12[a]	weeks 1–4			
Camilleri et al. [36]	PRU 2	207	30.9**	33.8**	2.6** [0.5]	47.3**	1.3**
	PRU 4	204	28.4**	36.3**	3.0** [0.5]	46.6**	1.0**
	PL	209	12.0	10.0	1.2 [0.4]	25.8	12.6
Ke et al. [39]	PRU 2	249	33.3**	34.5**	2.4** [0.3]	57.2**	1.56**
	PL	252	10.3	11.1	1.1 [0.3]	27.4	12.58
Quigley et al. [35]	PRU 2	214	23.9*	29.2**	1.9** [0.4]	42.6**	2.3**
	PRU 4	215	23.5*	28.9**	2.0** [0.5]	46.6**	1.9**
	PL	212	12.1	11.5	1.2 [0.4]	27.5	13.0
Tack et al. [34]	PRU 2	236	19.5*	23.7**	1.6** [0.4]	38.1**	4.7**
	PRU 4	237	23.6**	26.6**	1.9** [0.5]	44.1**	2.1**
	PL	240	9.6	10.4	1.0 [0.4]	20.9	20.5
Yiannakou et al. [33]	PRU 2	177	37.9**	29.9*	NR[b] [0.39]	53.7	4.6*
	PL	181	17.7	14.9	NR[b] [0.51]	45.3	9.1

The time period for analyses was during weeks 1–12, unless otherwise stated. Response was defined as an avg of ≥3 SCBMs/week

Avg average, *BL* baseline, *PL* placebo, *PRU* prucalopride, *pts* patients, *SCBM* spontaneous, complete bowel movement, ↑ indicates increase. * $p \leq 0.01$, ** $p \leq 0.001$ vs. PL

[a] Primary endpoint

[b] Absolute numbers were not reported; changes from baseline values were +2.17 in PRU vs. +1.25 in PL recipients ($p = 0.0001$)

medication [33–39] and had at least one post-baseline efficacy assessment [34, 36, 37]; one study [33] excluded patients from a site where a serious breach in good clinical practice was identified. The remaining trial [13] defined the mITT population as randomized patients who had stool data for at least 2 of the 4 treatment weeks. This section focuses on the approved dosage of 2 mg/day (1–2 mg/day in elderly patients) [4] unless otherwise specified.

4.1 Efficacy Versus Placebo

4.1.1 Shorter-Term Efficacy

This section discusses the efficacy of prucalopride versus placebo as determined in five large, randomized, double-blind, multicentre, phase III trials [33–36, 39]. Patients were aged ≥18 years and had a ≥6-month history of severe CIC [33–36, 39]. The majority of patients (86.6–90.8 %) in four of the studies [34–36, 39] were women; to provide additional data in men, the fifth study [33] enrolled only male patients. Following a 2- [34–36, 39] or 2- to 4-week [33] run-in (baseline) period, during which patients were generally additionally required to have an average of ≤2 SCBMs/week [34–36, 39], patients were randomized to receive 12 weeks' treatment with prucalopride 2 mg/day [patients aged ≥65 years in this group (43 %) in one study [33] received 1–2 mg/day] [33–36, 39], prucalopride 4 mg/day [34–36] or placebo [33–36, 39]. The primary endpoint was the response rate during the 12-week treatment period in the mITT population [33–36, 39].

In general, baseline characteristics did not significantly differ between treatment groups [33–36, 39]. In four trials, most patients were White (88.0–96.8 %) [33–36]; the remaining trial included mainly Asian patients (92.4 %), as it was conducted in the Asia-Pacific region [39]. A total of 9.7–44.0 % of patients had no SBMs/week over the last 6 months [33–36, 39], mean duration of constipation was 9.2–22.0 years [33–36, 39], and 55.3–83.7 % of patients had used previous constipation treatment and rated it as inadequate [34–36, 39].

Prucalopride was associated with a significantly greater response rate in weeks 1–12 (primary endpoint) than placebo in all five studies (Table 1) [33–36, 39]. The between-group difference in response rate also significantly favoured prucalopride in weeks 1–4 (Table 1) [33–36, 39], weeks 5–8 ($p \leq 0.001$) [33, 34, 36, 39] and weeks 9–12 ($p \leq 0.01$) [33, 34, 36, 39], where reported.

Moreover, the mean number of SCBMs per week was significantly improved and the median time to first SCBM (after first intake of study medication) was significantly shorter in prucalopride than in placebo recipients over weeks 1–12 in all studies (Table 1) [33–36, 39], and the percentage of patients with an average increase of ≥1 SCBM per week over weeks 1–12 versus baseline

was significantly higher with prucalopride than with placebo in four [34–36, 39] of the five studies (Table 1).

