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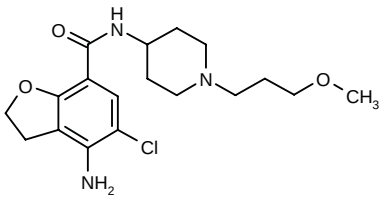
Prucalopride

Prop INN

Treatment of Irritable Bowel Syndrome
5-HT$_4$ Agonist

R-093877
R-93877
Resolor™

4-Amino-5-chloro-*N*-[1-(3-methoxypropyl)piperidin-4-yl]-2,3-dihydrobenzofuran-7-carboxamide



C18 H26 Cl N3 O3 Mol wt: 367.8790

CAS: 179474-81-8
CAS: 179474-84-1 (as monohydrobromide)
CAS: 179474-80-7 (as monohydrochloride)

EN: 254527

Synthesis

Prucalopride is synthesized by condensation of 4-amino-5-chloro-2,3-dihydrobenzofuran-7-carboxylic acid (I) with 1-(3-methoxypropyl)piperidin-4-amine (II) by means of ethyl chloroformate and triethylamine in chloroform (1). Scheme 1.

Introduction

Irritable bowel syndrome (IBS) constitutes the clinical expression of an underlying motility disorder which affects mainly the mid- and lower gut and is manifested by contractile abnormalities. For this reason, drugs affecting gastrointestinal motility have been widely used with the objective of correcting pain and altered bowel movements (2). Drugs that have been studied as a treatment for IBS include gut-selective muscarinic antagonists (zamifenacin, darifenacin), neurokinin NK_2 receptor blockers (MEN-10627, MEN-11420), β_3-adrenoceptor agonists (SR-58611A), selective gastrointestinal calcium channel blockers (pinaverium, octylonium), cholecystokinin CCK_1 receptor blockers (loxiglumide, dexloxiglumide), motilin agonists (erythromycin, other 14-member macrolides) and serotonin 5-HT_4 receptor agonists (prucalopride, tegaserod). A more detailed review of drugs under development for the treatment of IBS has already been published (3). The latter class of drugs has also been proposed for the treatment of idiopathic constipation, and clinical studies with prucalopride are under way (4).

The serotonin 5-HT_4 receptor has been found to play a key role in visceral sensitivity and gastrointestinal motility. Serotonin released from enterochromaffin cells and acting on 5-HT_4 receptors (in rats and human) or both 5-HT_4 and 5-HT_3 receptors (in guinea pigs) initiates the intestinal peristaltic reflex through activation of intramural sensory neurons that release calcitonin gene-related peptide (CGRP) (Fig. 1).

Thus, activation of 5-HT_4 receptors results in enhanced clearance and gastric emptying, hastening intestinal and colonic transit. Several classes of 5-HT_4 receptor agonists are being studied in clinical trials for a range of potential indications, including IBS, chemotherapy-induced emesis, gastroesophageal reflux disease (GERD) and anxiety. Two 5-HT_4 agonists, the title compound prucalopride and tegaserod maleate (Novartis), are at present advancing in phase III clinical trials for the treatment of IBS (3). Renzapride hydrochloride (Alizyme), a 5-HT_4 agonist and 5-HT_3 antagonist, is in phase II clinical trials for IBS.

Pharmacological Actions

Prucalopride increases the velocity of propulsion in vitro in guinea pig colon with an EC_{50} value of 37.4 nM (6), and according to other experimental pharmacological studies, prucalopride appears to be the first prokinetic agent selective for the colon with an activity mainly due to 5-HT_4 receptor stimulation (7). *In vitro* studies indicate that the enterokinetic effects of prucalopride do not appear to involve a prosecretory effect in the colon, and that the compound does not act as a 5-HT_3 receptor antagonist (8). The mechanism of action of this

