ORIGINAL ARTICLE

Gut and Liver, Vol. 9, No. 2, March 2015, pp. 208-213

Factors Predictive of Treatment-Emergent Adverse Events of Prucalopride: An Integrated Analysis of Four Randomized, Double-Blind, Placebo-Controlled Trials

Somchai Leelakusolvong*, MeiYun Ke†, Duowu Zou‡, Suck Chei Choi§, Jan Tack||, Eamonn M. M. Quigley¶, Andy Liu#, and JinYong Kim**

*Division of Gastroenterology, Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand, †Department of Gastroenterology, Peking Union Medical College Hospital, Chinese Academy of Medical Science, Beijing, ‡Department of Gastroenterology, Changhai Hospital, Second Military Medical University, Shanghai, China, §Division of Gastroenterology, Department of Internal Medicine, Wonkwang University College of Medicine, Digestive Disease Research Institute, Iksan, Korea, ||Department of Clinical and Experimental Medicine, Translational Research Center for GastroIntestinal Disorders (TARGID), University of Leuven, Leuven, Belgium, ¶Division of Gastroenterology and Hepatology, Houston Methodist Hospital and Weill Cornell Medical College, Houston, TX, USA, #Department of Statistical Programming, Janssen Research & Development, Shanghai, China, and **Regional Medical Affairs, Janssen Asia-Pacific, Singapore*

Background/Aims: This integrated analysis aimed to identify the factors associated with the most frequently reported treatment-emergent adverse events (TEAEs) in Asian and non-Asian patients with chronic constipation (CC) who receive prucalopride or placebo over 12 weeks. **Methods:** Pooled data from four randomized, double-blind, placebo-controlled, multicenter, phase III studies (NCT00488137, NCT00483886, NCT00485940, and NCT01116206) on patients treated with prucalopride 2 mg or placebo were analyzed. The associations between predictors and TEAEs were evaluated based on a logistic regression model. **Results:** Overall, 1,821 patients (Asian, 26.1%; non-Asian, 73.9%) were analyzed. Prucalopride treatment was significantly associated with diarrhea, headache, and nausea ($p<0.001$), but not with abdominal pain, compared with placebo. Differences in the prevalence of TEAEs between prucalopride and placebo decreased greatly after the first day of treatment. Compared with non-Asians, Asians were more likely to experience diarrhea and less likely to develop abdominal pain, headache, and nausea. Prior laxative use, CC duration, and body weight were not predictive of any of these TEAEs. **Conclusions:** Prucalopride treatment was positively associated with diarrhea, headache, and nausea. Asian patients tended to have a higher frequency of diarrhea but lower frequencies of headache, abdominal pain, and nausea compared with non-Asians. **(Gut Liver, 2015;9:208-213)**

Key Words: Adverse events; Chronic constipation; Predictors; Prucalopride

INTRODUCTION

Constipation is a common gastrointestinal disorder with an estimated prevalence ranging from 2% to 27%, mainly affecting women and elderly population.[1] It is associated with impaired lower gastrointestinal motility, often featuring reduction in the giant migrating contractions that normally provide the main propulsive force to fecal movement through the colon.[2,3] Rome III Diagnostic Criteria for Functional Gastrointestinal Diseases define constipation on the basis of multiple symptoms, including straining, lumpy or hard stools, a sensation of incomplete evacuation, a sensation of anorectal obstruction, and less than three bowel movements (BMs) per week.[4,5]

Chronic constipation (CC) is a heterogeneous disorder that significantly compromises patient's quality of life and results in an economic burden to the individual as well as to the society.[1] Though CC is a very common problem, only a small percentage of patients seek medical care.[6] Traditional remedies for CC include use of fibers, laxatives, prokinetic agents, biofeedback training, and surgery.[3] Despite the widespread and long-term use of laxatives and general acceptance of their efficacy, many patients report high levels of dissatisfaction, and long-term relief is often not achieved.[7] However, more tailored pharmacological approaches, which are directed at specific receptors in-