During weeks 1–12, prucalopride 2 mg/day was also associated with significant ($p \leq 0.05$) improvements relative to placebo in stool consistency (in four [34–36, 39] of the five trials), straining during the bowel motion (in three [35, 36, 39] of the trials), and rescue laxative use (in four [34–36, 39] of the trials). Treatment was patient-rated as "quite effective or extremely effective" in 32.9–46.7 % of prucalopride versus 8.8–30.4 % of placebo recipients ($p \leq 0.001$) in all studies [33–36, 39].

In general, patients felt prucalopride improved their constipation symptoms at week 12, as measured by the Patient Assessment of Constipation-Symptoms questionnaire (PAC-SYM). Prucalopride recipients reported significant ($p \leq 0.05$) improvements versus placebo in the overall PAC-SYM score in four [34–36, 39] of the five studies (−0.8 to −0.6 with prucalopride vs. −0.6 to −0.4 with placebo) [33–36, 39]. In the four studies reporting data for PAC-SYM subscale scores [34–36, 39], significant ($p \leq 0.05$) differences in improvement were observed in stool symptoms (−1.0 to −0.6 vs. −0.5 to −0.4) and abdominal symptoms subscale scores (−0.9 to −0.6 vs. −0.5 to −0.3) in all four studies [34–36, 39], and in the rectal symptoms subscale score (−0.6 vs. −0.4 to −0.3) in three studies [34, 35, 39]. In the study that did not report absolute subscale scores, a significantly greater proportion of prucalopride than placebo recipients had an improvement of ≥1 (clinically meaningful) in PAC-SYM stool symptom score (53.3 vs. 36.3 %; $p = 0.0005$), but no between-group differences were found in the proportion of patients who had the same level of improvement in abdominal symptom (39.1 vs. 35.1 %) or rectal symptom (34.9 vs. 29.2 %) scores [33].

Mean overall Patient Assessment of Constipation-Quality Of Life questionnaire (PAC-QOL) scores at week 12 were also improved to a significantly ($p < 0.05$) greater extent with prucalopride than with placebo [33–36, 39], and (where reported) a greater proportion of prucalopride than placebo recipients had an improvement of ≥1 (clinically meaningful) on the PAC-QOL satisfaction subscale at week 12 (43.5–52.7 vs. 21.8–38.8 %; $p < 0.01$) [33–36]. However, no significant differences in scores on the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) were observed between prucalopride and placebo recipients, where investigated [35, 36].

4.1.1.1 Efficacy in Elderly Patients A randomized, double-blind, placebo-controlled, multicentre, phase III trial [37] investigated the efficacy of prucalopride 1 ($n = 76$), 2 ($n = 75$) and 4 mg/day ($n = 80$) versus placebo ($n = 72$) in elderly (aged ≥65 years) patients with a ≥6-month history of CIC. The primary endpoint was the response rate in the mITT population during the 4 weeks of the trial [37]. Most patients were female (70 %), the mean age was 76 years, the median duration of constipation was ≈15 years, >70 % of patients were dissatisfied with their previous constipation treatment, and ≈30 % of patients had no SCBMs/week during the 2-week run-in period before the treatment period began. More than half the patients had comorbid cardiovascular (70 %), musculoskeletal (64 %), gastrointestinal (63 %) and/or genitourinary (50 %) diseases.

Prucalopride 1 and 2 mg/day recipients did not significantly differ from placebo recipients in response rates during the 4-week treatment period (primary endpoint; ranges of response rates for each week: 42.1–47.2 and 36.1–43.8 vs. 24.6–26.9 %, respectively) [37]. However, a significantly greater proportion of prucalopride 1 and 2 mg/day than placebo recipients had an average increase of ≥1 SCBM/week in week 1 (61.8 and 63.0 vs. 40.6 %, respectively; both $p < 0.05$), and significantly more prucalopride 1 mg/day but not 2 mg/day than placebo recipients had this outcome in week 4 (59.2 and 48.6 vs. 33.8 %, respectively; $p < 0.05$ for prucalopride 1 mg/day) [37]. Rates did not significantly differ for either prucalopride dosage versus placebo for weeks 2 or 3.

Both prucalopride 1 and 2 mg/day significantly increased the number of SCBMs per week from baseline relative to placebo (mean changes of +1.9 and +1.7 vs. +0.6 SCBMs/week; $p \leq 0.05$ for both) [37]. At week 4, 42 and 24 versus 16 % of prucalopride 1 and 2 mg/day versus placebo recipients rated their treatment as quite a bit or extremely effective ($p < 0.001$ and $p < 0.05$, respectively). At 4 weeks, some recipients of prucalopride 1 or 2 mg/day or placebo had improvements from baseline of ≥1 in PAC-SYM stool symptom score (48.5 and 31.3 vs. 21.9 %; $p \leq 0.05$ for prucalopride 1 mg/day vs. placebo) and of ≥1 in PAC-QOL satisfaction score (48.5 and 29.0 % vs. 25.8 %; $p \leq 0.05$ for prucalopride 1 mg/day vs. placebo) [37].

