PRODUCT MONOGRAPH

[Pr]JAMP PRUCALOPRIDE

Prucalopride Tablets

1 mg and 2 mg prucalopride as prucalopride succinate

Prokinetic agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Film-coated tablet 1 mg, 2 mg prucalopride, as prucalopride succinate	Lactose *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

JAMP Prucalopride (prucalopride succinate) is indicated for the treatment of chronic idiopathic constipation in adult female patients in whom laxatives failed to provide adequate relief.

- There were an insufficient number of male patients in the clinical trials to demonstrate efficacy.
- The efficacy of prucalopride has been established in double-blind, placebo-controlled studies for up to 3 months. In case of prolonged treatment the benefit should be re-assessed at regular intervals.
- If treatment with prucalopride is not effective during the first 4 weeks, therapy should be discontinued.

Geriatrics (>65 years of age):
Prucalopride succinate has been studied in subjects 65 years and older. Clinical studies demonstrate that efficacy similar to that seen in the study population under the age of 65 years may be achieved at a lower dose (i.e., 1 mg) (see **DOSAGE AND ADMINISTRATION** and **CLINICAL TRIALS**).

Pediatrics (<18 years of age):
JAMP Prucalopride is not recommended in children younger than 18 years old.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- Patients with renal impairment requiring dialysis.
- Patients with intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract, such as Crohn's disease, ulcerative colitis, and toxic megacolon/megarectum.

WARNINGS AND PRECAUTIONS

General

Patients with severe and clinically unstable concomitant disease (e.g., liver, cardiovascular or lung disease, neurological or psychiatric disorders, cancer or AIDS and other endocrine disorders) as well as patients with insulin-dependent diabetes mellitus have not been studied. Caution should be exercised when prescribing JAMP Prucalopride to patients with these conditions.

Carcinogenesis and Mutagenesis

Prucalopride tested weakly positive in the TA100 bacterial strain of the Ames assay and was negative or equivocal in several other *in vitro* and *in vivo* genotoxicity assays. Prucalopride increased liver, thyroid, mammary, pituitary, adrenal medulla, and pancreatic islet cell tumor incidences in mice and/or rats. Mechanistic studies indicated that the increased tumor incidences may be due to rodent-specific epigenetic mechanisms and/or occurred at >60-times human exposure (see **Product Monograph PART II, TOXICOLOGY**).

Cardiovascular

JAMP Prucalopride should be used with caution in patients with a history of arrhythmias or ischemic cardiovascular disease. Prucalopride succinate has been associated with a slight increase of heart rate in healthy volunteers, as well as a decrease in the PR interval (see **ACTIONS AND CLINICAL PHARMACOLOGY**, **Electrocardiography**). Caution should be observed in patients with conditions that might be worsened by an increase in heart rate, such as ischemic heart disease or tachyarrhythmias (see **ADVERSE REACTIONS**).

Caution should also be observed in patients with pre-excitation syndromes such as Wolff-Parkinson-White syndrome or Lown-Ganong-Levine syndrome, or atrio-ventricular nodal rhythm disorders, such as AV junctional rhythms with retrograde activation or ectopic atrial rhythms.

Palpitations have been reported during clinical studies. Clinical monitoring is recommended particularly in patients with cardiovascular conditions. If palpitations are severe and persistent patients should consult with their physician.

Gastrointestinal

In case of severe diarrhea, the efficacy of oral contraceptives may be reduced and the use of an additional contraceptive method is recommended to prevent possible failure of oral contraception (see the prescribing information of the oral contraceptive).

If severe or persistent diarrhea occurs during treatment, patients should be advised not to continue therapy with JAMP Prucalopride and consult their physician.

Ischemic colitis is a potential and rare adverse event. No cases of ischemic colitis have been reported with prucalopride succinate during the clinical studies. Nonetheless, patients should be advised to discontinue JAMP Prucalopride therapy and consult their physician if they develop severe, persistent, and/or worsening abdominal symptoms, bloody diarrhea or rectal bleeding.

Hepatic/Biliary/Pancreas

Caution should be exercised when prescribing JAMP Prucalopride to patients with severe hepatic impairment (Child-Pugh class C) due to limited data in patients with severe hepatic impairment (see **DOSAGE AND ADMINISTRATION**).

Psychomotor Impairment

No studies on the effects of prucalopride succinate on the ability to drive and use machines have been performed. Prucalopride succinate has been associated with dizziness and fatigue particularly during the first day of treatment which may have an effect on driving and using machines (see **ADVERSE REACTIONS**).

Psychiatric

Suicides, suicide attempts, and suicidal ideation have been reported in clinical trials. A causal association between treatment with prucalopride succinate and an increased risk of suicidal ideation and behavior has not been established. Patients should be monitored for persistent worsening of depression or the emergence of suicidal thoughts and behaviors. Counsel the patients and their caregivers and family members to be aware of any unusual changes in mood or behavior, and to discontinue JAMP Prucalopride and contact the healthcare provider immediately.

Renal

Renal excretion is the main route of elimination of prucalopride (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**). A dose of 1 mg is recommended in patients with severe renal impairment (see **DOSAGE AND ADMINISTRATION**). Patients with severe renal impairment should be closely followed due to limited safety data.

Sensitivity/Resistance

Galactose Intolerance

The tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose/galactose malabsorption must not take this medicinal product.

Special Populations

Pregnant Women: Experience with prucalopride succinate during pregnancy is very limited. Cases of spontaneous abortion have been observed during clinical studies, although, in the presence

of other risk factors, the relationship to prucalopride succinate is unknown. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. JAMP Prucalopride is not recommended during pregnancy. Women of childbearing potential should use effective contraception during treatment with JAMP Prucalopride.

Nursing Women: Prucalopride is excreted in breast milk. In the absence of human data, it is not recommended to use JAMP Prucalopride during breast-feeding.

Pediatrics (<18 years of age): JAMP Prucalopride is not recommended in children.

Geriatrics (>65 years of age): Limited evidence does not indicate a change in the safety profile of prucalopride other than an increase in some events that are associated with age in the general population.

Geriatric patients are likely to have reduced renal function and therefore a lower starting dose should be considered in this group of patients (see **WARNINGS AND PRECAUTIONS/Renal** and **DOSAGE AND ADMINISTRATION**).

Monitoring and Laboratory Tests

Laboratory parameters were reviewed to detect changes over time. The overall incidence of abnormal laboratory values was similar between placebo and prucalopride-treated subjects in Phase 2 and 3 double-blind, placebo-controlled studies. There were no consistent or clinically relevant treatment-related trends.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse events were compiled from Phase 2/3 controlled studies. Doses up to 4 mg prucalopride were used in these studies.

Prucalopride succinate has been given orally to 2,717 patients with chronic constipation in controlled clinical studies. Of these patients, 938 patients received prucalopride succinate at the recommended dose of 2 mg per day, while 1,361 patients were treated with 4 mg prucalopride succinate daily.

Overall, adverse events occurred in 69% of subjects treated with prucalopride and 60% of subjects treated with placebo. The most common adverse events (≥10%) encountered with prucalopride succinate are gastrointestinal (nausea, diarrhea, abdominal pain) and nervous system disorders (headache). Approximately half of the adverse events of nausea, diarrhea and headache occurred during the first 1 to 2 days of treatment. For abdominal pain about 36% occurred early on treatment. The majority of these adverse events were mild to moderate in severity. The incidence of these adverse events tended to increase with dose (see Table 1 below).

Serious treatment emergent adverse events (regardless of causality) were low and similar between the all prucalopride group (2.1%) and the placebo group (1.9%). Serious adverse events reported by ≥2 subjects that were suspected of being drug-related include abdominal pain and headache. Severe adverse events were reported in 18.4% of prucalopride group vs. 13.6% in the

placebo group and 7.1% and 2.8% of prucalopride- and placebo-treated patients discontinued treatment, respectively.

The most commonly reported adverse reactions leading to discontinuation were related to gastrointestinal disorders (reported by 5.0% of subjects treated with prucalopride and 1.5% in the placebo group) and nervous systems disorders such as headache (2.3% and 0.4%, respectively). The incidence of these adverse reactions tended to increase with dose.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Prucalopride succinate has been given orally to 2,717 patients with chronic constipation in controlled clinical studies. Of these patients, 938 patients received prucalopride succinate at the recommended dose of 2 mg per day, while 1,361 patients were treated with 4 mg of prucalopride succinate daily.

In the three pivotal studies a total of 659 patients have been treated with prucalopride 2 mg and 4 mg for a duration of up to 12 weeks. The total person-years exposure to prucalopride in the double-blind, placebo-controlled studies was 406 years, compared to 216 person-years of exposure in the placebo group.

Adverse events reported by at least 1.0% of the patients in any prucalopride treatment group and showing at least 0.5% difference between the all prucalopride and placebo groups in the Phase 2 (4 weeks duration), three Phase 3 studies (4 weeks duration) and three pivotal double-blind placebo-controlled trials (12 weeks duration) in patients with chronic idiopathic constipation are shown in Table 1.