Correspondence to: Somchai Leelakusolvong
Division of Gastroenterology, Department of Medicine, Siriraj Hospital, Mahidol University Faculty of Medicine, Bangkok 10700, Thailand
Tel: +66-2-419-7281, Fax: +66-2-411-5013, E-mail: somchai.lee@mahidol.ac.th
Received on July 29, 2014. Revised on September 21, 2014. Accepted on September 21, 2014. Published online on December 23, 2014
pISSN 1976-2283 eISSN 2005-1212 http://dx.doi.org/10.5009/gnl14290

volved in the modulation of motility offer considerable promise in promoting appropriate motor patterns and, thereby, improving bowel function.[8]

Prucalopride is a novel dihydrobenzofuran-carboxamide derivative with strong gastrointestinal prokinetic activities,[9] approved in many countries for the symptomatic treatment of CC, with a recommended dose of 1 mg/day for elderly patients and 2 mg/day for adults.[10,11] Prucalopride triggers proximal colonic motility, enhances gastro-pyloro-duodenal motility, and accelerates delayed gastric emptying by specific and selective stimulation of serotonin 5-hydroxytryptamine 4 (5-HT_4) receptors.[12] Clinical evidences support its safety and efficacy in the treatment of CC.[13-18]

A pooled analysis of 14 phase II/III, double-blind, placebo-controlled trials (duration, 4 to 12 weeks; prucalopride dose, 0.5 to 4 mg once daily) in patients with CC revealed that the most frequently reported treatment-emergent adverse events (TEAEs) with prucalopride were gastrointestinal symptoms (nausea, diarrhea, abdominal pain) and headache.[19] These TEAEs were mild-to-moderate in severity and the differences in percentage of patients reporting these adverse events (AEs) between prucalopride and placebo groups were reduced after day 1 of the first dose.[13]

In this study, the results of an integrated analysis of the pooled data from four phase III studies are reported.[14,16,18,20] An additional analysis was performed to evaluate the association of baseline factors with the most frequently reported TEAEs across the subgroups.

Objectives of these analyses were to assess if the most frequently reported TEAEs of prucalopride were similar between Asian and non-Asian subgroups of patients, and also to evaluate the association between the predictors and each of the most frequently reported TEAEs across these subgroups, who received a recommended dose of prucalopride (2 mg/day) or placebo for 12 weeks.

MATERIALS AND METHODS

Post hoc analyses were conducted on the pooled data from four phase III published studies: three pivotal studies (study 1, NCT00488137[18]; study 2, NCT00483886[14]; study 3, NCT00485940[20]) and one Asia-Pacific study (study 4, NCT01116206[16]).

The protocols for each study was approved by an Independent Ethics Committee or by an Institutional Review Board, at each site and all studies were conducted in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, applicable regulatory requirements, and the study protocols. All participants provided written informed consent to participate in the studies.

1. Study designs and population

All four studies were 12-week, randomized, multicenter, double-blind, and placebo-controlled, designed to evaluate the efficacy and safety of once-daily prucalopride in patients with CC. All studies consisted of a 2-week drug-free screening/run-in phase and a 12-week, double-blind, placebo-controlled treatment phase; study 4 (Asian study) included an additional follow-up phase of 7 days after the last dose of the study drug. Based on a computer-generated randomization schedule, patients were randomly assigned to receive 2 or 4 mg of oral prucalopride (except for study 4, where only 2 mg dose was used) or placebo treatment (one tablet daily) before breakfast.

Men and women aged ≥18 years (three pivotal studies) and ≥18–65 years (study 4) with a history of CC were enrolled, where CC was defined as an average of ≤2 spontaneous complete BM (nonlaxative induced) (≤2 spontaneous BM; study 4) per week over the past 6 months or more, accompanied by straining or sensation of incomplete evacuation or hard stools, at least 25% of the time (not preceded within 24 hours by the use of a laxative or an enema). Patients were not eligible for inclusion if their constipation was drug-induced or secondary to endocrine, metabolic or neurological disorders, surgery, known or suspected organic disorders of the large intestine, or megacolon. Other exclusion criteria were uncontrolled cardiovascular, liver or lung diseases, a serum creatinine level ≥180 μmol/L and clinically significant abnormal laboratory values.