4.1.2 Longer-Term Efficacy

A randomized, double-blind, placebo-controlled, multicentre, phase IV study investigated the efficacy of 24 weeks' treatment with prucalopride 2 mg/day (1–2 mg/day in patients aged ≥65 years) [$n = 182$] versus placebo ($n = 182$) in patients aged ≥18 years with CIC [38]. A run-in period of 2–4 weeks preceded the 24-week treatment period. The primary endpoint was the response rate during the 24-week treatment period in the mITT population [38]. Most patients (85.3 %) were female, 60.0 % had an average of no SCBMs/week over the past 6 months, and the mean duration of constipation was 14.7 years. A total of 19 % of prucalopride recipients were aged ≥65 years.

Prucalopride and placebo recipients did not significantly differ in response rate over the 24-week treatment period (25.1 vs. 20.7 %; primary endpoint; Fig. 1), nor did they significantly differ during weeks 1–12 (25.1 vs. 20.1 %) or

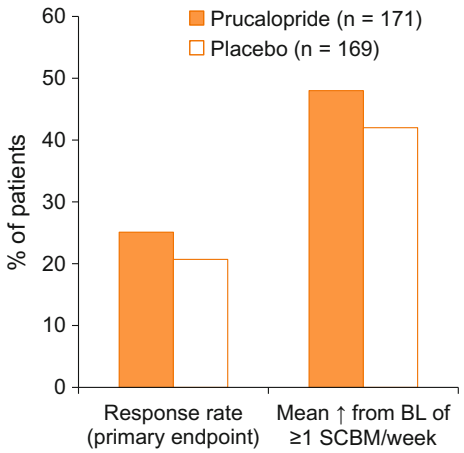

Fig. 1 Efficacy of prucalopride 1–2 mg/day versus placebo in patients with chronic idiopathic constipation, during weeks 1–24 of a phase IV trial [38]. Response was defined as a mean of ≥3 SCBMs/week. *BL* baseline; *SCBM* spontaneous, complete bowel motion, ↑ indicates an increase

13–24 (28.1 vs. 23.7 %) [38]. Three of four prespecified sensitivity analyses (using the per-protocol and completer populations and using multiple imputation) also showed no significant difference in the primary endpoint (26.9–30.4 % of prucalopride vs. 21.0–25.4 % of placebo recipients); one analysis using a generalized linear mixed model for repeated measures showed a significant difference (34.8 vs. 25.6 %; $p = 0.0003$).

No significant difference between prucalopride and placebo recipients was observed over the 24-week period for the proportion of patients with a mean increase from baseline of ≥1 SCBM/week (Fig. 1), the mean change from baseline in the number of SCBMs/week (+1.70 vs. +1.26), the median time to first SCBM (100.8 vs. 359.7 h), or the proportion of patients who rated treatment as quite or extremely effective (45.2 vs. 35.3 %) [38]. Moreover, no significant difference was observed with regard to consistency of stools or the presence of straining, or in the use of rescue medication.

At 24 weeks, overall PAC-SYM scores had changed by −0.55 versus −0.68 in prucalopride versus placebo recipients; changes on the stool subscale were −0.60 versus −0.75, on the abdominal subscale were −0.58 versus −0.70, and on the rectal subscale were −0.46 versus −0.68 [38]. Significantly fewer prucalopride than placebo recipients achieved an improvement from baseline of ≥1 in overall score (29.9 vs. 40.1 %; $p = 0.035$) and stool subscale score (35.9 vs. 48.5 %; $p = 0.024$); there were no significant differences for this outcome in abdominal subscale (33.3 vs. 41.3 %) or rectal subscale (29.9 vs. 37.1 %) scores.

No significant differences between prucalopride and placebo recipients in HR-QOL were observed [38]. The mean change from baseline to 24 weeks in PAC-QOL overall score was −0.67 versus −0.73, respectively, and a total of 44.0 versus 36.8 % of patients achieved an improvement from baseline of ≥1 in PAC-QOL satisfaction score.

In an earlier noncomparative extension study [40], 1455 patients from three [34–36] of the 12-week placebo-controlled trials continued prucalopride treatment for ≥24 months. Of the 500 patients still receiving prucalopride at 18 months, 67.2 % had an improvement from baseline of ≥1 in PAC-QOL satisfaction score (the proportion at 12 weeks was 43.4 %).

4.2 Efficacy Versus PEG-3350 + Electrolytes

The efficacy of oral prucalopride tablets ($n = 120$) versus oral PEG-3350 + electrolytes reconstituted powder ($n = 120$) in patients aged 18–75 years with a history of CIC of ≥6 months, and who were not satisfied with previous laxative treatment, was investigated in a randomized, double-blind, single-centre trial; this trial was in a controlled environment, conducted in a Phase I unit in Romania [13]. Patients underwent a 2-week run-in period, during the last week of which they were required to have <3 SCBMs, before randomization to 4 weeks' treatment with prucalopride 2 mg/day (1–2 mg/day in patients aged >65 years) or PEG-3350 + electrolytes [2 sachets/day (split dose); could be down-titrated to 1 sachet/day; each sachet contained PEG-3350 13.13 g, sodium chloride 0.35 g, sodium bicarbonate 0.18 g and potassium chloride 0.05 g].