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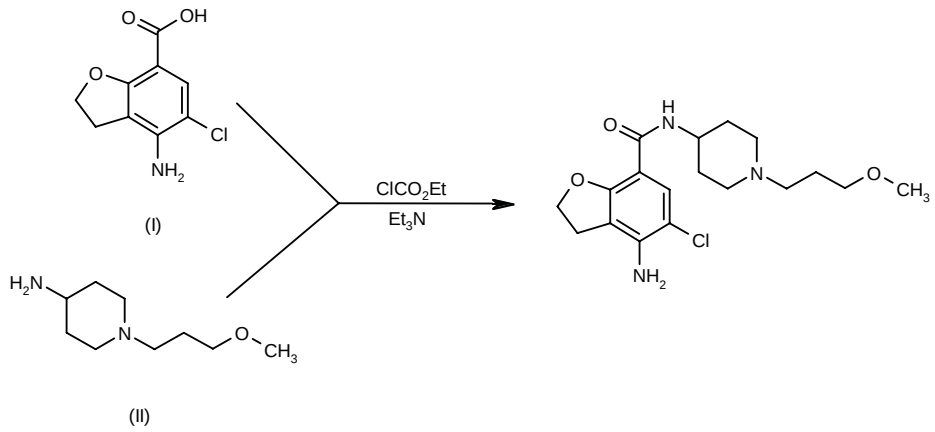
Scheme 1: Synthesis of Prucalopride