From the start of the 2-week run-in period until the end of the studies, patients recorded laxative and study drug intake and details of BMs (rating straining, consistency and feeling of incomplete evacuation for each BM) in a daily diary. Laxatives were allowed only for those patients who did not had a BM for 3 or more consecutive days during the studies. Bisacodyl was used as a rescue medicine. Enema was administered if no BMs were passed with bisacodyl. Rescue medications were not allowed within 48 hours before or after the start of the double-blind treatment.

2. Assessments

The incidence and types of TEAEs were recorded throughout the studies. The purpose of the analyses was to assess the relative prevalence of the most frequently reported TEAEs associated with 2 mg prucalopride and placebo in Asian and non-Asian patients with CC, and to identify the predictors (baseline factors or treatments) associated with the most frequently reported TEAEs. Additionally, changes in clinical laboratory test values, 12-lead electrocardiograms, physical examination, and vital signs were monitored from the screening phase through study completion.

3. Statistical analysis methods

All analyses were performed on the intent-to-treat analysis set, which included randomized patients who received at least one dose of study drug in the double-blind treatment phase. Only patients from the placebo and prucalopride 2 mg treatment

groups were included in these analyses. A logistic regression model was applied in the analysis of each TEAE as the dependent variable; treatment, race (Asian, non-Asian), sex, and prior laxative use were included as discrete independent variables, and age, weight and duration of CC as continuous independent variables. Odds ratios (OR) were estimated to assess the association between the predictors (i.e., the independent variables) and each TEAE based on the logistic regression model. An OR of >1 indicated a positive association and ≤1 indicated null or negative association between the TEAE and the predictor, with rest of the predictors adjusted in the model. If the 95% confidence interval of an OR excluded the value 1 (i.e., $p<0.05$), then it was indicative of a significant association between the TEAE and the predictor. The incidence of TEAEs on day 1 and after day 1 was also evaluated for all patients.

RESULTS

1. Patient demographics and baseline constipation history

Patient demographics and constipation history of patients are provided in Table 1. A total of 1,821 patients were included in this analysis (patients with nonmissing data were included in each analysis). There were no dropouts due to TEAEs from the set of patients used for this analysis. The Asian subgroup included 476 patients; 235 were assigned to placebo and 241 to prucalopride 2 mg. Similarly, in the non-Asian subgroup (n=1,345), 678 were assigned to placebo and 667 to prucalopride 2 mg. Majority of the patients were women (89.3%) and the mean (standard deviation) age was 45 (14.12) years. Overall, 82% (1,495/1,821) of patients reported prior laxative and/or enema use within the 6 months preceding study entry, of which, in majority of the patients (65.7%, 1,196/1,821), CC was not adequately relieved by laxatives. Standard laxative regimens that failed to provide adequate relief was observed to be higher in non-Asian patients (69.8%) relative to Asian patients (54%).

2. Most frequently reported TEAEs

In both subgroups, the most frequently reported TEAEs were diarrhea, nausea, abdominal pain, and headache (Table 2), with

Table 2. Incidence of Most Frequently Reported Treatment-Emergent Adverse Events by Treatment Group in Asian and Non-Asian Subgroups (Intent-to-Treat Analysis Set)

TEAEs	Asian		Non-Asian	
	Placebo (n=235)	Prucalopride (2 mg) (n=241)	Placebo (n=678)	Prucalopride (2 mg) (n=667)
Diarrhea	20 (8.5)	53 (22.0)	31 (4.6)	86 (12.9)
Nausea	6 (2.6)	28 (11.6)	68 (10.0)	130 (19.5)
Abdominal pain	5 (2.1)	16 (6.6)	72 (10.6)	83 (12.4)
Headache	5 (2.1)	24 (10.0)	96 (14.2)	176 (26.4)

Data are presented as number (%). Percentages of subgroups calculated with the number of patients per subgroup as the denominator. Incidence is based on the number of patients who experienced at least one adverse event, not the number of events.
TEAEs, treatment-emergent adverse events.