Table 1: Treatment Emergent Adverse Events Occurring More Frequently in The Combined prucalopride Group than The Placebo Group By at Least 0.5% and with at Least 1% Patients With an AE in Any prucalopride Dose Group Population: All Double-Blind Placebo-Controlled Phase II/III Studies in Patients with Chronic Constipation

System Organ Class Preferred Term Total no. of patients	Placebo		PRU 0.5mg		PRU 1mg		PRU 2mg		PRU 4mg		All PRU		All PRU minus placebo
	1369		110		308		938		1361		2717		
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	(Δ)
Gastrointestinal disorders													
Nausea	106	(7.7)	7	(6.4)	31	(10.1)	157	(16.7)	267	(19.6)	462	(17.0)	9.3
Diarrhea	45	(3.3)	5	(4.5)	23	(7.5)	111	(11.8)	191	(14.0)	330	(12.1)	8.8
Vomiting	32	(2.3)	5	(4.5)	6	(1.9)	43	(4.6)	72	(5.3)	126	(4.6)	2.3
Abdominal pain upper	37	(2.7)	4	(3.6)	12	(3.9)	40	(4.3)	71	(5.2)	127	(4.7)	2.0
Abdominal pain	128	(9.3)	7	(6.4)	22	(7.1)	110	(11.7)	142	(10.4)	281	(10.3)	1.0
Bowel sounds abnormal	5	(0.4)	1	(0.9)	3	(1.0)	16	(1.7)	17	(1.2)	37	(1.4)	1.0
Flatulence	52	(3.8)	3	(2.7)	11	(3.6)	43	(4.6)	67	(4.9)	124	(4.6)	0.8
Dyspepsia	29	(2.1)	2	(1.8)	4	(1.3)	23	(2.5)	42	(3.1)	71	(2.6)	0.5
Abdominal discomfort	13	(0.9)	0	(0.0)	4	(1.3)	11	(1.2)	22	(1.6)	37	(1.4)	0.5
Rectal hemorrhage	11	(0.8)	1	(0.9)	1	(0.3)	11	(1.2)	21	(1.5)	34	(1.3)	0.5
Stomach discomfort	5	(0.4)	1	(0.9)	1	(0.3)	3	(0.3)	19	(1.4)	24	(0.9)	0.5
Gastroenteritis	2	(0.1)	1	(0.9)	3	(1.0)	5	(0.5)	7	(0.5)	16	(0.6)	0.5
Nervous system disorders													
Headache	162	(11.8)	12	(10.9)	43	(14.0)	204	(21.7)	329	(24.2)	588	(21.6)	9.8
Dizziness	25	(1.8)	2	(1.8)	8	(2.6)	41	(4.4)	56	(4.1)	107	(3.9)	2.1
Migraine	9	(0.7)	2	(1.8)	4	(1.3)	13	(1.4)	14	(1.0)	33	(1.2)	0.5
General disorders and administration site conditions													
Fatigue	21	(1.5)	1	(0.9)	7	(2.3)	24	(2.6)	41	(3.0)	73	(2.7)	1.2
Malaise	5	(0.4)	1	(0.9)	2	(0.6)	6	(0.6)	18	(1.3)	27	(1.0)	0.6
Pyrexia	2	(0.1)	0	(0.0)	2	(0.6)	8	(0.9)	15	(1.1)	25	(0.9)	0.8
Musculoskeletal and connective tissue disorder													
Muscle spasms	15	(1.1)	3	(2.7)	2	(0.6)	18	(1.9)	26	(1.9)	49	(1.8)	0.7
Skin and subcutaneous tissue disorders													
Hyperhidrosis	1	(0.1)	0	(0.0)	3	(1.0)	3	(0.3)	10	(0.7)	16	(0.6)	0.5
Renal and urinary disorders													
Pollakiuria	3	(0.2)	0	(0.0)	1	(0.3)	12	(1.3)	17	(1.2)	30	(1.1)	0.9
Metabolism and nutrition disorders													
Anorexia	4	(0.3)	0	(0.0)	1	(0.3)	8	(0.9)	15	(1.1)	24	(0.9)	0.6
Cardiac disorders													
Palpitations	9	(0.7)	1	(0.9)	3	(1.0)	7	(0.7)	26	(1.9)	37	(1.4)	0.7

A total of 564 elderly patients (≥65 years) with chronic constipation were treated with prucalopride succinate in all double-blind studies. Similar to the younger age group, the most common adverse reactions with prucalopride treatment among the elderly (>65 years) groups were gastrointestinal disorders and headache. No clinically meaningful increase of adverse events was observed in prucalopride succinate treated groups as compared to placebo group.

Elderly patients (N=166) were followed-up for at least 6 months in an open-label study. The number (%) of elderly patients reporting adverse reactions were as follows:

dizziness 12 (7.2%), surgical intervention 12 (7.2%), anemia 8 (4.8%), creatine phosphokinase increased 8 (4.8%), anxiety 7 (4.2%), palpitation 6 (3.6%), extrasystoles 3 (1.8%), atrial fibrillation 3 (1.8%), aggravated hypertension 3 (1.8%), ECG abnormal specific 3 (1.8%), myocardial infarction 3 (1.8%), syncope 2 (1.2%), aggravated angina pectoris 1 (0.6%).

In Phase 2 and 3 double-blind, placebo-controlled clinical trials in patients with chronic constipation, the incidence of a composite endpoint of atrial rhythm-related adverse events (atrial fibrillation, supraventricular extrasystoles, atrial flutter, supraventricular tachycardia, arrhythmia supraventricular, sinus arrhythmia, sinus tachycardia) was higher with prucalopride 1 to 2 mg (0.6%) than with placebo (0.1%).

Suicidal behavior / ideation
In the double-blind clinical trials, one patient reported a suicide attempt 7 days after the end of treatment with prucalopride succinate 2 mg once daily; none were reported in patients on placebo. In the open-label trials, two patients reported a suicide attempt and another patient reported suicidal ideation. Completed suicide was reported in two patients, previously treated with prucalopride succinate 2 mg or 4 mg; both discontinued prucalopride succinate for at least one month prior to the event.

Less Common Clinical Trial Adverse Drug Reactions (≤1%)

General disorders and administration site conditions: fever, chest pain
Metabolism and nutrition disorders: anorexia
Nervous system disorders: tremors, migraine
Ear and labyrinth disorders: vertigo
Psychiatric disorders: anxiety
Renal: urinary incontinence

Serious adverse events during all double-blind controlled studies:
The overall incidence of serious treatment-emergent adverse events (regardless of causality) was low and similar between the all prucalopride group (2.1%) and the placebo group (1.9%). Serious adverse events reported by up to 3 prucalopride-treated subjects (0.1%) are provided below:

Infections and infestations: bronchitis, pneumonia
Surgical and medical procedures: abdominoplasty, hysterectomy
Gastrointestinal disorders: abdominal pain, constipation
Nervous system disorders: headache
Cardiac disorders: supraventricular tachycardia
Reproductive system and breast disorders: vaginal hemorrhage
General disorders: chest pain
Psychiatric disorders: anxiety
Discontinuation: The most commonly reported adverse reactions leading to discontinuation in Phase 2/3 double-blind, placebo-controlled studies were related to gastrointestinal disorders (reported by 5.0% of subjects treated with prucalopride and 1.5% in the placebo group, and headache (2.3% and 0.4%, respectively). Dizziness led to discontinuation in 0.5% and 0.1%, respectively. The incidence of these adverse reactions tended to increase with dose.

Serious adverse events during open-label follow-up studies (N=2,595)**:** SAE reported in at least 3 cases (0.1%) to at most 0.3% are below:

Surgical and medical procedures: hysterectomy, cholecystectomy, colectomy
Gastrointestinal disorders: abdominal pain, constipation, vomiting, nausea, diarrhea, pancreatitis
Infections and infestations: gastroenteritis, pneumonia, sinusitis, urinary tract infection
Nervous system disorders: headache, syncope
Cardiac disorders: angina pectoris, myocardial infarction, atrial fibrillation
Hepatobiliary disorders: cholelithiasis, cholecystitis
Pregnancy puerperium and perinatal conditions: pregnancy, abortion spontaneous
Reproductive system and breast disorders: ovarian cyst
Psychiatric disorders: confusional state, depression
General disorders and administration site conditions: chest pain
Respiratory, thoracic and mediastinal disorders: dyspnea

SAEs in Compassionate study: (in at least 2 cases) colectomy

DRUG INTERACTIONS

Overview

In vitro data indicate that prucalopride has a low interaction potential. Approximately 60% of the dose is excreted unchanged in urine via both passive filtration and active renal transporters (P-glycoprotein (P-gp) and BCRP) The therapeutic concentrations of prucalopride are not expected to affect the CYP-mediated metabolism of co-medicated medicinal products. Prucalopride is a weak substrate for P-gp and BCRP. Prucalopride is a weak *in vitro* inhibitor of P-gp and BCRP transporters, and it is not a significant inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, BSEP and MRP2 transporters.

Drug-Drug Interactions

Ketoconazole (200 mg b.i.d.), a potent inhibitor of CYP3A4 and of P-gp, increased the area under the curve (AUC) of prucalopride by approximately 40%. Interactions of similar magnitude as observed with ketoconazole may also occur with other potent inhibitors of P-gp such as verapamil, cyclosporine A and quinidine.

Studies in healthy subjects showed that there were no clinically relevant effects of prucalopride on the pharmacokinetics of warfarin, alcohol, paroxetine or oral contraceptives. There was a 10% decrease in the bioavailability of digoxin associated with prucalopride co-administration. Prucalopride co-administration increased erythromycin C_{max} by 40% and AUC_{24h} by 28%. The mechanism for this erythromycin-prucalopride interaction is not fully known, but the available data support that this is the consequence of the high intrinsic variability in erythromycin pharmacokinetics, rather than a direct effect of prucalopride.

Therapeutic doses of probenecid, cimetidine, erythromycin and paroxetine did not affect the pharmacokinetics of prucalopride. Although not formally tested, a drug-drug interaction study with alcohol suggests that the pharmacokinetics of prucalopride are unlikely to be affected to a clinically relevant extent by alcohol.

Because of the mechanism of action, the use of atropine-like substances may reduce the 5-HT_4 receptor mediated effects of prucalopride.

Drug-Food Interactions
Interactions with food have not been observed.
Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
No effects are known.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Due to the specific mode of action of JAMP Prucalopride (stimulation of propulsive motility), exceeding the daily dose of 2 mg is not expected to increase efficacy.
- If the intake of once daily JAMP Prucalopride is not effective during the first 4 weeks of treatment, therapy should be discontinued.
- The efficacy of prucalopride succinate has been established in double-blind, placebo-controlled studies for up to 3 months. In case of prolonged treatment the benefit should be re-assessed at regular intervals.

Recommended Dose and Dosage Adjustment

Adults: 2 mg once daily. If there is no bowel movement in 3-4 days, patients should be directed to inform their doctor and the doctor should consider an appropriate add-on laxative for acute treatment of constipation (e.g., rescue treatment) during the ongoing JAMP Prucalopride treatment.

Elderly (>65 years): 1 mg tablet once daily (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**); if needed the dose can be increased to 2 mg once daily.

Children (<18 years):
JAMP Prucalopride is not recommended in children younger than 18 years old (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**).

Patients with renal impairment:
The dose for patients with severe renal impairment (GFR <30 mL/min/1.73 m^2) is 1 mg once daily (see **CONTRAINDICATIONS** and **Pharmacokinetics**). No dose adjustment is required for patients with mild to moderate renal impairment.

