Prucalopride: novel drug for chronic idiopathic constipation

Pawan Dhull1, Sachin Maggo2*, Piyush Angrish3, Anuj Singh4, Uthara K. S.2, Akhila A. S.5

ABSTRACT

Chronic Idiopathic Constipation (CIC), defined as constipation in which the underlying cause is unknown, is a common medical illness with a profound negative impact on health-related quality of life and increased propensity for life threatening complications. Current treatment for CIC includes lifestyle modifications, over-the-counter medications, and prescription medications. Presently, the only approved, prescription products for CIC in the US are prosecretory agents. However, the current knowledge that serotonin plays an important role in colonic motility has opened new horizons in the treatment of CIC promoting use of prokinetic agents with a different mechanism of action. Prucalopride is a highly selective 5-hydroxytryptamine type 4 (5-HT4) receptor agonist that enhances propulsive motor patterns in the large intestine due to a high affinity for 5-HT4 receptors in gastrointestinal (GI) tissues. The onset of action of Prucalopride is fast, shows rapid absorption, oral bioavailability of 93% and linear pharmacokinetics. Most common adverse reactions seen are headache, nausea, diarrhea, and abdominal pain. Clinical trials for Prucalopride have been positive, and results suggest that the drug may be a new safe and effective option for CIC treatment, especially for patient’s refractory to prosecretory agents. As a prescription drug for the management of constipation and given the virtual demise of other prokinetic agents for this indication, prucalopride competes primarily with another class of agents: those that stimulate secretion. With Shire Pharmaceuticals having already received US FDA approval in Dec 2018, Prucalopride may soon be a new addition to the mounting armoury of drugs against CIC.

Keywords: Chronic Idiopathic Constipation, 5 HT4 receptor agonists, Prokinetic agents, Prucalopride

INTRODUCTION

Chronic Idiopathic Constipation (CIC), defined as constipation in which the underlying cause is unknown (i.e., not caused by another disease or a medication), is a common and often enervating medical illness encountered by physicians daily. Several working groups (World Gastroenterology Organization, American Gastroenterological Association, American College of Gastroenterology, and the Rome Foundation working group) have recognized that the condition comprises multiple symptoms, including straining during defecation, lumpy or hard stools, sensation of incomplete evacuation, and fewer than 3 defecations per week.1 (Table 1) Additionally, patients with CIC often feel bloated and have abdominal pain. CIC represents an extremely troublesome disorder with a profound negative impact on health-related...
quality of life as other chronic conditions such as diabetes or heart disease and depression in women.2,3 Also, CIC can lead to increased risk for serious complications and has been associated with comorbidities such as faecal impaction, diverticular disease, and rectal prolapse.4 The prevalence of chronic constipation is 10.0% -14.9% in the USA.5,6 An estimated 35 million adults have CIC in the United States (US).6 Chronic idiopathic constipation is more prevalent in women, non-Whites, and elderly patients. Chronic idiopathic constipation is associated with lower socioeconomic status, low fibre diet, and lack of exercise.6,9

Table 1: Modified ROME Foundation diagnostic criteria for functional constipation.

| Criteria | Definition |
|----------|------------|
| Straining during defecations | |
| Lumpy or hard stools | |
| Sensation of incomplete evacuation | |
| Sensation of anorectal obstruction/blockage | |
| Manual maneuvers to facilitate defecations (e.g., digital evacuation, support of pelvic floor) | |

SCBM: Spontaneous complete bowel movement

The goal of treatment for CIC is to reinstate normal bowel function, thereby increasing complete spontaneous bowel movement (CSBM) leading to an improvement in health-related quality of life. Current treatment for CIC includes lifestyle modifications, over-the-counter medications, and prescription medications. Presently, the only approved, prescription products for CIC in the US are prosecretory agents. In general, prosecretory agents act by enhancing fluid secretion into the GI tract.

Three drugs are currently licensed in the US: lubiprostone, linaclotide, and plecanatide. Tegaserod, a non-selective 5-HT4 agonist working by stimulating gut motility via 5-HT4 agonism was approved in the US in 2002 for the treatment of IBS-C and CIC but was later voluntarily withdrawn from the US market in 2007 market due to reports of serious cardiovascular ischemic events, unstable angina, heart attack, and stroke.