The primary endpoint was the response rate during the final week of treatment [13]. The noninferiority of PEG-3350 + electrolytes to prucalopride was tested in the per-protocol population, using a one-sided 97.5 % confidence interval lower limit of −20; if noninferiority was demonstrated, superiority was tested in the mITT population, with a one-sided 97.5 % CI lower limit of 0. Baseline characteristics were similar between treatment groups [13]. A total of 2 % of prucalopride recipients were aged >65 years and received the lower starting dose.

PEG-3350 + electrolytes was noninferior but not superior to prucalopride with regard to response rate during week 4 of treatment (primary endpoint), in patients with CIC (Fig. 2) [13]. Significantly fewer prucalopride than PEG-3350 + electrolytes recipients responded and had a mean increase of ≥1 SCBM/week during weeks 1–4 (35.3 vs. 58.3 %; $p = 0.0007$); this difference was also significant in weeks 1 and 3 ($p < 0.01$) but not weeks 2 and 4.

During the study, the weekly average increase in SCBMs was 1.54 versus 2.52 SCBMs/week in prucalopride versus PEG-3350 + electrolytes recipients ($p < 0.001$), and the mean number of SCBMs/week was significantly higher with PEG-3350 + electrolytes than with prucalopride throughout the study ($p < 0.01$) [13]. The mean time to first SCBM was 120 h with prucalopride and 114 h with PEG-3350 + electrolytes.

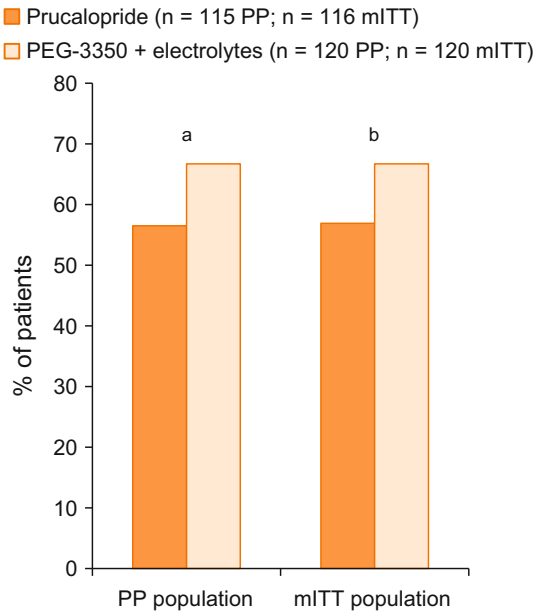

Fig. 2 Response rates during week 4 (primary endpoint) with prucalopride or PEG-3350 + electrolytes in patients with chronic idiopathic constipation in a double-blind trial [13]. *a* rate difference 10.1 % (97.5 % lower CI limit −2.7; noninferiority demonstrated); *b* rate difference 9.8 % (97 % lower CI limit −3.1; superiority not demonstrated). *mITT* modified intent to treat, *PP* per protocol

Consistency of stools, straining during the bowel motion, and the feeling of incomplete evacuation were improved to a significantly ($p < 0.05$) greater extent with PEG-3350 + electrolytes than with prucalopride over weeks 1–4 [13]. The use of rescue laxatives was low in both groups. Treatment was patient-rated as quite effective or extremely effective in significantly more PEG-3350 + electrolytes than prucalopride recipients ($p < 0.005$).

Overall PAC-SYM scores improved from baseline to a significantly greater extent with PEG-3350 + electrolytes than with prucalopride at weeks 1, 2 and 4 ($p < 0.05$), stool symptom scores at weeks 1, 2, 3 and 4 ($p < 0.0001$), and rectal symptom scores at week 1 ($p < 0.01$) [13]. Abdominal symptom scores improved to a significantly greater extent with prucalopride than PEG-3350 + electrolytes at week 1 ($p < 0.05$). PAC-SYM overall and subscale scores did not significantly differ between groups at all other time points.

PEG-3350 + electrolytes recipients had a significantly ($p < 0.05$) greater improvement in PAC-QOL satisfaction score than prucalopride recipients; however, no other between-group differences were found in PAC-QOL or European Quality of Life instrument (EQ-5D-3L) scores [13].