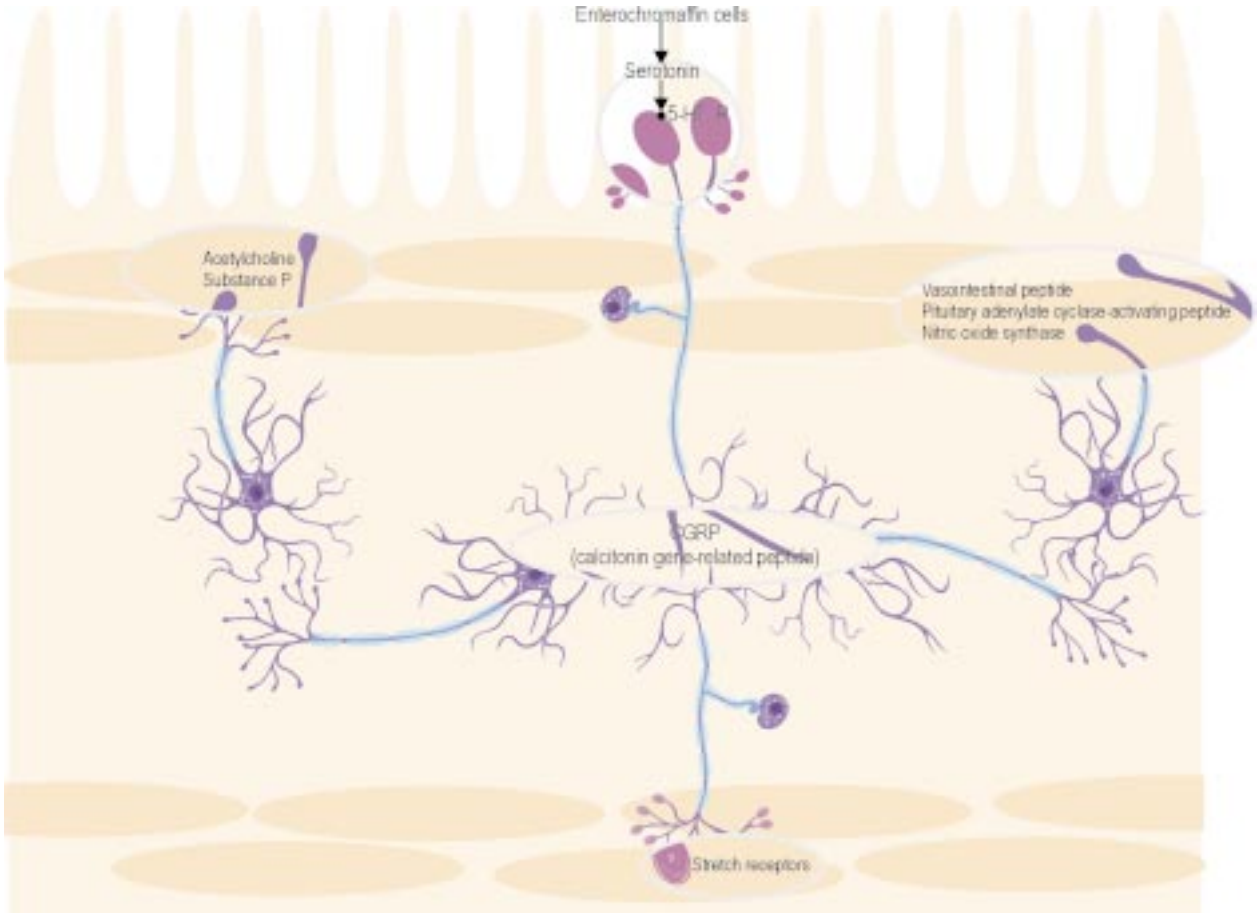


Fig. 1. Sensory pathways controlling the peristaltic reflex. Peristaltism can be activated by muscle stretch (extrinsic pathway) or by mucosal stimuli (intrinsic pathway) that lead to serotonin release from enterochromaffin cells. Serotonin acts on 5-HT_4 receptors of CGRP. In both cases, enteric CGRP cells act on interneurons connected to motor neurons that can release acetylcholine or substance P (excitatory motorneurons) or to vasointestinal peptide, pituitary adenylate cyclase-activating peptide or nitric oxide synthase motor neurons (inhibitory motor neurons) (5, 6).

compound was later determined to involve the stimulation of 5-HT_4 receptors through 5-HT_4 partial agonist, as seen *in vitro* (9) and *in vivo* in conscious beagle dogs. In the latter model, prucalopride induced changes in colonic contractile patterns and enhanced the occurrence of giant migrating contractions (10). Prucalopride had high oral bioavailability and potently accelerated delayed gastric emptying of a liquid meal in conscious dogs (11).

In contrast to cisapride and metoclopramide, prucalopride had no effect on transit after an abdominal skin incision or manipulation of the small intestine and cecum in anesthetized rats, but it significantly increased transit after laparotomy. The reference prokinetic agents significantly increased transit after the skin incision, but only cisapride increased transit after laparotomy and small intestine manipulation, whereas metoclopramide increased ileus after abdominal surgery. In rats treated simultaneously with prucalopride and granisetron, a 5-HT_3 receptor antagonist, transit increased after laparotomy and small intestine and cecum manipulation, but not after skin incision (12).

Prucalopride also acted synergistically with the δ-receptor antagonist naltrindole in increasing the velocity of colonic propulsion (13).

Clinical Studies

In preliminary clinical studies, prucalopride was well tolerated and had significant, consistent and dose-dependent intestinal prokinetic effects, suggesting that it is a promising treatment for patients with bowel symptoms of slow gut transit (14, 15).

The safety and tolerability of two different doses of prucalopride were assessed in 18 normal healthy volunteers in a double-blind, randomized, placebo-controlled, crossover trial. On three separate occasions, subjects were each administered single doses of 1 or 2 mg active drug or matching placebo by slow i.v. infusion. Colonic transit time, as measured by scintigraphy following ingestion of [^{111}In]-DPTA pH-sensitive capsules, decreased significantly from placebo; there was no significant difference, however, between the two doses of the active drug. Overall proportional changes in bowel movements were also significant when prucalopride and placebo were compared, but not when the 1- and 2-mg doses of active drug were compared. The consistency of most stools was normal, and there was no significant difference between the three treatment groups with respect to the proportion of normal stools. Headache and nausea were the most frequently reported adverse events (16).