Patients with hepatic impairment:
Patients with severe hepatic impairment (Child-Pugh class C) start with 1 mg once daily which may be increased to 2 mg if required to improve efficacy and if the 1 mg dose is well tolerated (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**). No dose adjustment is required for patients with mild to moderate hepatic impairment.

Missed Dose
Prucalopride has a terminal half-life of approximately 1 day. The dose should not be doubled to make up for a missed dose.

Administration
JAMP Prucalopride film-coated tablets are for oral use and can be taken with or without food, at any time of the day.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

In a study in healthy subjects, treatment with prucalopride succinate was well tolerated when given in an up-titrating scheme up to 20 mg once daily (10 times the recommended therapeutic dose). An overdose may result in symptoms resulting from an exaggeration of the medicinal product's known pharmacodynamic effects and include headache, nausea and diarrhea. Specific treatment is not available for JAMP Prucalopride overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Extensive fluid loss by diarrhea or vomiting may require correction of electrolyte disturbances.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action and Pharmacodynamics
Chronic constipation is a condition that comprises multiple symptoms, including infrequent defecation, straining, lumpy or hard stools, sensation of incomplete evacuation and painful abdominal symptoms. Chronic constipation is generally associated with a reduction in the giant migrating contractions that normally drive mass transits through the colon. Morphological alterations of the enteric nervous system may underlie motility impairment in these patients.

Investigations suggest an important role of serotonin 5-HT_4 receptors in mediating colonic motility.

Prucalopride is the first of a new class of dihydrobenzofurancarboxamide compounds with prokinetic activities. Prucalopride is a selective, high affinity serotonin (5-HT_4) receptor agonist, which is likely to explain its prokinetic effects. Functional *in vivo* and *in vitro* studies revealed that prucalopride enhances the peristaltic reflex and propulsive motor patterns in the gastrointestinal tract via 5-HT_4 receptor activation.

In *in vitro* studies, prucalopride demonstrated a high affinity (Ki <11 nM) for human 5-HT_4 receptors expressed in HEK293 cells. Its interaction with the 5-HT_4 receptor leads to the elevation of cAMP levels in the same cell line (EC_{50} = 5 nM). The affinity of prucalopride for 5- HT_4 receptors is at least 150 times higher than that for other receptors such as 5-$HT_{1,2}$ and human ether-à-go-go related gene (hERG) encoded I_{Kr} channel.

In dogs, prucalopride alters colonic motility patterns via serotonin 5-HT_4 receptor stimulation: it stimulates proximal colonic motility, enhances gastroduodenal motility and accelerates delayed gastric emptying. Furthermore, giant migrating contractions are induced by prucalopride. These are equivalent to the colonic mass movements in humans, and provide the main propulsive force to defecation. In dogs, the effects observed in the gastrointestinal tract are sensitive to blockade with selective 5-HT_4 receptor antagonists, illustrating that the observed effects are exerted via selective action on 5-HT_4 receptors.

Pharmacokinetics

The pharmacokinetic profile of prucalopride in man has been extensively studied. Prucalopride has a large volume of distribution and a low plasma clearance. The terminal half-life is about one day. After once-daily oral tablet administration, steady-state is attained in three days. The accumulation ratio after once-daily dosing ranges from 1.9 to 2.3. The pharmacokinetics of prucalopride appears dose-proportional and time-independent across a wide dose range up to at least five times the therapeutic dose level of 2 mg. A summary of 2 mg prucalopride (oral tablet; once daily) mean (±standard deviation) Pharmacokinetic Parameters in healthy subjects (n=12 subjects) are presented in Table 2 below.

Table 2: Summary of 2 mg prucalopride (oral tablet; once daily) Mean (± std dev) Pharmacokinetic Parameters in Healthy Subjects (n=12 Subjects)

	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)	$T_{1/2\ term}$ (h)	Cl (mL/min)‡
Single dose	2.6 ± 1.5	3.93 ± 0.73	57.3 ± 8.2	24.0 ± 3.6	-
Repeat dose†	1.7 ± 1.3	7.45 ± 1.48	109 ± 23	30.5 ± 4.6	196 ± 39

† steady-state obtained within 3-5 doses.

‡ determined following 2 mg prucalopride (oral solution; b.i.d.) (n=9 subjects)

Absorption: Prucalopride is rapidly absorbed following once-daily 2 mg oral tablet administration. Peak concentrations are generally attained in 2 to 3 hour after intake. At 2 mg once-daily, steady-state plasma concentrations fluctuate between trough and peak values of 2.5 and 7.5 ng/mL, respectively. The absolute oral bioavailability is >90%. Concomitant intake of food does not influence the oral bioavailability of prucalopride.

Distribution: Prucalopride is rapidly and extensively distributed and has a large volume of distribution (Vd_{ss}) of 567 L. The plasma protein binding of prucalopride is about 30%.

Metabolism: Metabolism is a minor route of prucalopride elimination. Prucalopride (0.5 mg oral solution; ^{14}C-radiolabelled) metabolism results in the production of eight metabolites. Metabolites overall account for 6.3-13.8% of the administered dose (n=3 subjects). The major

metabolite (R107504; formed by *O*-demethylation and oxidation of the resulting alcohol function to a carboxylic acid) accounts for 2.6-3.5% of the dose. Four of the identified metabolites (including R107504) exhibit lower or similar *in vitro* affinity to 5-HT_4 receptors as compared to prucalopride.

Excretion: Prucalopride (0.5 mg oral solution; ^{14}C-radiolabelled) is primarily excreted unchanged, 55.1-73.8% of the administered dose in urine and 3.7-8.1% in feces by 10 days following single-dose administration. After intravenous (single) and oral solution (steady-state) administration of 2 mg prucalopride, approximately 60% of the dose is recovered unchanged in the urine (during 72 h following administration). Half to two-thirds of the renal clearance of prucalopride is attributable to active renal secretion, while passive glomerular filtration of prucalopride is responsible for the remainder. The $t_{1/2\ term}$ is approximately one day.

Special Populations and Conditions

Population Pharmacokinetics: A population pharmacokinetic analysis suggested that the apparent total clearance of prucalopride was correlated with creatinine clearance, but that age, body weight, sex or race had no influence.

Pediatrics: Prucalopride is not recommended for use in the pediatric population due to an incomplete characterization of the clinical pharmacology and associated safety risks, including a potential risk of cardiac arrhythmia.

Geriatrics: Once-daily 1 mg oral tablet dose of prucalopride for 7 consecutive days resulted in an increased C_{max} (36.5%) and AUC_{0-24h} (40%), and reduced Cl_{ren} (20%) in geriatric patients compared with young adults (n=12/group). The elevation in plasma prucalopride concentration is attributed to a reduction in renal function associated with age, as prucalopride is primarily renally excreted by glomerular filtration and tubular secretion processes.

Hepatic Insufficiency: Non-renal elimination contributes up to about 35% of total elimination, and based on the available data, hepatic impairment is unlikely to affect the pharmacokinetics of prucalopride to a clinically relevant extent (see **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**).

The effect of moderate to severe hepatic impairment on the pharmacokinetics of prucalopride in comparison with healthy subjects was investigated in a pharmacokinetic study (8 patients per group, age 18-70). Hepatically impaired subjects received a single oral dose of 2 mg prucalopride.

In this study, the C_{max} and AUC of prucalopride were, on average, 10-20% higher in subjects with moderate to severe hepatic impairment compared with healthy subjects (see Table 3 below).

The increase in C_{max} and AUC observed in this study was not considered to be clinically relevant.

Table 3: Pharmacokinetic Parameters in Subjects with Moderate and Severe Hepatic Impairment and Healthy Subjects (N=24 Subjects)

	T_{max}* (h)	C_{max} (ng/mL)	AUC_{∞} (ng.h/mL)	$T_{1/2\ term}$ (h)	Cl/F (L/h)
Healthy Subjects	2.00 ± (1.00-4.00)	3.77 ± 0.91	96.2 ± 25.5	27.4 ± 5.56	22.0 ± 5.29
Moderate Hepatic Impairment	2.00 ± (1.00-3.00)	4.17 ± 0.75	115 ± 36.5	29.8 ± 10.3	19.0 ± 5.61
Severe Hepatic Impairment	1.50 ± (0.50-3.00)	4.43 ± 1.56	111 ± 42.2	27.4 ± 8.96	20.5 ± 7.95

*Values shown are mean (SD) except for T_{max} where median (range) is shown

Renal Insufficiency: Compared to subjects with normal renal function, plasma concentrations of prucalopride after a single 2 mg dose were on average 25% and 51% higher in subjects with mild (Cl_{CR} 50-79 mL/min) and moderate (Cl_{CR} 25-49 mL/min) renal impairment, respectively. In subjects with severe renal impairment (Cl_{CR} ≤24 mL/min), plasma concentrations were 2.3 times the levels in healthy subjects. The terminal half-life was extended from 30 h (normal renal function) to 34 h (mild), 43 h (moderate) and 47 h (severe), respectively (see **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**).

Electrocardiography: In a randomized, double-blind, placebo- and active-controlled, parallel arm study in healthy volunteers (n=60/treatment arm), subjects received a single dose of 2 mg prucalopride from days 1 to 5, with dosing escalated by 2 mg/day to 10 mg on day 9, with continued dosing with 10 mg prucalopride from days 10 to 13. ECG data were collected on days 5 and 13.

During the 2 mg treatment on day 5, heart rate was significantly increased at 9 of 12 time points, with a maximum difference versus placebo of mean 5.4 (90% CI 3.0, 7.8) bpm at 8 h post-dosing. During the 10 mg treatment on day 13, statistically significant heart rate increases were evident from 0 h to 12 h, inclusive, with a maximum difference versus placebo of mean 6.4 (90% CI 4.3, 8.5) bpm at 6 h post-dosing.

Prucalopride resulted in statistically significant shortening of the PR interval at all time points on days 5 and 13. On day 5 during treatment with 2 mg dose, the largest decrease was a mean -11.9 (90% CI -14.5, -9.3) ms at 3.5 h post-dosing, whilst during treatment with prucalopride 10 mg on day 10, the largest decrease was a mean -10.6 (90% CI -13.6, -7.7) ms at 2 h post-dosing (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular**).

There was no evidence of treatment-related effects on the QTc interval or the QRS duration in this study.

STORAGE AND STABILITY

JAMP Prucalopride tablets should be kept out of reach and sight of children. Store between 15-30°C.