In spite of available treatment options, there continues to be vast patient discontent with results and an overall unmet need for additional treatment options for CIC, while counting on a different mechanism of action than presently available prosecretory agents.10,11

Prucalopride is a highly selective 5-hydroxytryptamine type 4 (5-HT4) receptor agonist developed by Shire Pharmaceuticals that stimulates colonic motility providing substantial symptomatic improvement in patients with CIC. It acts by increasing the number and amplitude of high amplitude propagating contractions (HAPCs), ie, the peristaltic contractions moving the contents of the colon forward as against osmotic laxatives and prosecretory products which use alternative mechanisms of action. The US Food and Drug Administration (FDA) has approved Shire’s Prucalopride (Motegrity) in December 2018 for the treatment of CIC.12

MECHANISM OF ACTION

It has been found that serotonin plays important role in colonic motility; hence serotonin receptors have long been targets for research in treatment of CIC. Prucalopride is a dihydro-benzofuran carboxamide derivative approved in October 2009 by the European Medicine Agency for the treatment of Functional constipation (FC) in adults in whom treatment with laxatives failed to provide relief. It is a highly selective 5-hydroxytryptamine type 4 (5-HT4) receptor agonist that effectually enhances propulsive motility patterns in the large intestine due to a high affinity for 5-HT4 receptors in gastrointestinal (GI) tissues. It works by enhancing longitudinal smooth muscle contractions and promoting propulsion of luminal contents while reducing the resistance potentially produced by circular smooth muscle contractions.13,14 Moreover, administration of prucalopride induces HAPC, that are grossly decreased or absent in patients with CIC.15,16 The drug’s affinity for other receptors is present only at concentrations that exceed its 5-HT4 receptor affinity by at least 150 times. Prucalopride is therefore differentiated from other 5-HT4 receptor agonists such as tegaserod and cisapride, whose affinity for other receptors/channels such as 5-HT1.2 (tegaserod) and the 5-HT2 and human Ether-á-go-go Related Gene (hERG) channel (cisapride) is in the same range as their affinity for the 5-HT4 receptor.17

CLINICAL PHARMACOLOGY

Prucalopride has low plasma protein binding, with mean values ranging from 28.9% to 33.3%. It is rapidly absorbed from the gastrointestinal tract when given orally. The bioavailability of the drug is high (>93%) and is not altered by intake of food. The drug can be taken at any time of the day, however, in clinical practice it is usually suggested to take it early morning, as it supplements with the physiologic reflexes stimulating colonic motility. Once given orally, the maximum concentration is reached within 2-3 hours and its plasma terminal half-life is projected to be about 30 h.

The steady state is achieved after 4-7 days of treatment, and plasma concentration directly increases by increasing the dose. Because of these characteristics prucalopride can reach the therapeutic effect rapidly, with the first spontaneous bowel movement expected after a median of 2.5 hours and the first spontaneous complete bowel movement within a median of 50-54 hours.18,19

International Journal of Basic & Clinical Pharmacology | August 2019 | Vol 8 | Issue 8  Page 1924
individual determine renal clearance (Cl renal) and apparent total clearance of the drug; in subjects with mild renal impairment, the reduced clearance does not significantly alter the PK profile; however, in subjects with moderate and severe renal impairment, area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC0-∞) is 1.5- and 2.3-fold higher, and t1/2 is prolonged by about 40% and 50%, respectively.

Findings from PD studies indicate that prucalopride decreases total colonic transit time and thereby increases motility of the colon in both healthy subjects and patients with CIC. An integrated analysis of 3 randomized, placebo-controlled, Phase 2 dose-finding studies in 280 patients with CIC showed a clear correlation between constipation symptom severity and increased colonic transit time, and that improvements in CIC response correlated with decreased colonic transit time.20-22

DOSAGE, CLINICAL EFFICACY AND DRUG INTERACTIONS

Three dose-response studies (PRU-INT-1, PRU-INT-2, and PRU-USA-3), supported the testing of 2 mg and 4 mg QD in the initial Phase 3 studies (Studies 6, USA-11, and USA-13). Results of these studies showed that the 4 mg QD prucalopride dose provided no significant benefit over the 2 mg QD dose. Therefore, a dose of 2 mg QD is considered appropriate for the treatment of CIC in adult patients. Only the 2 mg QD dose was investigated in Studies 3001 and 302.