4.3 Pooled Analyses

An integrated analysis of six phase III and IV trials (five 12-week [33–36, 39] and one 24-week [38]) demonstrated that prucalopride ≤2 mg/day ($n = 1237$) was more effective than placebo ($n = 1247$) at improving bowel function and quality of life in patients with CIC [41]. The response rate during weeks 1–12 was 27.8 versus 13.2 %, respectively [$p < 0.001$; overall odds ratio 2.68 (95 % CI 2.16–3.33)]. Moreover, 47.0 versus 29.9 % of patients had a mean increase of ≥1 SCBM/week during weeks 1–12 ($p < 0.001$), and mean changes in overall PAC-SYM (−0.7 vs. −0.4) and PAC-QOL (−0.7 vs. −0.5) scores were significantly greater with prucalopride than placebo (both $p < 0.001$). An integrated analysis of the female patients in four trials [34–36, 39] ($n = 1596$) supported the analysis in the mixed population; prucalopride was significantly more effective than placebo in the treatment of CIC (response rates of 34 vs. 11 % in Asian and 25 vs. 11 % in non-Asian patients; both $p < 0.001$) [42].

These results were also supported by a meta-analysis of data from five studies ($n > 2500$), where prucalopride was significantly more effective than placebo with regard to the proportion of patients with an average increase of ≥3 SCBMs [relative risk (RR) 2.45; 95 % CI 1.94–3.07] and ≥1 SCBM (RR 1.82; 95 % CI 1.59–2.08) at week 12 [43]. A meta-analysis of nine trials comparing prucalopride with placebo (eight trials) or PEG-3350 + electrolytes (one trial) found that prucalopride was associated with a significantly greater response rate (RR 1.63; 95 % 1.07–2.49) and proportion of patients with a mean improvement of ≥1 SCBM/week (RR 1.58; 95 % CI 1.18–2.12) than the control (placebo or PEG-3350 + electrolytes) [44]. A separate study found a strong correlation (r = 0.710) between improvements in PAC-SYM and PAC-QOL scores [45].

Integrated analyses in women in whom laxatives had failed, using data from three phase III trials ($n = 936$), also demonstrated that prucalopride was significantly more effective than placebo in the treatment of CIC [46, 47]. In one analysis, the response rate during weeks 1–12 was 24.7 versus 9.2 %, respectively ($p < 0.0001$), and the proportion of patients with an average increase of ≥1 SCBM/week was 44.2 versus 22.6 % ($p < 0.0001$) [47]. In the other analysis, the proportion of patients with an improvement of ≥1 in PAC-SYM total score was 34.9 versus 20.8 % ($p < 0.001$); moreover, significantly more prucalopride than placebo recipients had this degree of improvement in each PAC-SYM subscale (all $p < 0.01$) [46].

5 Tolerability of Prucalopride

Prucalopride was generally well tolerated in patients with CIC [4, 13, 33–39, 41]. Most adverse events were transient [4, 34, 36], occurring primarily on the first day of treatment [4, 36], and of mild to moderate severity [4, 13, 33–38, 41].

In 12-week, placebo-controlled, phase III trials, a total of 39–81 % of prucalopride ≤2 mg/day and 34–71 % of placebo recipients experienced adverse events [33–37, 39], 1–2 and 1–4 % experienced serious adverse events [33, 35–37, 39], and 3–8 and 1–7 % discontinued as a result of adverse events [33–37, 39]. No patients died during treatment [33–36, 39], except in the trial in elderly patients [37], where one placebo recipient died of a myocardial infarction. Prucalopride was also generally well tolerated in a 24-week, placebo-controlled, phase IV study [38]. In this study, 42 % of prucalopride and 42 % of placebo recipients had at least one adverse event, 2 % of patients in both groups had serious adverse events, and 8 and 5 % of patients discontinued treatment as a result of adverse events. No patients died during treatment [38].

The most common adverse events in prucalopride ≤2 mg/day versus placebo recipients in an integrated analysis of six phase III and IV trials are shown in Fig. 3, and include headache, nausea, diarrhoea and abdominal pain [41]. In this analysis, no serious adverse events occurred in more than one prucalopride recipient [41]. In an integrated analysis of data from four trials [34–36, 39] ($n = 1281$), diarrhoea, headache and nausea, but not abdominal pain, were significantly ($p < 0.001$) more likely to occur with prucalopride than with placebo [48]. In the same analysis, Asian patients had a higher risk of diarrhoea and a lower risk of abdominal pain, headache and nausea than non-Asian patients (all $p < 0.001$), women had a higher risk of nausea than men ($p < 0.05$), and younger patients had a higher risk of headache than older patients ($p < 0.001$) [48].

In the study investigating prucalopride versus PEG-3350 + electrolytes, the incidence of at least one adverse event was 85 versus 68 %, respectively; the most common adverse events were headache (55 vs. 37 %), dysmenorrhea (16 vs. 13 %), nausea (13 vs. 6 %) and pharyngitis (11 vs. 6 %) [13]. Other adverse events of note included vomiting (7 vs. 3 %), abdominal pain (6 vs. 3 %), urinary tract infections (1 vs. 3 %) and back pain (0 vs. 5 %). At least one serious adverse event occurred in 1 % of prucalopride and 0 % of PEG-3350 + electrolytes recipients.