Another double-blind, crossover, placebo-controlled trial in 17 healthy volunteers compared the effects of 1-week treatment with prucalopride (1 or 2 mg/day) and placebo, preceded by a 1-week no-treatment period and followed by a 1-week washout. Prucalopride significantly increased the number of stools per week and the percent of loose or watery stools; however, stool frequency and consistency returned to normal immediately after discontinuing treatment. Orocecal and whole gut transit was accelerated in all subjects on both doses of prucalopride. No effects on visceral sensitivity or sphincter function were detected. Side effects possibly related to prucalopride were transient headache in 7 subjects and mild elevation of liver aminotransferases in 1 subject, effects which disappeared upon discontinuation of treatment. Thus, prucalopride appeared to be safe and effective for the treatment of patients with large bowel symptoms or slow gut transit (17).

A validated scintigraphic technique was used in a double-blind, randomized, placebo-controlled clinical trial to measure gastrointestinal and colonic transit times in 50 healthy volunteers receiving a daily dose of 0.5, 1, 2 or 4 mg prucalopride or placebo for 7 days. Significant acceleration of overall colonic transit and proximal colonic emptying was noted at 4, 8, 24 and 48 h, with the doses of 0.5, 2 and 4 mg being almost equieffective compared to placebo. No effect was seen on gastric emptying or small bowel transit (18, 19).

Box 1: Effects of prucalopride on symptoms of patients with severe chronic constipation (20) [Prous Science CSline database].

Design	Double-blind, randomized, placebo-controlled clinical study
Population	Patients with chronic constipation (n = 53)
Treatments	Prucalopride (PR), 4 mg/d p.o. x 4 wk (n = 27) Placebo (P) (n = 26)
Adverse events	PR: 88.9% [headache, nausea, abdominal pain] P: 46.2% [headache, nausea, abdominal pain]
Results	Stool frequency (BM/wk): PR (2.3) > P (1.5) Stool consistency and straining improved from baseline in PR patients [p <0.05] Time (h) to first stool: P (75) > PR (13) [p = 0.027] Patient-assessed therapeutic efficacy at wk 4: PR > P [p <0.01] Investigator-assessed change in constipation was significant at wk 2 but not at wk 4
Conclusions	Prucalopride at 4 mg/day was safe and effective in patients with severe chronic constipation

Box 2: Effects of prucalopride on symptoms of patients with chronic constipation (21) [Prous Science CSline database].

Design	Multicenter, randomized, placebo-controlled, dose-finding clinical study
Population	Patients with chronic constipation (n = 172)
Treatments	Prucalopride (PR), 0.5 mg/d p.o. x 4 wk (n = 46) PR, 1 mg/d p.o. x 4 wk (n = 43) PR, 2 mg/d p.o. x 4 wk (n = 40) Placebo (P) (n = 43)
Adverse events	P: 25% PR2: 48% Most events occurred during the initial days of treatment Most frequently reported events: abdominal pain, headache, nausea
Results	Total gut transit time (h), change: PR1* (-10) > PR2* (-9) > P (+8) [*p <0.01 *vs.* P] Median time (h) to first stool: PR2 (2.25) < PR1 (5.5) < P (24.5) Stool consistency, straining and feeling of incomplete evacuation improved from baseline in patients taking PR Stool frequency increased in patients taking PR2: from 4/wk at baseline to 7.5/wk at 4 wk Investigator-assessed improvement at endpoint: PR2* > PR1* > PR0.5* > P [*p <0.05 *vs.* P]
Conclusions	Prucalopride was safe and effective in the treatment of chronic constipation; the findings suggest a rapid onset of enterokinetic activity

Box 3: Safety and efficacy of prucalopride in patients with chronic constipation (22) [Prous Science CSline database].