Table 1. Baseline Patient Demographics and Characteristics of Constipation History during the Previous 6 Months (Intent-to-Treat Analysis Set)

Characteristic	Asian (n=476)	Non-Asian (n=1,345)	Total (N=1,821)
Sex			
Women	424 (89.1)	1,202 (89.4)	1,626 (89.3)
Men	52 (10.9)	143 (10.6)	195 (10.7)
Age, yr	41.4±13.00	46.2±14.30	45.0±14.12
Baseline BMI, kg/m^2	22.3±3.11	25.4±5.10*	24.6±4.86†
Prior laxative/enema use and effect			
Not used	142 (29.8)	184 (13.7)	326 (17.9)
Used and adequate	77 (16.2)	222 (16.5)	299 (16.4)
Used and inadequate	257 (54.0)	939 (69.8)	1,196 (65.7)
AVG BMs/wk	2.3±1.16	5.4±3.63‡	4.5±3.45§
AVG SBMs/wk	1.1±1.03	3.5±3.78‡	2.9±3.45§
AVG SCBMs/wk	0.3±0.46	0.4±0.68‡	0.4±0.63§
AVG bisacodyl/wk	1.6±1.73	2.0±2.43‡	1.9±2.28§
AVG enema/wk	0.1±0.45	0.1±0.33‡	0.1±0.36§
AVG no. of days with bisacodyl/wk	0.9±0.81	0.9±0.94	0.9±0.91

Data are presented as number (%) or mean±SD.
BMI, body mass index; AVG, average; BM, bowel movement; SBM, spontaneous bowel movement; SCBM, spontaneous complete bowel movement.
*n=1,343; †N=1,819; ‡n=1,341; §N=1,817.

most of these TEAEs occurring during the first week of the treatment. Overall, these TEAEs were more prevalent in the prucalopride groups than in the placebo groups. In Asian patients, the incidence of TEAEs in prucalopride group was 38.2% compared with 14.5% in placebo; whereas in non-Asian patients, the incidence of TEAEs was 43.6% in the prucalopride group compared with 29.5% in placebo group.

3. Predictors of TEAEs

Prucalopride treatment versus placebo was significantly associated with TEAEs of diarrhea, headache, and nausea (all p<0.001), but not abdominal pain, after adjustment for patients' race, sex, age, body weight, duration of CC, and prior laxative use. Relative to non-Asian patients, Asian patients were more likely to experience diarrhea and less likely to experience abdominal pain, headache, and nausea (all p<0.001). Women were more likely to experience nausea relative to men (p<0.05), and younger patients were more likely to experience headache (p<0.001) relative to the older patients. Prior laxative use, duration of CC, and body weight did not show any significant association with any of the TEAEs (Table 3).

4. Most frequently reported TEAEs with onset on day 1 versus after day 1

Overall, most TEAEs were reported as mild to moderate in severity and were generally transient. On day 1, the prucalopride group had a higher incidence of most frequently reported TEAEs than placebo in both Asian and non-Asian patients. On the first day of treatment, abdominal pain, diarrhea, headache, and nausea were more commonly reported in the prucalopride group compared with the placebo group. Except for diarrhea, the incidence of all other TEAEs after day 1 was comparable between

Table 3. Odds Ratios for the Association between Each Predictor and Treatment-Emergent Adverse Events (Intent-to-Treat Analysis Set)

Factor	Adverse event			
	Abdominal pain	Diarrhea	Headache	Nausea
Treatment (PRU, PLA)	1.353 (0.986–1.856)	3.073 (2.194–4.305)†	2.420 (1.854–3.160)†	2.480 (1.842–3.339)†
Race (Asian, non-Asian)	0.301 (0.183–0.497)†	1.911 (1.329–2.750)†	0.205 (0.133–0.316)†	0.413 (0.274–0.622)†
Sex (women, men)	1.595 (0.806–3.155)	1.249 (0.705–2.216)	1.719 (0.966–3.060)	1.999 (1.061–3.768)*
Age (18–95 yr)	0.992 (0.979–1.005)	1.002 (0.990–1.014)	0.979 (0.969–0.990)†	0.996 (0.985–1.008)
Weight (38–141 kg)	0.993 (0.981–1.006)	1.002 (0.989–1.015)	0.991 (0.981–1.002)	0.995 (0.984–1.006)
Duration of CC (0.5–77 yr)	0.999 (0.987–1.011)	1.000 (0.988–1.013)	1.009 (0.999–1.019)	0.995 (0.984–1.005)
Prior laxative use (yes, no)	0.812 (0.536–1.230)	0.793 (0.542–1.159)	0.756 (0.537–1.064)	1.466 (0.957–2.245)