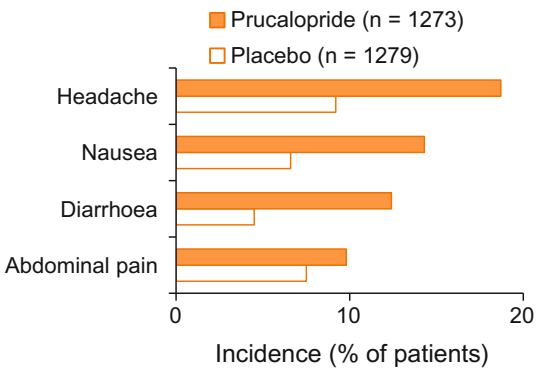

Fig. 3 Tolerability of prucalopride ≤2 mg/day versus placebo in patients with chronic idiopathic constipation. Adverse events occurring in ≥5 % of prucalopride recipients in an integrated analysis of six trials [41]

No cardiovascular safety issues have arisen with prucalopride treatment. In a pooled analysis of four trials, the number needed to harm with regard to a QTc using Bazett's formula (QTcB) value of >500 ms was 159 [49]. Moreover, the RR for prucalopride 2 mg/day versus placebo of a QTc using Fridericia's formula (QTcF) or QTcB value of >450 ms was 1.03 (95 % CI 0.81–1.31) and 0.88 (95 % CI 0.68–1.30), respectively, in a meta-analysis of five studies ($n > 2500$) [50]. In the trials in Sect. 4.1.1, the incidence of prolonged QTcF at week 12 was ≤1 % in both prucalopride ≤2 mg/day and placebo recipients in most studies [33–36, 39]; in the study in elderly patients [37], the incidence was 6 and 6 % of prucalopride 1 and 2 mg/day versus 14 % of placebo recipients. In placebo-controlled trials, palpitations occurred in <1 % of prucalopride 1 and 2 mg/day and placebo recipients [4].

Prucalopride overdosage (up to ten times the recommended dosage) was generally well tolerated in healthy volunteers [4].

6 Dosage and Administration of Prucalopride

Oral prucalopride film-coated tablets are indicated in the EEA for symptomatic treatment of CIC in adults in whom laxatives fail to provide adequate relief [4, 5]. The approved dosage is 2 mg once daily, with or without food, in patients aged ≤65 years. Patients aged >65 years or those with severe hepatic (Child-Pugh class C) impairment should initiate treatment with 1 mg/day; this can be increased to 2 mg/day if required. Prucalopride should not be administered to patients aged younger than 18 years. Patients with severe renal impairment (glomerular filtration rate of <30 mL/min/1.73 m^2) should receive prucalopride 1 mg/day. No dosage adjustment is necessary for patients with mild to moderate renal or hepatic impairment.

Prucalopride treatment is contraindicated in patients with renal impairment requiring dialysis; intestinal perforation or obstruction as a result of a structural or functional disorder of the gut wall; obstructive ileus; severe inflammatory conditions of the intestinal tract (e.g. Crohn's disease or ulcerative colitis); toxic megacolon/megarectum; and hypersensitivity to the active substance or any of the excipients [4]. Caution is recommended when administering prucalopride to patients with severe and clinically unstable concomitant disease (e.g. a history of arrhythmias or ischaemic cardiovascular disease). Local prescribing information should be consulted for further, detailed information, including special warnings and precautions and drug interactions.

7 Place of Prucalopride in the Management of Chronic Idiopathic Constipation

In a treatment algorithm proposed by a group of European experts in constipation, prucalopride treatment was recommended if patients with chronic functional constipation do not experience relief following education, lifestyle and dietary measures and treatment with two courses of laxatives [51]. The most widely accepted criteria for chronic (functional or idiopathic) constipation are the ROME III criteria [1]. Trials discussed in this review included patients using criteria generally based on ROME III (Sect. 4).

The primary endpoint selected in most clinical trials was response rate (proportion of patients with ≥3 SCBMs/week) during the treatment period (Sect. 4). This is considered to be a clinically meaningful endpoint, as it combines a subjective measure (sensation of evacuation completeness) with an objective measure (number of bowel movements occurring >24 h after the last use of laxatives), and 3 SCBMs/week is towards the lower end of the expected number of bowel movements per week with normal bowel function [34, 36]. In these trials, patients generally began with fewer than 2 SCBMs per month at baseline (Sect. 4.1).

In twelve-week clinical trials, prucalopride was significantly more effective than placebo in adults with CIC, increasing the number of SCBMs and decreasing the time to first SCBM, as well as generally improving other constipation-related symptoms and HR-QOL (Sect. 4.1.1). While most pivotal, placebo-controlled trials had a very high proportion of female patients (>85 %), data from these trials were supported by one trial [33] that only included male patients (Sect. 4.1.1).