SPECIAL HANDLING INSTRUCTIONS

Store in the original blister package in order to protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

JAMP Prucalopride is available as film-coated tablets containing 1 mg or 2 mg of prucalopride (as prucalopride succinate). Both strengths of JAMP Prucalopride film-coated tablets are available in aluminium/aluminium perforated and Alu- PVC/PE/PCTFE unit dose blisters containing 7 tablets. Each pack contains 28 film-coated tablets:

- 1 mg – white to off-white circular, film coated tablet with "C" debossed on one side and "11" on the other side.
- 2 mg – pink, circular, film coated tablet with "C" debossed on one side and "12" on the other side.

Composition

JAMP Prucalopride tablets contain the following inactive ingredients:

1 mg Tablets

Tablet core: anhydrous colloidal silica, lactose monohydrate, microcrystalline cellulose and magnesium stearate.

Coating: hypromellose, , titanium dioxide, macrogol 400 and polysorbate 80.

2 mg Tablets

Tablet core: anhydrous colloidal silica, lactose monohydrate, microcrystalline cellulose and magnesium stearate.

Coating: hypromellose, titanium dioxide, macrogol 400, iron oxide red and polysorbate 80.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name: Prucalopride

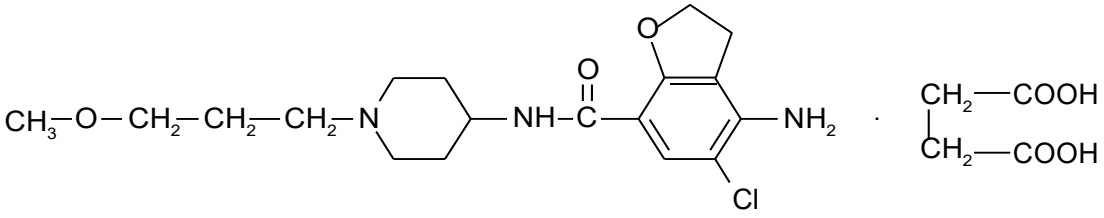
Chemical name: 4-amino-5-chloro-2,3-dihydro-N-[1-(3-methoxypropyl)-4-piperidinyl]-7-benzofurancarboxamide butanedioate (1:1)

Prucalopride succinate

Prucalopride butanedioate

Molecular formula: $C_{18}H_{26}ClN_3O_3.C_4H_6O_4$
Molecular weight: 485.96 g/mol

Structural formula:



$C_{18}H_{26}ClN_3O_3.C_4H_6O_4$ Molecular weight: 485.96

Physicochemical properties: Prucalopride succinate is a white to almost white powder with a melting point of ~198˚C. Prucalopride succinate is soluble in N,N-dimethylformamide, sulfinylbismethane and N,N-dimethylacetamide and sparingly soluble in methanol. It is freely soluble in acidic aqueous media. However, this solubility decreases with increasing pH. The pK_a for the piperidine moiety of prucalopride succinate is 8.5, determined at 20°C. The pK_a for the amino moiety of prucalopride succinate is less than 3, determined at 20°C.

CLINICAL TRIALS

Comparative Bioavailability Data

JAMP-PURCALOPRIDE 1 mg and 2 mg tablets have satisfied the criteria for a Biopharmaceutics Classification System (BCS)-based biowaiver in comparison to the Canadian Reference Product, RESOTRAN® (prucalopride as prucalopride succinate) 1 mg and 2 mg tablets (Janssen Inc.).

Study demographics and trial design

Table 4 - Summary of Patient Demographics for Key prucalopride Clinical Trials in Chronic Constipation

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n = number) ATP*	Mean Age (Range)	Gender
PRU-INT-6	Double-blind, parallel group, placebo-controlled study.	Oral administration of prucalopride 2 mg and 4 mg tablets over a 12-week treatment phase.	n=716 (238 for 2 mg; 238 for 4 mg; 240 for placebo)	43.9 years (17, 89)	650 F 66 M
PRU-USA-11	Double-blind, parallel group, placebo-controlled study.	Oral administration of prucalopride 2 mg and 4 mg tablets over a 12-week treatment phase.	n=620 (207 for 2 mg; 204 for 4 mg; 209 for placebo)	48.3 years (18, 85)	545 F 75 M
PRU-USA-13	Double-blind, parallel group, placebo-controlled study.	Oral administration of prucalopride 2 mg and 4 mg tablets over a 12-week treatment phase.	n=641 (214 for 2 mg; 215 for 4 mg; 212 for placebo)	47.9 years (18, 95)	555 F 86 M
PRU-INT-12	Double-blind, parallel group, placebo-controlled study in elderly patients	Oral administration of prucalopride 1 mg, 2mg and 4 mg tablets over a 4-week treatment phase.	n=303 (76 for 1 mg; 75 for 2 mg; 80 for 4 mg; 72 for placebo)	76.4 years (64-95)	211 F 92 M

* ATP: randomized patients who received treatment: "All Treated Patients".

Pivotal Studies

PRU-INT-6, PRU-USA-11 and PRU-USA-13

The efficacy of prucalopride was established in three multicentre, randomized, double-blind, 12- week, placebo-controlled studies in patients with chronic idiopathic constipation (n=1279 on prucalopride with 1124 females and 155 males [based on intent-to-treat population]). Mean age in the pooled studies was 46.9 (range 17, 95). Patients were predominantly white (89.8%).

The prucalopride doses studied in each of these three studies included 2 mg and 4 mg dosing once daily. Patients included in the study had the mean duration (range) of chronic constipation of 20 (0.3 to 83) years. The reported main complaints were infrequent defecation (about 29%), abdominal bloating (25%), abdominal pain (15%), feeling of incomplete evacuation (14%), straining (11%) and hard stool (6%). More than half of the patients had used diet or bulk

forming agents (not defined as laxatives in protocol while widely classified as such in different textbooks), and approximately 85% of the patient population used laxatives for their condition in the 6 months preceding the study. More than 80% of these patients who used laxatives or bulk forming agents considered the therapeutic effect of these previous therapies inadequate.

Patients were included in the study if they had ≤2 CSBM/week as well as the occurrence of one or more of the following for at least 6 months before the study: very hard stool for at least a quarter of the stools, sensation of incomplete evacuation following at least a quarter of the stools, and/or straining at defecation at least a quarter of the time. Constipation was not induced by secondary causes of constipation.

Patients were excluded from the study if:

- Suffering from secondary causes of chronic constipation including endocrine disorders, metabolic disorder, neurologic disorders, all of which are not controlled by appropriate medical therapy except insulin-dependent diabetes mellitus, megacolon/megarectum or pseudo-obstruction and known or suspected organic disorders of the large bowel (i.e., obstruction, carcinoma, or inflammatory bowel disease).
- Untreated colonic polyps by colonoscopy at screening.
- Presence of severe and clinically uncontrolled cardiovascular, liver, or lung disease, neurologic or psychiatric disorders (including active alcohol or drug abuse), cancer or AIDS, and other gastrointestinal or endocrine disorders.
- Impaired renal function, i.e., serum creatinine concentration >2 mg/dL (>180 mcmol/L), or creatinine clearance ≤50 mL/min.
- Clinically significant abnormalities of hematology, urinalysis, or blood chemistry.

Study results

Primary Endpoint

The primary efficacy endpoint was the proportion (%) of patients that reached normalization of bowel movements defined as an average of three or more spontaneous, complete bowel movements (SCBM) per week over a 4-week and 12-week treatment period. SCBMs are defined as spontaneous (i.e., 24 hours without the use of laxatives or other aids) bowel movements with a sense of complete evacuation.

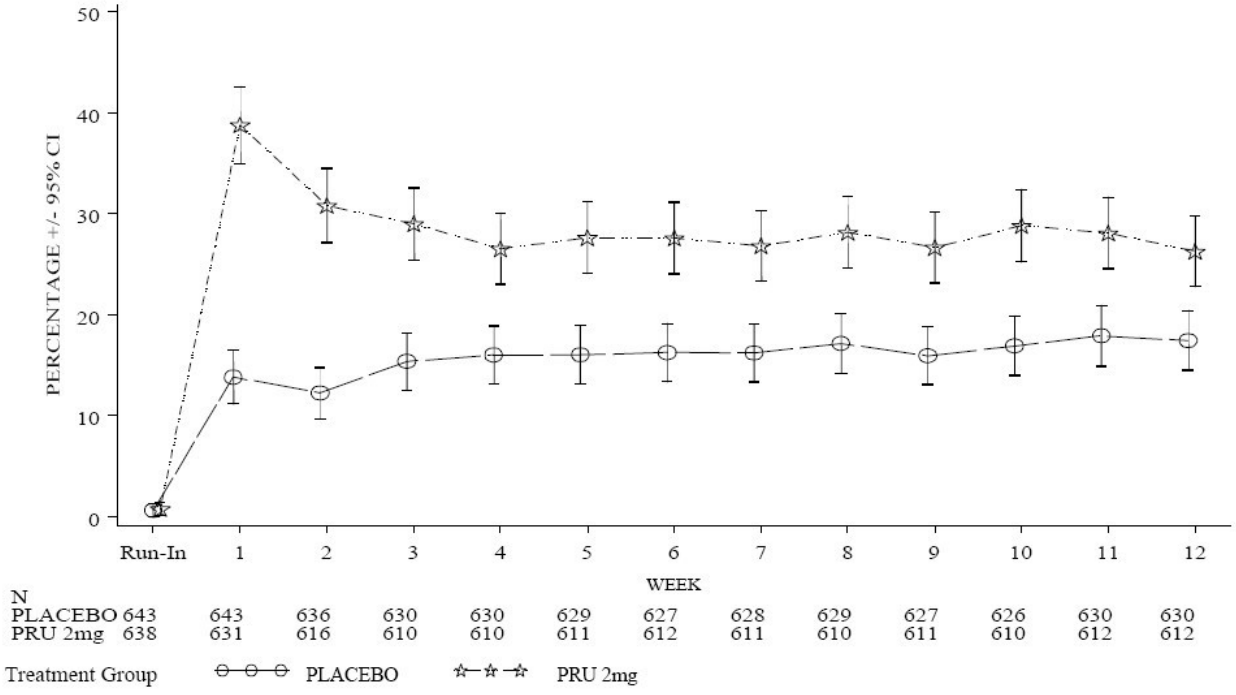
Both doses were statistically superior ($p<0.001$) to placebo at the primary endpoint in each of the three studies, with no incremental benefit of the 4 mg dose over the 2 mg dose. The proportion of patients treated with the recommended dose of 2 mg prucalopride that reached an average of ≥3 SCBM per week was 27.8% (Weeks 1-4) and 23.6% (Weeks 1-12), versus 10.5% (Weeks 1-4) and 11.3% (Weeks 1-12) on placebo (Table 5, Figure 1).