Design	Double-blind, randomized, placebo-controlled, dose-finding clinical study
Population	Patients with chronic constipation (n = 251)
Treatments	Prucalopride (PR), 0.5 mg b.i.d. p.o. x 12 wk (n = 67) PR, 1 mg b.i.d. p.o. x 12 wk (n = 62) PR, 2 mg b.i.d. p.o. x 12 wk (n = 60) Placebo (P) (n = 62)
Adverse events	Occurred mainly during the initial days of treatment with PR and were related to its gastrointestinal enterokinetic effects
Results	Stool frequency increased with PR1 and PR2 [p <0.01 *vs.* P] Stool consistency improved with PR as compared to P Clinical Global Impression of Change score, change at wk 2: PR > P [p <0.01] Severity of constipation at wk 2: PR < P [p <0.02] Treatment effects were maintained at wk 4 and 12 with the higher doses of PR PR1 and PR2 were associated with shorter transit time and a significant time difference in the colon descendens as compared to P [p <0.05] Median time (h) to first spontaneous bowel movement: PR2 (3) < P (22.4) [$p \leq 0.04$]
Conclusions	Prucalopride was safe and at 1 and 2 mg was effective in treating chronic constipation

In a pilot, double-blind, placebo-controlled study in patients with severe chronic constipation, once-daily treatment with prucalopride (4 mg/day) for 4 weeks led to significant improvements in bowel function as compared to placebo. Therapeutic efficacy was evident after 2 weeks of treatment and reached significance by week 4. Stool consistency – confirmed by percent dry weight in feces – and straining improved in prucalopride-treated patients, accompanied by positive, although not significant, effects on the feeling of incomplete evacuation. The time to first stool after administration of prucalopride was 13 h *versus* 75 h for placebo. More than 1 adverse event, generally headache, nausea and abdominal pain, was reported by 88.9% and 46.2% of patients receiving active drug and placebo, respectively; adverse events were rated severe in one-third of patients in both groups. Prucalopride plasma levels in this patient group were similar to those obtained in other studies in healthy volunteers (20) (Box 1).

In another study, the efficacy and safety of prucalopride were evaluated in 172 patients at several centers according to a randomized, double-blind, placebo-

Box 4: Efficacy and safety of prucalopride in patients with chronic constipation (23) [Prous Science CSline database].

Design	Placebo-controlled, randomized, double-blind clinical study
Population	Patients with chronic constipation (n = 231)
Treatments	Prucalopride (PR), 0.5 mg/d x 4 wk (n = 42) PR, 1 mg/d x 4 wk (n = 48) PR, 2 mg/d x 4 wk (n = 47) PR, 4 mg/d x 4 wk (n = 46) Placebo (P) (n = 46)
Adverse events	PR: most common adverse events were nausea and diarrhea
Results	Response rate at 4 wk: PR4* (54) > PR2 (32) > PR0.5 (26) ≥ PR1 (23) ≥ P (13) [*p <0.05 *vs.* P]
Conclusions	Prucalopride was well tolerated and at single daily doses of 2 and 4 mg improved the symptoms of chronic constipation and increased the number of spontaneous, complete bowel movements

controlled design. After a 4-week run-in period, patients were treated for 4 weeks with placebo or one of three doses of prucalopride (0.5, 1 or 2 mg/day). Onset of enterokinetic activity was rapid, with time to first stool decreasing in a dose-dependent fashion on prucalopride (median of 2.3 and 5.5 h for 2 and 0.5 mg prucalopride *vs.* 24.5 h for placebo). Stool frequency also increased dose-dependently with the active drug, from 4 stools/week at baseline to 7.5 stools/week after treatment with the highest dose of prucalopride. Total gut transit time decreased from 49 h to 39 h and from 63 h to 72 h with 1- and 2-mg doses of prucalopride, respectively, and increased from 65 h to 72 h on placebo. Improvements were also seen in stool consistency, straining and feeling of incomplete evacuation. Prucalopride was well tolerated, with most adverse events reported on the first day of dosing (21) (Box 2).