Unexpectedly, while the primary endpoint was met in the 12-week trials, a 24-week trial did not support these results; prucalopride and placebo recipients did not significantly differ in most endpoints, including the primary endpoint (response rate) during weeks 1–24 or 1–12 (potentially a result of a high placebo response) [Sect. 4.1.2]. Moreover, significantly fewer prucalopride than placebo patients showed improvements in PAC-SYM overall score and stool subscale scores in this study; in contrast, the 12-week studies generally showed that prucalopride was more effective than placebo with regard to PAC-SYM scores. PAC-SYM scores were means of all patients, not just those with PAC-SYM (abdominal, rectal and stool) symptoms present at baseline.

However, an integrated analysis including the 24-week and 12-week trials upheld the significant difference between prucalopride and placebo during weeks 1–12 in constipation symptoms, including response rate and HR-QOL (Sect. 4.3). Other integrated and meta-analyses supported this treatment difference, including one integrated subgroup analysis involving women in whom laxatives had failed (the approved indication is adults in whom laxatives have failed) [Sect. 4.3]. Further long-term, comparative trials investigating the efficacy of prucalopride are warranted, as CIC is a chronic problem, requiring long-term treatment; if it is found in additional trials that prucalopride does not significantly differ from placebo in the long term, alternative treatment courses may be necessary, such as repeated short-term courses. A noncomparative, single-centre study ($n = 155$) in patients with CIC or IBS-C, with a median follow-up of 24 months, found that of the 96 prucalopride 1–2 mg/day recipients who reported a good symptomatic improvement (response) at 4 weeks, were not lost to follow-up, and followed medication protocol, 63.5 % retained their responder status (39.3 % of the initial population) [52].

CIC appears to be a particular issue in elderly patients, with an estimated prevalence of 15–50 % [37]. While the primary endpoint (response rate) was not achieved in a 4-week trial in elderly patients with CIC at the approved dosages, several other constipation symptoms were improved with prucalopride versus placebo (Sect. 4.1.1.1). The primary endpoint was considered an ambitious target in these patients [37].

A 4-week trial comparing prucalopride with PEG-3350 + electrolytes in patients with CIC, conducted in a phase I unit in Romania, found that PEG-3350 + electrolytes was noninferior but not superior to prucalopride, in terms of the primary endpoint of response rate during the final study week (Sect. 4.2). Several secondary endpoints improved to a significantly greater extent with PEG-3350 + electrolytes than with prucalopride. While the use of a controlled environment in the phase I unit does standardize environmental factors, allowing for a clearer comparison between treatments, it is also an artificial environment for the patients and may not accurately reflect normal life [13, 53]. Moreover, the 4-week evaluation period (the maximum duration possible in this environment) was shorter than the usual evaluation period for constipation studies [13], and the primary endpoint was not one commonly used, with only results from the final week being included instead of an average across the treatment period [53]. Further comparisons of prucalopride and PEG-3350 + electrolytes, of longer duration and in a more 'real-world' setting, would be of great interest to clarify any differences in efficacy and tolerability. However, as PEG-3350 is a laxative, and prucalopride is indicated in patients in whom laxatives have failed to provide relief, comparisons of prucalopride with other, non-laxative, common constipation treatments, such as linaclotide and lubiprostone (both prosecretory agents with demonstrated efficacy and tolerability in CIC and IBS-C [3]) would potentially be of greater interest, particularly in patients who have already received laxative treatment.

Prucalopride was generally well tolerated in clinical trials in patients with CIC; most adverse events were transient and of mild to moderate severity, and primarily occurred on the first day of treatment (Sect. 5). The most common adverse events were headache, diarrhoea, nausea and abdominal pain. The favourable tolerability profile of prucalopride was maintained in the longer term. An integrated analysis of data from four trials found that there may be altered relative risks of specific adverse events in certain patient subgroups (e.g. a higher risk of diarrhoea in Asian patients or a higher risk of nausea in women); further investigation into these potential differences would be of interest.

The nonselective 5-HT_4 agonists cisapride and tegaserod, previously available for the treatment of constipation in some markets, were withdrawn from most markets as a result of their potential association with an increased risk of cardiovascular events (QT prolongation and ischaemia, respectively) [26]. The increased risk with cisapride treatment was attributed to interactions with the hERG cardiac potassium channel; the exact mechanism for the potential increased risk with tegaserod is unknown, although there is some evidence to suggest that it may be associated with its interaction with 5-HT_1 receptor subtypes [26]. Highly selective 5-HT_4 agonists are not expected to cause cardiovascular adverse events; the cardiovascular concerns associated with these two nonselective drugs were not observed with selective 5-HT_4 agonists (prucalopride, velusetrag, naronapride) or for nonselective 5-HT_4 agonists with no hERG or 5-HT_1 affinity (renzapride, clebopride, mosapride), in a systematic review [26].