Table 5: Number (%) of Patients with ≥3 SCBMs per Week – Pooled Data from PRU-INT-6, PRU-USA-11, and PRU-USA-13, ITT Analysis Set

	Placebo N=645		PRU 2 mg N=640		Difference (%) (95% CI) [PRU 2 mg - Placebo)]
Time-point	**N**	**n (%)**	**N**	**n (%)**	
Run-in	643	4 (0.6)	638	5 (0.8)	
Weeks 1-12	645	73 (11.3)	640	151 (23.6)	12.3 (8.2, 16.4) *
Weeks 1-4	645	68 (10.5)	640	178 (27.8)	17.3 (13.1, 21.5) *
Weeks 5-8	628	83 (13.2)	612	147 (24.0)	10.8 (6.5, 15.1) *
Weeks 9-12	630	89 (14.1)	612	154 (25.2)	11.0 (6.7, 15.4) *

*: p< 0.001 (Comparison vs placebo).

Figure 1: Proportion of Patients with ≥3 SCBM per Week Over Twelve Weeks (Pooled Data from PRU-INT-6, PRU-USA-11, and PRU-USA-13, ITT Population)



Secondary Endpoints

Secondary endpoints were the proportion of patients with an average increase of ≥1 SCBM per week, average numbers of SCBM and SBM per week, constipation symptoms, time to first bowel movement; and patient satisfaction.

A clinically meaningful improvement of ≥1 SCBM per week, the most important secondary efficacy endpoint, was achieved in 48.1% (Week 4) and 43.1% (Week 12) of patients treated with 2 mg prucalopride versus 23.4% (Week 4) and 24.6% (Week 12) of placebo patients (Table 6).

Table 6: Number (%) of Patients with an Increase of ≥1 SCBMs per Week (Data from PRU-INT-6, PRU-USA-11, and PRU-USA-13, ITT Population)

Time point	Placebo	PRU 2.0 mg	P-value PRU 2.0 mg vs. Placebo[a]
Weeks 1-4	148/632 23.4%	295/613 48.1%	<0.001 (PRU-INT-6) ≤0.001 (PRU-USA-11) ≤0.001 (PRU-USA-13)
Weeks 1-12	155/630 24.6%	264/612 43.1%	0.002 (PRU-INT-6) ≤0.001 (PRU-USA-11) ≤0.01 (PRU-USA-13)

[a] p-values are from the individual pivotal Phase III studies

The treatment with prucalopride resulted in a significant increase of average frequency of S(C)BM/week as compared to placebo (Table 7). Despite the mean change from baseline being lower than 3 SCBM/week indicating that the majority of patients did not reach a nonconstipated state, about a quarter of prucalopride-treated patients did achieve normalization of bowel function (≥3 SCBM/week) (Table 5).

Table 7: Average Number of Weekly S(C)BM – Pooled Data from PRU-INT-6, PRU-USA-11, and PRU-USA-13, ITT Analysis Set

Time Interval	Placebo			PRU 2 mg				PRU 4 mg			
	N	Mean	Mean Change[a]	N	Mean	Mean Change[a]	Difference in LS Mean Chg vs Placebo (95% CI)[b]	N	Mean	Mean Change[a]	Difference in LS Mean Chg vs Placebo (95% CI)[b]
Average SCBM/week											
Baseline	643	0.4		638	0.4			639	0.5		
Weeks 1-12	630	1.1	0.7	612	1.9	1.5	0.8 (0.56, 1.07)	593	2.1	1.6	0.9 (0.62, 1.13)
Weeks 1-4	632	1.0	0.6	613	2.1	1.7	1.1 (0.81, 1.37)	596	2.4	1.9	1.3 (0.98, 1.55)
Average SBM/week											
Baseline	643	3.3		638	3.7			639	3.5		
Weeks 1-12	630	4.2	0.9	612	6.3	2.6	1.8 (1.38, 2.20)	593	6.3	2.8	2.1 (1.66, 2.48)
Weeks 1-4	632	4.4	1.1	613	7.2	3.5	2.5 (2.04, 2.96)	596	7.4	3.9	2.9 (2.43, 3.36)

[a] Mean change reflects mean change from run-in values

[b] Difference in least-square-mean (LS Mean) changes from run-in was based on ANCOVA model with treatment and trial as factors and baseline value as covariate.

Patients continued using laxatives during treatment (Table 8). However, the mean average number of bisacodyl tablets taken per week was reduced from run-in during the 12-week treatment period from approximately 2 to 1 tablet/week in the prucalopride groups while in the placebo group no reduction was found.

Table 8: Patients Using Laxatives During Run-In and Weeks 1-12 (pooled pivotal studies) - ITT Analysis Set

	Placebo N=645 n (%)	**PRU 2 mg N=640 n (%)**	**PRU 4 mg N=639 n (%)**
Bisacodyl use*			
Run-in	434 (67)	429 (67)	421 (66)
Weeks 1-12	444(69)	390 (61)	359 (56)
Enema*			
Run-in	57 (9)	53 (8)	57 (9)
Weeks 1-12	87 (14)	50 (8)	56 (9)
Other laxatives**			
Run-in	67 (10)	56 (9)	69 (11)
Weeks 1-12	50 (8)	46 (7)	45 (7)

* From diary-rescue medication; ** From CRF as concomitant medication

Bowel Movement Symptoms (from diaries)

- consistency of each bowel movement (watery, loose, normal, hard, very hard [little balls])
- degree of straining (no straining, mild straining, moderate straining, severe straining, very severe straining)
- feeling of complete evacuation (emptying) after a bowel movement was passed (yes/no)

Table 9: Bowel Movement Symptoms - Between Group Comparison – Pooled Data from PRU-INT-6, PRU-USA-11, and PRU-USA-13, ITT Analysis Set

	Placebo			PRU 2 mg				PRU 4 mg			
Time Interval	N	Mean	Mean Change[a]	N	Mean	Mean Change[a]	Difference in LS Mean Chg vs. Placebo (95% CI)[b]	N	Mean	Mean Change[a]	Difference in LS Mean Chg vs. Placebo (95% CI)[b]
% SBM with normal consistency											
Run-in	564	23.5		553	25.2			582	27.7		
Weeks 1-12	606	39.1	16.2	607	46.6	21.2	6.2 (2.95, 9.37)	588	48.8	21.1	8 (4.83, 11.23)
Weeks 1-4	585	38.1	14.6	600	42.5	16.9	3.6 (0.24, 6.94)	590	45.9	18.4	6.8 (3.48, 10.14)
% SBM with hard/very hard consistency											
Run-in	564	57.8		553	54.9			582	53.5		
Weeks 1-12	606	43.9	-13.5	607	30.5	-24.4	-12.6 (-15.83, -9.3)	588	29.1	-23.7	-13.1 (-16.34, -9.85)
Weeks 1-4	585	46.3	-11.3	600	29.7	-25.2	-15.8 (-19.32, -12.32)	590	27.7	-25.3	-17 (-20.47, -13.53)
% SBM with no straining											
Run-in	563	10.8		553	12.8			583	13.8		
Weeks 1-12	606	13.9	2	607	18.7	6.4	5.1 (2.33, 7.82)	588	20.2	5.9	5.3 (2.59, 8.05)
Weeks 1-4	585	11.8	0.6	600	20.2	8.4	8.6 (5.73, 11.45)	590	22.6	8.5	9.6 (6.77, 12.44)
% SBM with severe/very severe straining											
Run-in	563	42.1		553	40			583	38		
Weeks 1-12	606	31.1	-10.7	607	23.1	-17.9	-8.1 (-11.21, -5.03)	588	21.9	-15.9	-8 (-11.1, -4.95)
Weeks 1-4	585	32.7	-8.9	600	21.8	-19.1	-11.1 (-14.26, -7.89)	590	20.7	-17.3	-10.9 (-14.05, -7.72)
% SBM with sensation complete evacuation											
Run-in	564	14.4		553	13.3			582	18.3		
Weeks 1-12	606	25	11.1	607	29	16.9	4.9 (1.58, 8.29)	587	33.4	16.1	6.7 (3.35, 10.03)
Weeks 1-4	585	22.7	8.6	600	28.2	16.3	6.9 (3.5, 10.24)	590	32.4	15.5	8.7 (5.4, 12.09)

[a] Mean change reflects mean change from run-in

[b] Difference in least-square-mean (LS Mean) changes from run-in was based on ANCOVA model with treatment and trial as factors and baseline value as covariate.

Most of the % SBM characteristics improved slightly (<10%) over placebo, however, the trend in the changes support the primary efficacy variable.

The time to first SCBM and SBM after the first intake on Day 1 and on Day 29 was statistically significantly shorter in the prucalopride groups (Table 10).

Table 10: Time to First S(C)BM After Day 1 Dose – Pooled Data from PRU-INT-6, PRU-USA-11, and PRU-USA-13, ITT Analysis Set

	Placebo N=645	**PRU 2 mg N=640**	**PRU 4 mg N=639**
	Median (hh:mm) (range)	Median (hh:mm) (range)	Median (hh:mm) (range)
Time to first SCBM	375:00 (85:37; -)	56:10 (4:15; 651:00)*	38:14 (2:55; 513:00)*
Time to first SBM	26:30 (4:43; 98:00)	2:30 (1:05; 13:15)*	1:50 (1:00; 7:02)*

range: 25 – 75% interval
*p<0.001 vs. placebo

In all three studies, treatment with prucalopride resulted in small improvements in the Patient Assessment of Constipation Symptoms (PAC-SYM), a validated and disease-specific set of symptom measures, including abdominal, stool and rectal symptoms determined at Week 4 and Week 12. PAC-SYM questionnaire evaluation was rated with a 5-point scale: 0=absent through 4=very severe.