The 1 mg dose is the recommended dose in patients with severe renal impairment (glomerular filtration rate less than 30 mL/min/1.73 m2).23 As Prucalopride is not dependant on cytochrome P450 system metabolism, and minimally binds to plasma protein, the drug displays very low drug-drug interactions; thus, it is possible to administer prucalopride together with other laxatives featuring a different mechanism of action (e.g. osmotics, bulking agents, softeners, etc.)

SAFETY AND ADVERSE DRUG REACTIONS

The lack of selectivity of most serotonin receptor agonist developed in these recent years caused serious, especially cardiovascular, adverse events.24 However, prucalopride is a completely different serotonin receptor agonist, because its molecular structure (benzofurancarboxamide derivative) has high affinity for the human 5HT4 receptors. Its high selectivity may explain the relatively low number of adverse events reported after treatment.

Indeed, no significant hemodynamics or ECGs changes (in particular, no increase in the incidence of prolongation of the QTc interval) were found both in healthy controls and patients.25 In healthy subjects, heart rate (HR) increases of 5-8 bpm have been seen at 3 hours [Cmax] of first-time administration of prucalopride, however the same returned to baseline at steady state. No other cardiovascular effects have been noted in nonclinical species at concentrations of at least 50 times the therapeutic plasma concentrations in humans. Also, the drug has not shown any effect on coronary artery contraction or platelet aggregation at concentrations exceeding those seen with the therapeutic dose of 2 mg once daily (QD).26 Due to concerns regarding possible cardiovascular risk in patients treated with non-selective 5-HT4 agonist products, Shire conducted extensive proactive and retrospective analyses on cardiovascular and major adverse cardiovascular events (MACE) risk. All investigations have been unable to demonstrate increased cardiovascular risk.27

Concerning adverse events, there were 4 AEs reported with an incidence of >5%: headache (17%), nausea (14%), diarrhea (12%), and abdominal pain (10%). These 4 AEs occurred at a higher rate in patients on prucalopride than placebo and were consistently reported among the 16 randomized controlled studies. (Table 2) However, adverse events were generally transient and lasted <5 days. The majority of these AEs were mild or moderate in severity. There was a low incidence of severe AEs, with only 2-3% of patients reporting a severe headache, nausea, diarrhea, or abdominal pain over the entire course for each of the controlled studies.28,29

| Table 2: Commonly Reported (>5%) Adverse Events in Pooled Randomized Double-blind Placebo-controlled Studies ≥4 Weeks. |
|---------------------------------------------------------------|
|                     | Placebo | Prucalopride | Prucalopride |
|                     | N=1973  | 1 mg         | 2 mg         |
| Total               | N=3305  | N=330        | N=1516       |
| Any AE              | 1058 (53.6%) | 2146 (64.9%) | 184 (55.8%)  | 964 (62.4%) |
| Headache            | 186 (9.4%)  | 642 (19.4%)   | 44 (13.3%)   | 265 (17.5%) |
| Nausea              | 126 (6.4%)  | 509 (15.4%)   | 32 (9.7%)    | 206 (13.6%) |
| Diarrhoea           | 72 (3.6%)   | 396 (12.0%)   | 27 (8.2%)    | 179 (11.8%) |
| Abdominal pain      | 153 (7.8%)  | 321 (9.7%)    | 22 (6.7%)    | 151 (10.0%) |

Note: Randomized DBPC=16 Phase 2-4 studies ≥4 weeks duration in chronic idiopathic constipation. * Includes all patients titrated from prucalopride 1 mg to 2 mg.
CLINICAL TRIALS

Prucalopride is a highly selective serotonin 5-HT4 receptor agonist which has been shown to stimulate gut motility in vitro and in vivo. Scintigraphic studies conducted in healthy volunteers have revealed that the drug accelerated whole gut and colonic transit, however it does not affect gastric emptying or small bowel transit. Among patients with constipation, nevertheless, the very same authors using the exact same scintigraphic technique found that prucalopride in doses of 2 or 4 mg daily accelerated whole gut, gastric, small bowel and colonic transit in constipated patients. Importantly, prucalopride does not have any adverse effects on anorectal motor function or rectal sensation in either healthy volunteers or patients with constipation. In studies of colonic motility, prucalopride has been shown to be stimulatory.