As a result of these concerns, however, the cardiovascular safety profile of prucalopride has been extensively investigated (Sects. 2, 5). The commonly accepted safety margin between a drug's IC_{50} for hERG potassium channel agonist activity and its maximum unbound concentration in humans is a 30-fold separation, to reduce the risk of cardiac proarrhythmia [28]. Prucalopride has a binding affinity that is $\approx$2 to 3 orders of magnitude lower for hERG channels than for h5-HT_4 receptors (Sect. 2), and the safety margin is at least 200 times the therapeutic plasma concentration, well outside the 30-fold safety threshold [28]. Cisapride, by contrast, has only a <10-fold difference in selectivity for 5-HT_4 receptors and hERG channels, and no discernible safety margin between its hERG IC_{50} value and its therapeutic concentration [28].

Moreover, a thorough QT study demonstrated that prucalopride at therapeutic and supratherapeutic dosages had no effect on cardiac repolarization in healthy volunteers (Sect. 2), and no cardiovascular safety issues were observed in patients with CIC receiving prucalopride (Sect. 5). However, further investigation of the long-term effects of prucalopride on cardiovascular safety in large samples of patients with CIC is necessary to draw more accurate conclusions on this endpoint.

As yet, studies investigating the cost effectiveness of prucalopride in patients with CIC are limited; further pharmacoeconomic studies would be of great benefit in placing this drug among the treatment options currently available for this disease. In one study, utilizing a Markov model and from the perspective of Dutch payers in 2011, and using data from patients with CIC who had received standard laxative treatment, the cost effectiveness of prucalopride versus continued laxative treatment was calculated at €9015 per quality-adjusted life-year (QALY) gained [54]. Assuming a willingness-to-pay threshold of €20,000 per QALY gained, probabilistic sensitivity analysis indicated that there was a >80 % probability that prucalopride was cost effective compared with continued laxative use [54].

A retrospective case-series audit study, using real-world data from 40 women in Ireland with CIC who had not responded to at least two different classes of laxatives and who were treated with prucalopride, compared data from 12 months of treatment with prucalopride with data from the 12-month baseline period, during which patients were receiving laxatives [55]. While prucalopride medication costs were higher than with laxatives only, prucalopride recipients experienced a significantly lower number of investigations and procedures in the 12 months of the study, ultimately resulting in cost savings of €1048.08 per patient per year (2012 cost data).

As a prokinetic drug, prucalopride may be of most use in patients with slow-transit constipation rather than 'outlet-type' constipation; further investigation into patient subclasses would be of great interest.

Prucalopride should not be administered to patients aged younger than 18 years (Sect. 6). Despite beneficial effects in a small, noncomparative trial in children with functional constipation aged 4–12 years [56], results from a large, randomized, double-blind, placebo-controlled, phase III trial, conducted as part of EMA post-approval commitments, indicated that 8 weeks' treatment with prucalopride did not significantly differ from placebo in children with functional constipation aged 6 months to 18 years [57]. The difference in prucalopride efficacy between these children and the adults in Sect. 4 may be the result of a lower prevalence of abnormal-transit constipation in children than in adults (e.g. the prevalence of slow-transit constipation in children is 13–25 %; prevalence in adults is 60–71 % [58]); prucalopride, as a prokinetic drug, would thus conceivably have a lesser effect in children. Other potential reasons for the difference include behavioural differences between adults and children and differences in the chosen primary endpoints.

As yet, no quality data are available regarding the efficacy and tolerability of prucalopride in only patients with IBS-C. There is a potential for overlap in the diagnosis of CIC and IBS-C, with the main difference being greater

pain or discomfort in the latter [3]. As pain plays such a factor in IBS-C, it would be of great interest to observe whether the efficacy of prucalopride extends into this group, particularly given the potential overlap in diagnoses.

In conclusion, in five well-designed, 12-week trials in adult patients with CIC, oral prucalopride 2 mg/day was significantly more effective than placebo at improving bowel function, HR-QOL and patient satisfaction; however, no significant difference between prucalopride and placebo was observed in one 24-week trial. Oral PEG-3350 + electrolytes reconstituted powder was found to be noninferior but not superior to prucalopride in a 4-week, controlled-environment trial. Prucalopride was generally well tolerated, and was not associated with any cardiovascular safety issues. Although further long-term and comparative data would be beneficial, prucalopride provides an additional treatment option for patients with CIC.

Data selection sources:

Relevant medical literature (including published and unpublished data) on Prucalopride was identified by searching databases including MEDLINE (from 2013), PubMed (from 2013) and EMBASE (from 2013) [searches last updated 6 November 2015], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Constipation, prucalopride, Resolor, Resotran, Resotrans.
Study selection: Studies in patients with constipation who received prucalopride. When available, large, well-designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Acknowledgments During the peer review process, the manufacturer of prucalopride was also offered an opportunity to review this article. Any changes resulting from comments received were made on the basis of scientific and editorial merit.

Compliance with Ethical Standards

Funding The preparation of this review was not supported by any external funding.

Conflict of interest Karly Garnock-Jones is a salaried employee of Adis/Springer, is responsible for the article content and declares no relevant conflicts of interest.

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