Table 11: Overall and Subscale Symptom Scores in The PAC-SYM Questionnaire – Pooled Data from PRU-INT-6, PRU-USA-11, and PRU-USA-13, ITT Analysis Set

	Placebo			PRU 2 mg				PRU 4 mg			
Time Interval	N	Mean	Mean Change[b]	N	Mean	Mean Change[b]	Difference in LS Mean Chg vs. Placebo (95% CI)[c]	N	Mean	Mean Change[b]	Difference in LS Mean Chg vs. Placebo (95% CI)[c]
PAC-SYM overall score											
Baseline	641	2.0		639	2.0			636	1.9		
Week 12[a]	641	1.6	-0.4	627	1.4	-0.7	-0.3 (-0.34, -0.17)	620	1.3	-0.6	-0.3 (-0.36, -0.19)
Week 4[a]	641	1.7	-0.3	626	1.4	-0.6	-0.3 (-0.37, -0.21)	620	1.3	-0.6	-0.3 (-0.41, -0.25)
PAC-SYM stool symptoms											
Baseline	640	2.5		638	2.5			636	2.4		
Week 12[a]	641	2.1	-0.4	627	1.8	-0.7	-0.3 (-0.4, -0.18)	620	1.7	-0.7	-0.3 (-0.41, -0.19)
Week 4[a]	641	2.1	-0.4	626	1.8	-0.7	-0.4 (-0.46, -0.25)	620	1.7	-0.7	-0.4 (-0.47, -0.26)
PAC-SYM abdominal symptoms											
Baseline	641	2.0		638	2.1			636	1.9		
Week 12[a]	641	1.6	-0.4	627	1.4	-0.7	-0.3 (-0.4, -0.18)	620	1.2	-0.7	-0.3 (-0.45, -0.23)
Week 4[a]	641	1.7	-0.4	626	1.4	-0.7	-0.3 (-0.43, -0.24)	620	1.2	-0.7	-0.4 (-0.51, -0.31)
PAC-SYM rectal symptoms											
Baseline	639	1.1		637	1.2			636	1.1		
Week 12[a]	640	0.8	-0.3	627	0.7	-0.5	-0.1 (-0.23, -0.05)	620	0.7	-0.4	-0.1 (-0.24, -0.06)
Week 4[a]	640	0.8	-0.3	626	0.8	-0.4	-0.1 (-0.19, -0.01)	620	0.6	-0.4	-0.2 (-0.26, -0.09)

[a] Data at endpoint

[b] Mean change reflects mean change from baseline values

[c] Difference in least-square-mean (LS Mean) changes from run-in was based on ANCOVA model with treatment and trial as factors and baseline value as covariate.

PAC-SYM questionnaire evaluation is rated with a 5-point scale: 0=absent through 4=very severe. Lower scores indicated improvement.

In all three studies, a significant benefit on a number of Quality of Life measures (PAC-QOL), such as degree of satisfaction with treatment and bowel habits, physical and psychosocial discomfort and worries and concerns, was observed at both the 4 and 12 week assessment time points during study visits. Table 12 provides an overview of PAC-SYM and PAC-QOL data.

Table 12: Overview of PAC-SYM and PAC-QOL Data for 12-Week Treatment Period (Pooled Data from PRU-INT-6, PRU-USA-11, PRU-USA-13, ITT Population)

	Placebo N=645	PRU 2 mg N=640
PAC-SYM overall score:		
% patients with ≥1 improvement	21.5%	33.2%*
PAC-SYM stool symptom score:		
% patients with ≥1 improvement	29.4%	40.8%*
PAC-SYM abdominal symptom score:		
% patients with ≥1 improvement	27.9%	42.2%*
PAC-SYM rectal symptom score:		
% patients with ≥1 improvement	21.6%	30.4%*
PAC-QOL overall score:		
% patients with ≥1 improvement	18.6%	36.5%*
PAC-QOL satisfaction score:		
% patients with ≥1 improvement	22.2%	44.0%*
% patients with mild or absent severity	21.8%	36.7%*
% patients with extremely or quite a bit effective treatment	17.8%	35.3%*

*p<0.001 vs. placebo

Studies in Elderly

In PRU-INT-12, a Phase 3, double-blind, placebo-controlled trial in the elderly (≥65 years), 305 elderly patients were randomized to receive placebo, 1 mg, 2 mg or 4 mg once daily of prucalopride for 4 weeks. For the primary efficacy parameter, the number of patients with ≥3 SCBM per week, there was a higher proportion of patients reaching ≥3 SCBM per week in all 3 prucalopride groups compared with placebo: 39.5% on 1 mg prucalopride, 32% on 2 mg, and 31.6% on 4 mg vs. 20% on placebo. For the key secondary efficacy parameter (proportion of patients with increase of ≥1 SCBM per week), there were significantly higher proportions of patients with increases from run-in: 61.1% on 1 mg, 56.9% on 2 mg, 50.7% on 4 mg vs. 33.8% on placebo (p≤0.05). Other secondary endpoints tend to support the primary efficacy variable (Table 13).

Overall, the results indicate that all 3 doses were more effective than placebo but no advantage was gained by increasing the dose beyond 1 mg.

Table 13: Results for Efficacy Endpoints - From Trial in Elderly Patients - PRU-INT-12

Parameter	Placebo N=70	PRU 1 mg N=76	PRU 2 mg N=75	PRU 4 mg N=79
Number of patients with an average ≥3 SCBM per week, n/N (%)				
Weeks 1-4	14/70 (20.0)	30/76 (39.5)*	24/75 (32.0)	25/79 (31.6)
Number of patients with an average increase ≥1 SCBM per week, n/N (%)				
Weeks 1-4	22/65 (33.8)	44/72 (61.1)*	41/72 (56.9)*	37/73 (50.7)*
Mean change from baseline in SCBM per week				
Weeks 1-4	0.6	1.9	1.7	1.8
Mean change from baseline in overall PAC-SYM symptoms score				
Week 4	-0.23	-0.53	-0.37	-0.55
Mean change from baseline in overall PAC-QOL symptoms score				
Week 4	-0.20	-0.53	-0.30	-0.38

p<0.05 vs. placebo (CMH test with Holm's multiple comparison procedure)

DETAILED PHARMACOLOGY

Animal Pharmacology

In vitro studies

In a range of *in vitro* gastrointestinal studies on isolated tissue taken from the esophagus, stomach, small intestine and large intestine (up to the distal colon) from mouse, rat, guinea pig, dog, pig and man, prucalopride facilitated the release of neurotransmitters. Depending on the location of the 5-HT_4 receptor these were acetylcholine from myenteric neurons (enhanced amplitude of contractions), calcitonin-gene-related-peptide (CGRP) and acetylcholine from intrinsic sensory neurons (stimulation of peristalsis) or nitric oxide from myenteric nerves (improved relaxation). Prucalopride could also act on 5-HT_4 receptors located directly on the smooth muscle cells to relax the smooth muscle layer (reduction of resistance to aboral propulsion). The consequence of these actions was improved propulsion as demonstrated in *in vitro* experiments on fecal pellet expulsion from the guinea pig colon.

EC_{50} values obtained in these gastrointestinal tests were low, in the nanomolar range in all species including man (16 to 32 nM human gastric and colon tissue). These *in vitro* effects induced by prucalopride were blocked by a selective 5-HT_4 receptor antagonist, confirming that the effects of prucalopride are likely mediated via 5-HT_4 receptors.

Four metabolites of prucalopride found in rat, dog and human were tested to establish and compare their 5-HT_4 receptor agonistic properties *in vitro*. All four metabolites behaved as 5-HT_4 receptor agonists with a similar efficacy as prucalopride, but with different potencies. The 3-hydroxy product was virtually equipotent to prucalopride and the two carboxylic acids were both less potent than prucalopride, while the trans-N-oxide was the least potent 5-HT_4 receptor agonist. Other metabolites were also tested for their affinity for the human 5-HT_4 receptor. They all had affinity for the receptor with K_i values ranging from 21 to 218 nM, being somewhat

above the K_i value of prucalopride in the same test system (8.7 nM). In humans, these metabolites with an affinity lower than prucalopride, are formed only to a very limited extent (<4%) and, therefore, their contribution to the clinical effect of prucalopride is expected to be limited.

In vivo studies

In several *in vivo* gastrointestinal motility studies prucalopride was shown to stimulate gastrointestinal motility, with a pronounced effect on the large bowel. In conscious dogs, it induced a pattern of enhanced motility in the proximal colon and reduced motility in the distal colon, facilitating propulsion of luminal contents. In addition, it induced propulsive waves of contractions starting in the proximal colon and progressing all the way to the anal sphincters, i.e., the canine equivalent of human large bowel mass movements. Prucalopride administered orally was effective in dogs at a dose as low as 0.04 mg/kg. Confirmation of the colon stimulating effect of prucalopride was obtained in a double-blind, placebo-controlled study in cats where prucalopride increased the number of observed defecations.

In studies in dogs and rats prucalopride was shown to stimulate gastric and small intestinal motility and to accelerate gastric emptying.

As in the *in vitro* studies, the *in vivo* effects in the gastrointestinal tract observed in all animal species are sensitive to blockade with a selective 5-HT_4 receptor antagonist, indicating that prucalopride exerts its effects via a selective action on 5-HT_4 receptors. In dogs, efficacy after oral and intravenous (I.V.) dosing was similar, illustrating the high bioavailability of prucalopride in this species.

<u>Human Pharmacology</u>

Safety pharmacology

Prucalopride did not affect I_{Kr} current in hERG-transfected HEK293 or COS-7 cells, at a concentration up to 1 mcM (49x the therapeutic plasma concentration). The EC50 values determined ranged between 4.1 and 22 mcM (or 200x - 1100x the therapeutic plasma concentration). Prucalopride had no effect on action potential duration up to 1µM in experiments using various isolated tissues, such as rabbit and dog Purkinje fibers, rabbit heart and guinea pig papillary muscles. When studied *in vivo* in various animal species, intravenous administration of prucalopride caused increases in systolic and diastolic blood pressure in conscious dogs and in anesthetized pigs. However there were no other relevant cardiovascular effects at prucalopride concentrations comparable to and exceeding the plasma concentrations achieved after therapeutic doses in humans (7.5 ng/mL).