Data are presented as odds ratio (95% confidence intervals).
PRU, prucalopride; PLA, placebo; CC, chronic constipation.
*p<0.05; †p<0.001.

Table 4. Most Frequently Reported Treatment-Emergent Adverse Events with Onset on Day 1 versus after Day 1 by Treatment Group in Asian and Non-Asian Subgroups (Intent-to-Treat Analysis Set)

Variable	Asian		Non-Asians	
	Placebo (n=235)	Prucalopride (2 mg) (n=241)	Placebo (n=678)	Prucalopride (2 mg) (n=667)
Total no. of patients with adverse events	34 (14.5)	92 (38.2)	200 (29.5)	291 (43.6)
Onset on day 1	4 (1.7)	62 (25.7)	31 (4.6)	166 (24.9)
Abdominal pain	1 (0.4)	7 (2.9)	9 (1.3)	36 (5.4)
Diarrhea	0	31 (12.9)	0	46 (6.9)
Headache	1 (0.4)	20 (8.3)	17 (2.5)	108 (16.2)
Nausea	2 (0.9)	25 (10.4)	10 (1.5)	72 (10.8)
Onset after day 1	30 (12.8)	49 (20.3)	178 (26.3)	191 (28.6)
Abdominal pain	4 (1.7)	9 (3.7)	64 (9.4)	54 (8.1)
Diarrhea	20 (8.5)	36 (14.9)	31 (4.6)	45 (6.7)
Headache	4 (1.7)	5 (2.1)	82 (12.1)	96 (14.4)
Nausea	4 (1.7)	5 (2.1)	61 (9.0)	69 (10.3)

Data are presented as number (%). Percentages of treatment subgroups calculated with the number of patients per subgroup as the denominator. Incidence is based on the number of patients who experienced at least one adverse event, not the number of events.

prucalopride and placebo groups in both Asian and non-Asian patients (Table 4).

DISCUSSION

This integrated analysis focuses on the results obtained from the data of four phase 3 randomized, multicenter, double-blind, placebo-controlled studies on the efficacy and safety of once-daily prucalopride (2 mg) for 12 weeks in patients with CC. Prucalopride treatment and race were the factors associated with the most frequently reported TEAEs. Consistent with the previous studies, the results of the present analysis indicate that prucalopride treatment is more associated with diarrhea, headache, and nausea when compared to placebo.[13,20] The most frequently reported TEAEs were transient. Difference between the onset of TEAEs in the prucalopride and placebo groups greatly decreased after the first day of treatment. Compared to non-Asians, Asians were more likely to experience diarrhea and less likely to develop abdominal pain, headache, and nausea. Ethnicity, which is a significant demographic variable contributing to the interindividual variability in the metabolism of, and response to, a drug, may be one of the reasons for these differences observed between Asian and non-Asian patients.[21] Overall, non-Asian patients were more sensitive to treatment in terms of the likelihood of developing and AE; cultural differences may have contributed to non-reporting of TEAEs by Asian patients, irrespective of the treatment.