**Figure 1: Primary Endpoint- Proportion of patients achieving ≥3 CSBM’s/week over weeks 1-12 in randomized double blind placebo controlled studies ≥12 weeks.**

**Figure 2: Forest Plot of Primary Efficacy Endpoint Results in Randomized Double blind Placebo-controlled Studies ≥12 Weeks.**
The evidence of efficacy of prucalopride comes from 6 randomized, double-blind, placebo-controlled studies of ≥12 weeks duration in patients with confirmed CIC: Studies 3001, 302, 6, USA-11, USA-13, and 401. Patients were selected for the studies based on modified ROME Foundation diagnostic criteria for functional constipation. Exclusion criteria for the studies included patients with constipation caused by secondary causes (drug-induced or after surgery), organic disorders of the large bowel (megacolon/megarectum, pseudo-obstruction), those with comorbidities (uncontrolled cardiovascular, liver, or lung disease, neurologic or psychiatric disorders, cancer or acquired immune deficiency syndrome) and impaired renal function (creatinine clearance <30/≤50 mL/min). Prucalopride 2 mg and 4 mg were included in the initial studies; however, the 4 mg dose was omitted from the later studies due to lack of increased efficacy compared to the 2 mg dose. In Studies 302 and 401, patients ≥65 years of age started at a dose of 1 mg prucalopride QD, with the option to increase to 2 mg QD.

If the dose was increased to 2 mg QD, the patient remained on this dose for the duration of the study. Since the majority of patients who initially started on prucalopride 1 mg increased to 2 mg during the study, the efficacy results for these studies were combined into a single group identified as 2 mg. Five of the 6 studies (3001, 302, 6, USA-11, and USA-13) met the primary endpoint, showing a higher proportion of patients treated with prucalopride achieving ≥3 CSBMs per week over the 12-week treatment period (Figure 1.2). The absolute treatment effect between the arms was statistically significant in Studies 3001, 302, 6, USA-11, and USA-13 (p<0.01). Importantly, the effects of prucalopride on CSBMs/week occurred quickly and persisted. In the 5 positive efficacy studies with prucalopride, the response was attained within the first week and maintained over the entire treatment period.36

Prucalopride consistently showed numerically and/or statistically significantly better results compared with placebo on the secondary efficacy endpoints, including the proportion of patients with an average increase of ≥1 CSBM, the increase in average number of CSBMs, the time to first CSBM, and improvement in PAC–SYM and PAC–QOL scores. Overall, prucalopride increased the frequency of bowel movements and improved symptoms and health-related quality of life in patients with CIC.36

CONCLUSION, PLACE IN THERAPY

As on date, prosecretory agents are the current first line treatment for chronic idiopathic constipation not responsive to other over-the-counter medications. In the current scenario, the restriction to laxative failures is also very much in keeping with a number of authoritative guidelines which suggest a step-up approach to the treatment of constipation: beginning with dietary and lifestyle changes, progressing through osmotic laxatives (such as polyethylene glycol derivatives) and reserving pharmacological therapies for people whose condition fails to respond to these steps. It must be stressed that there are very few studies comparing the efficacy of a new pharmacological agent with a traditional laxative; for this reason, the real therapeutic gain attributable to prucalopride over and above a laxative remains somewhat conjectural. In contrast, as seen in day to day practice, there is a large group of patients who either do not respond or tolerate or have contraindications to prosecretory agents. This has led to an inevitable requirement for discovering safe and effective CIC treatments.

Prucalopride is a highly selective serotonin 5-HT4 receptor agonist which acts as a prokinetic in the gut. Clinical trials for Prucalopride to date have been positive, and maiden results suggest that prucalopride may be a new safe and effective option for CIC treatment, especially for patient’s refractory to or unable to tolerate prosecretory agents. As a prescription drug for the management of constipation and given the virtual demise of other prokinetic agents for this indication, prucalopride competes primarily with another class of agents: those that stimulate secretion.