In vivo studies

Pharmacodynamic effects related to the GI prokinetic activity of prucalopride were studied in healthy subjects and in subjects with chronic constipation, at doses ranging from 0.5 to 4 mg once daily (o.d.). Effects on GI and colonic transit, colonic response to eating, colonic motility, and anorectal manometry were studied and symptoms associated with chronic constipation and bowel habit were documented.

Pharmacodynamic studies assessing various direct and indirect outcome measures suggest that prucalopride may accelerate colonic transit. In a randomized, double-blind, placebo-controlled, parallel-group study and a randomized, double-blind, placebo-controlled, 2-way cross-over study in patients with chronic constipation, prucalopride was associated with a non-significant trend toward an accelerated transit through the stomach, small bowel, and colon in patients with constipation unassociated with a rectal evacuation disorder.

Thorough QT Study

A thorough double-blind QT study, M0001-C102, was performed to evaluate the effects of prucalopride on the QT interval at therapeutic (2 mg) and supratherapeutic doses (10 mg). This study did not show significant differences between prucalopride and placebo at either dose, based on mean QT_c measurements (largest increase in mean double-delta QT_c [subject-specific correction] was 3.83 msec for 2 mg and 3.03 msec for 10 mg) and outlier analysis. This confirmed the results of two earlier, placebo controlled studies which included QT measurements. The three studies confirmed that the incidence of QT-related adverse events and ventricular arrhythmias was low and comparable to placebo.

Human Pharmacokinetics

Based on a population pharmacokinetic analysis on data from Phase 1, 2, and 3 studies, it was demonstrated that the apparent plasma clearance of prucalopride is similar in healthy subjects and subjects with chronic constipation. Due to limited pharmacokinetic information collected from studies with patients suffering from chronic constipation, the model included a 39% residual error for patient data. However, the model building process and model evaluation suggests that this pharmacokinetic model can sufficiently describe the plasma pharmacokinetics data observed in both healthy subjects and patients treated with prucalopride. Based on this modeled analysis, the apparent clearance of prucalopride was not affected by age, body weight or BMI, sex, or race, but as expected, creatinine clearance had a significant effect.

An open-label, parallel-design trial in healthy elderly (n=12 [8M/4F]; median age 71 years [range 65-81 years]) and young (n=12 [8M/4F]; median age 23 years [range 20-32 years]) subjects indicated that a once-daily 1 mg oral tablet dose of prucalopride for 7 consecutive days resulted in an increase in C_{max} (36.5%) and $AUC_{0\text{-}24h}$ (40%), and reduction in Cl_{ren} (20%) in elderly compared with young subjects. The elevation in plasma prucalopride concentration is attributed to a reduction in renal function associated with age, as prucalopride is primarily renally excreted by glomerular filtration and tubular secretion processes. Based on the limited data available at this time to demonstrate safety and efficacy of a 2 mg oral dose of prucalopride in an elderly population and the elevation of prucalopride plasma concentrations in elderly compared with young subjects following 1 mg oral dose of prucalopride, a prucalopride dose reduction (e.g., 1 mg) may be recommended in elderly subjects.

An open-label trial in subjects with mild (n=8 [6M/2F]; mean age 62.6 years [range 46-74]), moderate (n=7 [5M/2F]; 62.7 years [43-69]), or severe (n=9 [3M/6F]; 51.8 years [45-59]) renal impairment indicated that a single 2 mg oral capsule dose of prucalopride resulted in a progressively greater AUC_∞ and $t_{1/2\ term}$ with degree of renal impairment compared to subjects with normal renal function (n=10 [5M/5F]; 59.4 years [52-68]). AUC_∞ increased 1.25-fold (mild), 1.5-fold (moderate), and 2.3-fold (severe), while $t_{1/2\ term}$ increased from 30 h (normal

renal function) to 34 h (mild), 43 h (moderate), and 47 h (severe). It is noted that in this study, the $t_{1/2\ term}$ reported in subjects with normal renal function was greater (25%) than that observed in the majority of other prucalopride trials (30 h vs. 24 h). There were no observed marked differences in other absorption parameters (i.e., T_{max} or C_{max}) associated with degree of renal impairment. There were no adverse events classified as heart rate and rhythm disorders. There were no atrial or ventricular arrhythmias, or changes in electrocardiogram parameters considered to be clinically relevant. There were observed fluctuations in heart rate, PR interval and QT/QTc data, however these changes appear to reflect random effects as the degrees of renal impairment did not predict alteration of QT/QTc. No dose reduction is recommended in patients with mild or moderate renal impairment, however, a dose of 1 mg o.d. is recommended in patients with severe renal impairment. No data are available in dialysis subjects; however, it is likely that only minor amounts of prucalopride will be removed by dialysis. Prucalopride is contraindicated in dialysis subjects.

Prucalopride is not recommended for use in the pediatric population due to an incomplete characterization of the clinical pharmacology and associated safety risks, including a potential risk of cardiac arrhythmia.

An open-label trial in healthy lactating female subjects (n=8; median age 33 years [extremes 27-36 years]) indicated that a 2 mg oral tablet dose (o.d.) of prucalopride for 4 days resulted in the transfer of prucalopride into breast milk. The mean (extremes) ratio of prucalopride concentration in breast milk to plasma (as per AUC_{24h}) was 2.65(2.31-3.33), however, prucalopride concentration in breast milk (unlike plasma) did not appear to reach steady-state kinetics by day 4). At this time, prucalopride is not recommended for use during breast feeding.

Studies in healthy subjects showed that there were no clinically relevant effects of prucalopride on the pharmacokinetics of warfarin (25 mg), alcohol (0.7 g/kg) or paroxetine (10-20 mg/kg). Although not formally tested, a drug-drug interaction study with alcohol suggests that the pharmacokinetics of prucalopride is unlikely to be affected to a clinically relevant extent by alcohol. There was a 10% decrease in the bioavailability of digoxin (0.25 mg) associated with prucalopride (4 mg o.d.) co-treatment.

Probenecid (800 mg b.i.d.) and cimetidine (500 mg b.i.d.), potent inhibitors of renal anion and cation transport, respectively, did not result in a clinically significant effect on the pharmacokinetics of prucalopride. As both drugs were studied at relatively high doses, it is considered unlikely that renal excretion of prucalopride will be influenced by other drugs with similar action.

Therapeutic doses of erythromycin and paroxetine did not affect the pharmacokinetics of prucalopride. Concurrent administration of prucalopride increased the bioavailability of erythromycin (500 mg q.i.d.) by 20-40%. The mechanism for this erythromycin-prucalopride interaction is not fully known, but the available data support that this is the consequence of the high intrinsic variability in erythromycin pharmacokinetics, rather than a direct effect of prucalopride.

Ketoconazole (200 mg b.i.d.), a potent inhibitor of CYP3A4 and of P-gp, increased the area under the curve (AUC) of prucalopride by approximately 40%. Interactions of similar magnitude as observed with ketoconazole may also occur with other potent inhibitors of P-gp, such as verapamil, cyclosporine A and quinidine.

TOXICOLOGY

The oral toxicological profile of prucalopride has been investigated in a full set of studies, i.e., single-dose studies in mice and rats, repeat-dose studies in rats and dogs, fertility and pre- and postnatal developmental studies in rats, embryo-fetal developmental studies in rats and rabbits, *in vitro* and *in vivo* mutagenicity studies, carcinogenicity studies in rats, mice and neonatal mice, juvenile toxicity studies in rats and dogs, local tolerance studies, studies of impurities and degradation products, and finally, mechanistic studies in mice and rats.

Single oral gavage administration of prucalopride did not lead to mortality up to 320 mg/kg in male mice and up to 160 mg/kg in female mice. In rats, the highest oral dose tested of 640 mg/kg did not cause mortality in males, while in females mortality occurred at 548 mg/kg, but not at 320 mg/kg. A single intravenous dose of 40 mg/kg in rats and of 80 mg/kg in mice was devoid of lethal effects.

In the repeated dose oral toxicity studies (1, 6 and 12 [dogs only] months), 5 and 10 mg/kg/day were the No-Observed-Adverse-Effect-Levels (NOAEL) in rats and dogs, respectively. The $AUC_{0\text{-}24h}$ exposure ratios at NOAEL versus humans (dosed at 2 mg daily) were 5 and 12 in male and female rats, respectively, and 244 in dogs. In rats, slight toxicity was evidenced by increased liver and heart weights, that were without notable microscopic correlates with the exception of slight increases in focal infiltration of chronic inflammatory cells in the heart of males at 80 mg/kg, and prolactin-mediated changes considered due to prucalopride antagonism of the dopamine D2 receptors in the pituitary gland at ≥20 mg/kg. The latter consisted of mammary gland stimulation in females at ≥20 mg/kg and males at 80 mg/kg and in the female genital tract, indicative of decreased estrus cycle activity, at 40 and 80 mg/kg. Other anatomic pathology changes consisted of: increased thymus weight at ≥20 mg/kg and slight individual cell necrosis and phagocytosis in the thymus at 80 mg/kg in a 6-month study; increased kidney and pancreas weight at ≥40 mg/kg and adrenal weight at 80 mg/kg without microscopic correlates; and increased thyroid weight at ≥40 mg/kg in a 4-week study and a slight increase in thyroid follicular epithelial height at 80 mg/kg in a 6-month study. In dogs, toxicity was seen at 20 and 30 mg/kg (CNS effects, histological changes in the liver and female genital tract, and lethality in 3/8 dogs at 30 mg/kg where the exposure margin was more than 500 times that at the 2 mg human dose).

Genotoxicity studies revealed a slight but reproducible positive result in the *in vitro* Ames reverse mutation test using the TA100 strain with and without metabolic activation.
Prucalopride also increased unscheduled DNA synthesis (UDS) in rat hepatocytes *in vitro* at cytotoxic concentrations ≥100 mcg/mL, but not at ≤50 mcg/mL. DNA adduct formation occurred in mouse and rat liver (but not other tissues) after oral prucalopride administration, although only under non-standard assay conditions and the adducts did not contain prucalopride or its known

metabolites and therefore any relationship to treatment is unclear. However, prucalopride was negative in the majority of the genetic toxicity assays that consisted of: most bacterial strains used in the Ames assay, SOS-repair, mouse lymphoma cell, human peripheral blood lymphocyte, *in vivo* mouse micronucleus, *in vivo* UDS, and *in vivo* transgenic Big Blue (evaluates mutagenicity and adduct formation in rat liver) assays. A Structural Alert Relationship analysis did not show any alert for genotoxicity of prucalopride or its metabolites. Therefore, from a weight of evidence perspective, prucalopride is considered to have low *in vivo* genotoxic potential.