Another multicenter study provided further evidence of the efficacy and safety of prucalopride in 251 patients with chronic constipation. Following a 4-week run-in period, patients were treated with oral prucalopride (0.5, 1 or 2 mg/day) or placebo for 12 weeks. Stool frequency increased significantly and stool consistency improved throughout the entire treatment period on the two higher active doses. Improvements were also seen in gut transit time and time to first spontaneous stool. Prucalopride was well tolerated, with adverse events limited mostly to the first day of treatment. At doses of 1 or 2 mg/day, prucalopride was considered to be effective and safe in the treatment of chronic constipation over a period of 12 weeks (22) (Box 3).

Another clinical study in 234 patients with chronic constipation treated with 0.5, 1, 2 or 4 mg/day prucalopride gave respective response rates of 26, 23, 32 and 54% after 4 weeks of treatment, compared to 13% for placebo. Prucalopride at once-daily doses of 2 and 4 mg was well tolerated and significantly improved constipation, as defined by less than 2 spontaneous, complete bowel movements with no laxatives per week (23) (Box 4).

Manufacturer

Janssen Pharmaceutica NV (BE).

References

1. Hendrickx, M.L., Van Daele, G.C.E., Van Daele, P.J.V., Van Daele, G.K.L. (Janssen Pharmaceutica NV). *Enterokinetic benzamide.* EP 807110, JP 97512832, US 5854260, WO 9616060.

2. Scarpignato, C., Pelosini, I. *Management of irritable bowel syndrome: Novel approaches to the pharmacology of gut motility.* Can J Gastroenterol 1999, 13(Suppl. A): 50A-65A.

3. Graul, A., Silvestre, J., Castañer, J. *Tegaserod maleate.* Drugs Fut 1999, 24: 38-44.

4. Briejer, M.R., Schuurkes, J.A., Sarna, S.K. *Idiopathic constipation: Too few stools and too little knowledge.* Trends Pharmacol Sci 1999, 20: 1-3.

5. Grider, J.R., Foxx-Orenstein, A.E., Jin, J.G. *5-Hydroxytryptamine$_4$ receptor antagonists initiate the peristaltic reflex in human, rat, and guinea pig intestine.* Gastroenterology 1998, 115: 370-80.

6. Jin, J.G., Foxx-Orenstein, A.E., Grider, J.R. *Propulsion in guinea pig colon induced by 5-hydroxytryptamine (HT) via 5-HT$_4$ and 5-HT$_3$ receptors.* J Pharmacol Exp Ther 1999, 288: 93-7.

7. Bosmans, J.P.R.M.A., Schuurkes, J.A.J., Van Daele, G.H.P., De Cleyn M.A.J. *R93877 - The first selective colonkinetic agent.* 214th ACS Natl Meet (Sept 7-11, Las Vegas) 1997, Abst MEDI 266.

8. Wermelskirchen, D., Fritzen, S., Kokerbeck, D., Schuurkes, J.A.J. *Effect of R093877 on electrical field stimulation-induced secretion in the guinea-pig colon in vitro.* Dig Dis Week (May 10-16, Washington DC) 1997, Abst 4134.

9. Briejer, M.R., Meulemans, A.L., Bosmans, J.P., Van Daele, P., Schuurkes, J.A.J. *In vitro pharmacology of the novel enterokinetic R092877.* Dig Dis Week (May 10-16, Washington DC) 1997, Abst 1942.

10. Briejer, M.R., Ghoos, E., Eelen, J., Schuurkes, J.A.J. *Serotonin 5-HT$_4$ receptors mediate the R093877-induced changes in contractile patterns in the canine colon.* Dig Dis Week (May 10-16, Washington DC) 1997, Abst 4133.