To date, cardiac toxicity, which bedevilled other drugs in this class, has not been a major issue. Long-term studies and post marketing data will be critical in assessing the real benefits and risks of this promising compound.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterol. 2006Apr1;130(5):1480-91.
2. Belsey J, Greenfield S, Candy D, Geraint M. Systematic review: impact of constipation on quality of life in adults and children. Alimentary pharmacol & therapeutics. 2010May;31(9):938-49.
3. Wald A, Scarpiognato C, Kamm MA, Mueller-Lissner S, Helfrich I, Schuitt C, et al. The burden of constipation on quality of life: results of a multinational survey. Alimentary pharmacol & therapeutics. 2007Jul1;26(2):227-36.
4. Cook JJ, Talley NJ, Benninga MA, Rao SS, Scott SM. Chronic constipation: overview and challenges. Neurogastroenterol and Motility. 2009Dec;21:1-8.
5. Camilleri M, Ford AC, Mawe GM, Dinning PG, Rao SS, Chey WD, et al. Chronic constipation. Nature reviews Disease primers. 2017Dec14;3:17095.
6. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. The American J Gastroenterol. 2011Sep;106(9):1582.
7. Bossard H, Drehn R, Schnegg JF, Bula CJ. The treatment of chronic constipation in elderly people. Drugs Aging. 2004Dec1;21(14):911-30.
8. Higgins PD, Johanson JF. Epidemiology of constipation in North America: a systematic review. Am J Gastroenterol. 2004 Apr;99(4):750.

9. Peppas G, Alexiou VG, Mourtzoukou E, Falagas ME. Epidemiology of constipation in Europe and Oceania: a systematic review. BMC gastroenterol. 2008 Dec;8(1):5.

10. Prather CM, Camilleri M, Zinsmeister AR, McKinzie S, Thomforde G. Tegaserod accelerates orocecal transit in patients with constipation-predominant irritable bowel syndrome. Gastroenterol. 2000 Mar 1;118(3):463-8.

11. Loughlin J, Quinn S, Rivero E, Wong J, Huang J, Krakstein J et al. Tegaserod and the risk of cardiovascular ischemic events: an observational cohort study. J cardiovascular pharmacol and therae. 2010 Jun;15(2):151-7.

12. Tack J, Van Outryve M, Beyens G, Kerstens R, Vandeplassche L. Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. Gut. 2009 Mar 1;58(3):357-65.

13. Shin A, Camilleri M, Kolar G, Erwin P, West CP, Murad MH. Systematic review with meta-analysis: highly selective 5-HT4 agonists (prucalopride, velusetrag or naronapride) in chronic constipation. Aliment Pharmacol Ther. 2014,39:239-53.

14. Mawe GM, Hoffman JM. Serotonin signalling in the gut—functions, dysfunctions and therapeutic targets. Nat Rev Gastroenterol Hepatol. 2013,10:473-86.

15. Bassotti G, Chistolini F, Nzepe FS, Morelli A. Colonics propulsive impairment in intractable slow-transit constipation. Arch Surg. 2003,138:1302-4.

16. De Schryver AM, Andriesse GI, Samsom M, Smout AJ, Gooszen HG, Akkermans LM. The effects of the specific 5HT(4) receptor agonist, prucalopride, on colonic motility in healthy volunteers. Aliment Pharmacol Ther. 2002,16:603-12.

17. De Maeyer JH, Lefebvre RA, Schuurkes JA. 5-HT4 receptor agonists: similar but not the same. Neurogastroenterol Motil. 2008,20:99-112.

18. Van De Velde VJ, Amsja JJ, Vandeplassche LM. Kinetics and absolute oral bioavailability of prucalopride. Gastroenterol. 2010,138(5 Suppl 1):S-230.

19. Tack J, Quigley E, Camilleri M, Vandeplassche L, Kerstens R. Efficacy and safety of oral prucalopride in women with chronic constipation in whom laxatives have failed: an integrated analysis. United European Gastroenterol J. 2013,1:48-59.

20. Bouras EP, Camilleri M, Burton DD, Thomforde G, McKinzie S, Zinsmeister AR. Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder. Gastroenterol. 2001 Feb;120(2):354-60.