Carcinogenicity studies with prucalopride resulted in an increased incidence of tumours in the two-year mouse and rat bioassays, while no drug-related tumour incidence increases were found in the neonatal mouse carcinogenicity study. The increased incidences consisted of: mammary gland adenocarcinomas in female mice at the high dose level of 80 mg/kg and in male and female rats at the high dose levels of 80 and 40 mg/kg, respectively. Other increases in rats consisted of pheochromocytomas, pancreatic islet cell adenomas, and pituitary adenomas in males at 80 mg/kg, hepatocellular adenomas in males at 40 and 80 mg/kg and females at 40 mg/kg, and thyroid follicular adenomas in males at 80 mg/kg and females at 40 mg/kg.
According to recent ICH Guidance, positive tumorgenicity findings in rodents at doses above those producing a 25-fold exposure over that in humans would not generally be considered likely to reflect a relevant risk to humans. The increased tumour incidences in the prucalopride carcinogenicity studies all occurred at exposure (AUC) margins greater than 60 times that in humans at the 2 mg therapeutic dose and the no-effect margins were close to or greater than 25-fold with the exception of the liver tumours in the mid-dose male rats where the margin is only six times that at the 2 mg human dose.

The tumour profile was considered to reflect rodent-specific epigenetic responses related to a weak CAR-mediated pleiotropic response in the liver including organ weight increases and microsomal enzyme induction (rat) with respect to the liver tumours and thyroid tumours, and stimulation of prolactin secretion (rat and mouse) in the case of the mammary and pituitary tumours. The increased incidence of thyroid tumours was likely a consequence of hepatic microsomal enzyme induction resulting in increased metabolism and excretion of thyroxine and stimulation of the thyroid gland. The increased prolactin levels were likely due to prucalopride antagonism of the dopamine D_2 receptors in the pituitary gland. It is concluded that the tumorigenic risk from prucalopride to humans is low.

Oral reproductive toxicology studies in rats did not elicit adverse effects up to 20 mg/kg in Segment I and Segment III studies. Increased precoital interval and pre-implantation loss at 80 mg/kg may have been due to maternal prolactin-mediated effects in the segment I study. In the Segment III study, a slight decrease in the weight of the gravid uterus and a marginal decrease in the number of corpora lutea were seen in the 80 mg/kg high dose group. In the oral Segment II studies in rats and rabbits, no teratogenicity or other embryotoxicity was seen up to the highest doses of 80 mg/kg, corresponding with exposure ratios versus humans of 938 in rats (based upon C_{max}; AUC was not available) and 38 in rabbits (based upon $AUC_{0\text{-}24h}$). Further, one-week and one-month neonatal/juvenile toxicity studies were performed in rats and dogs, resulting in a NOAEL of 5 mg/kg in the dog; however effects, including reduced body weight gain, occurred at all prucalopride dose levels (5-80 mg/kg) tested.

Exposure margins in the nonclinical species relative to that after a human therapeutic dose of 2 mg for principal findings in pivotal toxicology studies are summarized in Table 14.

Table 14: Summary of Exposure Margins in Pivotal Toxicology Studies

Study Type	Species and Specific Study	NOAEL (mg/kg)	Dose Level Ratio[a]	Exposure Ratio[a] (AUC unless specified)
Single-dose (mortality)	- mice - rats	160(F) - 320(M) 320(F) - 640(M)	4000 - 8000 16000	NA NA
Repeat-dose	- 6-month rat - 12-month dog	5 10	125 250	5 (M) -12 (F) 244
Reproductive/ developmental	- Segment I rat - Segment II F rat - Segment II F rabbit - Segment III F rat	20 80 80 20	500 2000 2000 500	~102[b] 938[c] 38 ~102[b]
Neonatal / Juvenile	- 4-week rat - 4-week dog	< 5 5	NA 125	NA ~54[d]
Genotoxicity (*in vivo*)	- Micronucleus (mice) - UDS (M rat) - Big Blue rat (M rat)	640 548 80	16000 13700 2000	NA 3208[c] ~430[e]
Carcinogenicity	- 24-month rat - 24-month mice - 12-month neonatal mice	5 (M) -10 (F) 80 (M) -20 (F) 300	125 (M)-250 (F) 2000(M)-500 (F) 7500	6 (M); 40 (F) 219 (M); 24 (F) 1606 (M); 1679 (F)

Key: M: Males F: Females; NA: Not available

[a] Human dose of 2 mg/50 kg/day (AUC_{24h} 7 days: 109 ng.h/mL).

[b] Exposure ratio based on AUC_{1-8h} of 11081 ng•h/mL at 20 mg/kg dose level on day 16 of pregnancy in rat Segment II study where AUC was only determined at mid-dose level.

[c] Exposure ratio based on C_{max} in humans after 7 days at 7.45 ng/mL.

[d] Exposure ratio based on estimated AUC from one-week exploratory study in neonatal dogs.

[e] AUC_{0-24h} based on a comparable study in Wistar rats at 80 mg/kg.

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10. Product Monograph ^{Pr}RESOTRAN®, Janssen Inc., Submission Control No: 221385, Date of Revision: February 04, 2019

PART III: CONSUMER INFORMATION

[Pr]JAMP Prucalopride
Prucalopride Tablets
(as prucalopride succinate)

This leaflet is a summary and will not tell you everything about JAMP Prucalopride. Contact your doctor or pharmacist if you have any questions about the drug. This leaflet is Part III of a three-part "Product Monograph" published when JAMP Prucalopride was approved for sale in Canada and is designed specifically for Consumers.

ABOUT THIS MEDICATION

What the medication is used for:
Treatment of chronic constipation in adult females when laxatives do not provide adequate relief.

What it does:
JAMP Prucalopride increases the frequency of bowel movements to provide a feeling of complete evacuation by stimulating peristalsis, the muscular contractions of the gut needed for bowel movements.

When it should not be used:
- If you are allergic to any of the ingredients in JAMP Prucalopride (see **What the nonmedicinal ingredients are**)
- If you need dialysis
- If you have serious problems with your gut like blockages, holes in your intestine, Crohn's disease or ulcerative colitis

JAMP Prucalopride is not recommended in children younger than 18 years old.

What the medicinal ingredient is:
Prucalopride succinate

What the nonmedicinal ingredients are:
1 mg prucalopride tablets:
Anhydrous colloidal silica, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, macrogol 400, polysorbate 80 and titanium dioxide.

2 mg prucalopride tablets:
Anhydrous colloidal silica, hypromellose, iron oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, macrogol 400, ploysorbate 80 and titanium dioxide.

What dosage forms it comes in:
Tablets, 1 mg and 2 mg prucalopride, as prucalopride succinate

WARNINGS AND PRECAUTIONS

BEFORE you use JAMP Prucalopride talk to your doctor or pharmacist if:

- You have any diseases affecting the liver, kidney, and/or lung;
- You have any neurological problems (these affect your nervous system) or suffer from psychiatric problems;
- You have cancer, AIDS or endocrine disorders;
- You have a history of abnormal heartbeat (arrhythmia) or heart disease;
- You have insulin-dependent diabetes;
- You are using oral contraceptives for birth control;If you develop severe diarrhea, oral contraceptives may lose effectiveness and an additional method of contraception is recommended. Cases of unintended pregnancies have been reported for JAMP Prucalopride;
- If you have a rare hereditary problem of galactose intolerance, Lapp deficiency or glucose/galactose malabsorption, then you should not use JAMP Prucalopride as it contains lactose;
- You are required to drive and use machines or other equipment;
- You are pregnant, planning to become pregnant, breastfeeding or planning to breastfeed. Prucalopride is excreted in human breast milk.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with JAMP Prucalopride include: ketoconazole, and erythromycin. Atropine-like substances may reduce the effect of JAMP Prucalopride.

PROPER USE OF THIS MEDICATION

Usual dose:
Adults (18 years of age and older): 2 mg once daily

Elderly (over 65 years of age): 1 mg once daily. Your doctor may increase the dose to 2 mg once daily if needed.

Patients with severe kidney impairment: 1 mg once daily.

Patients with severe liver impairment: 1 mg once daily. Your doctor may increase the dose to 2 mg once daily if needed.

Do not exceed a dosage of 2 mg per day. This will not add to the relief of constipation.

If there is no bowel movement in 3-4 days, contact your doctor. Your doctor may recommend an additional appropriate medication (e.g., laxative) for relief of immediate, acute constipation, at the same time as ongoing JAMP Prucalopride treatment.

Overdose:

If you think you have taken too much JAMP Prucalopride, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed dose:
Do not double your dose. Take your regular dose when you remember.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, JAMP Prucalopride can cause side effects, although not everybody gets them. Please do not be alarmed by this list of side effects, you may not experience any of them.

The most common side effects include headache, stomach pain, nausea, and diarrhea. These usually occur on the first day of treatment, and then go away within a day or so. Other common side effects include passing gas, enlargement of the abdomen or stomach, upset stomach, dizziness, tiredness, back pain, sinusitis, and kidney and urinary disorders.

Uncommon side effects include migraine and spinning sensation (vertigo)

Most of these side effects are mild to moderate in intensity. If you suffer dizziness or tiredness, use caution in driving or operating machinery. In case of persistent, severe or bloody diarrhea, anal bleeding, or worsening abdominal symptoms, discontinue JAMP Prucalopride and consult your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common	Severe, persistent or bloody diarrhea or worsening abdominal symptoms (pain)			✓
Uncommon	Strong or irregular or racing heartbeat		✓	
	Chest pain		✓	
Very Rare	Unusual changes in mood or behavior; Worsening depression, feeling sad or hopeless; Suicidal thoughts or actions about hurting or killing yourself.			✓

This is not a complete list of side effects. For any unexpected effects while taking JAMP Prucalopride, contact your doctor or pharmacist.

HOW TO STORE IT

JAMP Prucalopride should be kept out of the reach and sight of children. Store between 15- 30°C. Protect from moisture.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

Note: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

If you want more information about Jamp Prucalopride:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); or by contacting the sponsor, JAMP Pharma Corporation, at: 1-866-399-9091.

This leaflet was prepared by Jamp Pharma Corporation.
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