11. Briejer, M.R., Meulemans, A.L., Wellens, A., Schuurkes, J.A.J. *R093877 dose-dependently accelerates delayed gastric emptying in conscious dogs.* Dig Dis Week (May 10-16, Washington DC) 1997, Abst 4043.

12. De Winter, B.Y., Boeckxstaens, G.E., De Man, J.G., Moreels, T.G., Herman, A.G., Pelckmans, P.A. *Effect of cisapride and metoclopramide on postoperative ileus in rats.* Brit J Pharmacol 1998, 123(Suppl.): Abst 192P.

13. Foxx-Orenstein, A.E., Fin, J.G., Grider, J.R. *5-HT_4 receptor agonists and δ-opioid receptor antagonists act synergistically to stimulate colonic propulsion.* Am J Physiol 1998, 275: G979-83.

14. Poen, A.C., Felt-Bersma, R.J.F., Meuwissen, S.G.M. *A placebo controlled study to evaluate the effects of repeated oral doses of R093877 on gastrointestinal transit and anorectal manometry in healthy volunteers.* Dig Dis Week (May 10-16, Washington DC) 1997, Abst 4135.

15. Vandeplassche, G., Crabbé, R., De Smedt, H., Podoor, M., Lauwers, L.F. *A placebo controlled study to evaluate the effects of single increasing oral doses of R093877 (R) on bowel habit, safety and tolerability in healthy volunteers.* Dig Dis Week (May 10-16, Washington DC) 1997, Abst 4136.

16. Hagger, R., Benson, M., Lloyd, R., Britten, A., Masoomi, M., Gaines, G., Antonelli, K., Joseph, A., Kumar, D. *A placebo-controlled study to evaluate the effect on colonic transit of R093877 in healthy volunteers.* Dig Dis Week (May 17-20, New Orleans) 1998, Abst 2957.

17. Emmanuel, A.V., Kamm, M.A., Roy, A.J., Antonelli, K. *Effect of a novel prokinetic drug, R093877, on gastrointestinal transit in healthy volunteers.* Gut 1998, 42: 511-6.

18. Bouras, E.P., Burton, D.D., McKinzie, S., Zinsmeister, A.R., Camilleri, M. *Dose-related effects of R093877, a benzofurane 5HT_4 agonist, on gastrointestinal and colonic transit in health.* Dig Dis Week (May 17-20, New Orleans) 1998, Abst 3269.

19. Bouras, E.P., Camilleri, M., Burton, D.D., McKinzie, S. *Selective stimulation of colonic transit by the benzofuran 5HT_4 agonist, prucalopride, in healthy humans.* Gut 1999, 44: 682-6.

20. Coremans, G., Kerstens, R., De Pauw, M., Stevens, M. *Effects of a new enterokinetic drug, prucalopride, on symptoms of patients with severe chronic constipation: A double-blind, placebo-controlled pilot study.* Dig Dis Week (May 16,19, Orlando) 1999, Abst 3656.

21. Felt-Bersma, R.J.F., Bouchoucha, M., Wurzer, H., Van Outryve, M., Bosseckert, H., Van't Kooster, G. *Effects of a new enterokinetic drug, prucalopride, on symptoms of patients with chronic constipation: A double-blind, placebo-controlled, multicenter study in Europe.* Dig Dis Week (May 16,19, Orlando) 1999, Abst 3655.

22. Otten, M.H., Schneider, H., Wurzer, H., Tefera, S., Van Eeghem, P., Graf, W., Van't Klooster, G. *A double-blind, placebo-controlled evaluation of safety and efficacy of 12-week, twice-daily treatment with prucalopride in patients with chronic constipation.* Dig Dis Week (May 16,19, Orlando) 1999, Abst 3654.

23. Miner, P.B. Jr., Nichols, T., Silvers, D.R., Joslyn, A., Wookds, M. *The efficacy and safety of prucalopride in patients with chronic constipation.* Dig Dis Week (May 16,19, Orlando) 1999, Abst 2306.