21. De Schryver AM, Andriesse GI, Samsom M, Smout AJ, Gooszen HG, Akkermans LM. The effects of the specific 5HT4 receptor agonist, prucalopride, on colonic motility in healthy volunteers. Alimentary pharmacol Ther. 2002 Mar 1;16(3):603-12.

22. Emmanuel A, Cools M, Vandeplassche L, Kerstens R. Prucalopride improves bowel function and colonic transit time in patients with chronic constipation: an integrated analysis. The American J gastroenterol. 2014 Jun;109(6):887.

23. Diederik K, Mugie SM, Benninga MA. Efficacy and safety of prucalopride in adults and children with chronic constipation. Expert Opin. Pharmacother. 2015,16:407-416.

24. Stillman MJ, Tepper DE, Tepper SJ, Cho L. QT prolongation, Torsade de Pointes, myocardial ischemia from coronary vasospasm, and headache medications. Part 2: review of headache medications, drug-drug interactions, QTc prolongation, and other arrhythmias. Headache. 2013,53:217-24.

25. Mendezlevski B, Amsja J, Chanter DO, Robinson P, Kerstens R, Vandeplassche L, et al. Assessment of the cardiac safety of prucalopride in healthy volunteers: a randomized, double-blind, placebo- and positive-controlled thorough QT study. Br J Clin Pharmacol. 2012,73:203-9.

26. Conlon K, De Maeyer JH, Bruce C, Schuurkes JA, Christie L, McRedmond J, et al. Nonclinical Cardiovascular Studies of Prucalopride, a Highly Selective 5-Hydroxytryptamine 4 Receptor Agonist. J Pharmacol Exp Ther. 2018 Feb;364(2):156-69.

27. Gilsenan A, Fortuny J, Planes E, Ruigómez A, Karlsson P, Flynn RW, et al. 386-Non-interventional cohort study of the relative incidence of major cardiovascular events among patients initiating prucalopride versus a matched comparator cohort initiating polyethylene glycol 3350 (PEG). Gastroenterol. 2018 May 1;154(6):S-92.

28. Leeukasolvong S, Ke M, Zou D, Choi SC, Tack J, Quigley EM, et al. Factors predictive of treatment-emergent adverse events of prucalopride: an integrated analysis of four randomized, double-blind, placebo-controlled trials. Gut Liver. 2015,9:208-13.

29. Camilleri M, Beyens G, Kerstens R, Robinson P, Vandeplassche L. Safety assessment of prucalopride in elderly patients with constipation: a double-blind, placebo-controlled study. Neurogastroenterol Motil. 2009,21:1256-e117

30. Sanger GJ, Quigley EM. Constipation, IBS and the 5-HT4 receptor: what role for prucalopride? Clinical Medicine. Gastroenterol. 2010 Jan;3:CGast-S4136.

31. Bouras EP, Camilleri M, Burton DD, McKinzie S. Selective stimulation of colonic transit by the benzofuran 5HT4 agonist, prucalopride, in healthy humans. Gut. 1999 May;44(5):682-6.

32. Bouras EP, Camilleri M, Burton DD, Thomforde G, McKinzie S, Zinsmeister AR. Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder. Gastroenterol. 2001 Feb;120(2):354-60.

33. Coremans G. Prucalopride: the evidence for its use in the treatment of chronic constipation. Core evidence. 2008 Jun;3(1):45.

34. De Schryver AM, Andriesse GI, Samsom M, Smout AJ, Gooszen HG, Akkermans LM. The effects of the
specific 5HT4 receptor agonist, prucalopride, on colonic motility in healthy volunteers. Alimentary Pharmacol Ther. 2002 Mar;16(3):603-12.
35. Quigley EM. Prucalopride: safety, efficacy and potential applications. Therapeutic advances in gastroenterol. 2012 Jan;5(1):23-30.
36. Camilleri M., Piessevaux H., Yiannakou Y., Tack J., Kerstens R., Quigley E. et al. Efficacy and Safety of Prucalopride in Chronic Constipation: An Integrated Analysis of Six Randomized, Controlled Clinical Trials. Dig Dis Sci. 2016;61:2357-72.

Cite this article as: Dhull P, Maggo S, Angrish P, Singh A, Uthara KS, Akhila AS. Prucalopride- Novel drug for chronic idiopathic constipation. Int J Basic Clin Pharmacol 2019;8:1923-9.