Prucalopride, through its selective action on 5-HT_4 receptors, induces colonic propulsions and accelerated transit from the proximal colon.[22,23] Such propulsion could facilitate the passage of stool of looser consistency which could explain an association of diarrhea with prucalopride treatment. An association of diarrhea was more prominent in Asian patients relative to non-Asian patients. All TEAEs reported were believed to be related to the secretory and prokinetic effects of prucalopride.[24,25] Overall, incidence of all TEAEs was more in the prucalopride group than the placebo group in both Asian and non-Asian patients on day 1. However, all the TEAEs were transient as the difference in the emergence of TEAEs reached to a nonsignificant level as the treatment progressed, indicating that the adverse reactions with prucalopride occur predominantly at the start of therapy and usually disappear within a few days with continued treatment.[10]

Prucalopride has been found to be well-tolerated and efficacious in the treatment of constipation irrespective of the age of the patients.[26,27] The present analysis further reinforced the fact that the safety profile of prucalopride is independent of the age of the patients except for the incidence of headache.[26,27] Furthermore, the results indicate that prior laxative use, body weight, and duration of CC had no effect on the emergence of TEAEs during the studies. All reported TEAEs were transient, either mild or moderate, and may have been related to the pharmacological effect of prucalopride, and do not appear to outweigh the risk to benefit ratio.

In this analysis, the majority of the patients were women, suggesting a higher prevalence of CC in women, which is consistent with the fact that CC is more prevalent in women. This was one of the major limitations of the analysis. However, despite the inadequate number of men in the analysis, the OR indicated that prucalopride provided a similar safety profile in both men and women except for the incidence of nausea. A higher percentage of non-Asian patients (73.9%) relative to Asian patients (26.1%) were part of the analysis; however, the number of Asian patients was sufficient for this exploratory analysis.

In conclusion, this pooled data analysis showed that prucalopride treatment was more likely to be associated with the most frequently reported TEAEs of diarrhea, headache, and nausea compared with placebo in patients with CC. Relative to non-Asians, Asian patients tended to have a higher frequency of diarrhea but lower frequencies of other common TEAEs of headache, abdominal pain, or nausea. Overall, prucalopride provides a safe and a convenient option for those who fail to respond with the conventional laxatives.

CONFLICTS OF INTEREST

Dr. Somchai Leelakusolvong has served as an advisor to Takeda. Drs. MeiYun Ke, Duowu Zou, and Suck Chei Choi have no conflict of interest to disclose. Dr. Jan Tack has served as an advisor to Almirall, Johnson and Johnson, and Shire-Movetis and has received honoraria for speaking engagements from Abbott, Almirall, AstraZeneca, Danone, Janssen, Menarini, Novartis, Shire-Movetis, Takeda, and Zeira. Dr. Jan Tack has also received consultancy fees from Almirall, AstraZeneca, Cosucra, Danone, GI Dynamics, GlaxoSmithKline, Ironwood, Janssen, Menarini, Novartis, Rhythm, Shire, Takeda, Theravance, Tranzyme, Tsumura, Will pharma, Zeria. Dr. Eamonn M. M. Quigley has served as an advisor to Janssen and Shire-Movetis and has received honoraria for speaking engagements from Janssen and Shire-Movetis. Mr. Andy Liu is a contract employee of Janssen Research & Development, Shanghai, China. Dr. JinYong Kim is an employee of Janssen Asia-Pacific, Singapore.

ACKNOWLEDGMENTS

We acknowledge Dr. Vaibhav Deshpande (SIRO Clinpharm Pvt., Ltd.) for providing writing assistance and Dr. Venugopal Madhusudhana (SIRO Clinpharm Pvt., Ltd.) for additional editorial support for the development of this manuscript. The authors also thank the study participants of the four studies, without whom the studies would never have been accomplished.

The studies presented in this report are supported by Janssen Research & Development. The Janssen companies are members of the Johnson & Johnson companies. The sponsor also provided a formal review of this manuscript.

REFERENCES

1. Sanchez MI, Bercik P. Epidemiology and burden of chronic constipation. Can J Gastroenterol 2011;25 Suppl B:11B-15B.
2. Bassotti G, Gaburri M, Imbimbo BP, et al. Colonic mass movements in idiopathic chronic constipation. Gut 1988;29:1173-1179.
3. Schiller LR. New and emerging treatment options for chronic constipation. Rev Gastroenterol Disord 2004;4 Suppl 2:S43-S51.
4. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology 2006;130:1480-1491.
5. Lacy BE, Levenick JM, Crowell M. Chronic constipation: new diagnostic and treatment approaches. Therap Adv Gastroenterol 2012;5:233-247.
6. Tack J, Müller-Lissner S, Stanghellini V, et al. Diagnosis and treatment of chronic constipation: a European perspective. Neurogastroenterol Motil 2011;23:697-710.
7. Camilleri M, Van Outryve MJ, Beyens G, Kerstens R, Robinson P, Vandeplassche L. Clinical trial: the efficacy of open-label prucalopride treatment in patients with chronic constipation: follow-up of patients from the pivotal studies. Aliment Pharmacol Ther 2010; 32:1113-1123.
8. Krishnamurthy S, Schuffler MD, Rohrmann CA, Pope CE 2nd. Severe idiopathic constipation is associated with a distinctive abnormality of the colonic myenteric plexus. Gastroenterology 1985; 88(1 Pt 1):26-34.
9. Frampton JE. Prucalopride. Drugs 2009;69:2463-2476.
10. Prucalopride (Resolor®). Summary of product characteristics [Internet]. Borgo San Michele: Janssen Cilag S.P.A.; 2011 [cited 2014 Apr 15]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001012/WC500053998.pdf.
11. Australian public assessment report for prucalopride (AusPAR) [Internet]. Symonston: Therapeutic Goods Administration (TGA), Australian Government Department of Health and Ageing; 2011 [cited 2014 Apr 16]. Avaiable from: http://www.tga.gov.au/auspar/auspar-prucalopride.
12. Camilleri M, Deiteren A. Prucalopride for constipation. Expert Opin Pharmacother 2010;11:451-461.
13. 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.
14. Camilleri M, Kerstens R, Rykx A, Vandeplassche L. A placebo-controlled trial of prucalopride for severe chronic constipation. N Engl J Med 2008;358:2344-2354.
15. Coremans G, Kerstens R, De Pauw M, Stevens M. Prucalopride is effective in patients with severe chronic constipation in whom laxatives fail to provide adequate relief: results of a double-blind, placebo-controlled clinical trial. Digestion 2003;67:82-89.
16. Ke M, Zou D, Yuan Y, et al. Prucalopride in the treatment of chronic constipation in patients from the Asia-Pacific region: a randomized, double-blind, placebo-controlled study. Neurogastroenterol Motil 2012;24:999-e541.
17. Mendzelevski B, Ausma J, Chanter DO, 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;73:203-209.
18. 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;58:357-365.
19. Camilleri M, Robinson P, Kerstens R, Vandeplassche LM. Safety and adverse event profiles of oral prucalopride are similar in elderly and adult patients with chronic constipation. Gastroenterology 2011;140 Suppl 1:S606-S607.
20. Quigley EM, Vandeplassche L, Kerstens R, Ausma J. Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation: a 12-week, randomized, double-blind, placebo-controlled study. Aliment Pharmacol Ther 2009;29:315-328.
21. Alomar MJ. Factors affecting the development of adverse drug reactions. Saudi Pharm J 2014;22:83-94.
22. Quigley EM. Prucalopride: safety, efficacy and potential applications. Therap Adv Gastroenterol 2012;5:23-30.
23. Sanger GJ, Quigley EM. Constipation, IBS and the 5-HT4 receptor: what role for prucalopride? Clin Med Insights Gastroenterol 2010; 3:21-33.
24. Priem E, Van Colen I, De Maeyer JH, Lefebvre RA. The facilitating effect of prucalopride on cholinergic neurotransmission in pig gastric circular muscle is regulated by phosphodiesterase 4. Neuropharmacology 2012;62:2126-2135.
25. Woodward S. The use of Resolor (prucalopride) for chronic constipation in women. Br J Nurs 2012;21:982, 984-986.
26. Müller-Lissner S, Rykx A, Kerstens R, Vandeplassche L. A double-blind, placebo-controlled study of prucalopride in elderly patients with chronic constipation. Neurogastroenterol Motil 2010;22:991-e255.
27. Winter HS, Di Lorenzo C, Benninga MA, et al. Oral prucalopride in children with functional constipation. J Pediatr Gastroenterol Nutr 2013;57:197-203.