RESOTRANS®

prucalopride (as succinate)

DATA SHEET

1. PRODUCT NAME

RESOTRANS 1 mg film-coated tablet

RESOTRANS 2 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RESOTRANS is available as film-coated tablets containing 1 mg or 2 mg of prucalopride (as prucalopride succinate).

Excipient(s) with known effect:

Each 1 mg film-coated tablet contains 151.3 mg lactose monohydrate.

Each 2 mg film-coated tablet contains 167 mg lactose monohydrate.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Film-coated tablets

1 mg – white to off-white, round, biconvex tablets marked “PRU 1” on one side

2 mg – pink, round, biconvex tablets marked “PRU 2” on one side.

4. CLINICAL PARTICULARS

4.1 Indications

RESOTRANS is indicated for the treatment of chronic constipation in adults in whom laxatives fail to provide adequate relief.

4.2 Dose and method of administration

Dosage

RESOTRANS film-coated tablets are for oral use and can be taken with or without food.

Adults: 2 mg once daily.

Elderly (>65 years): Start with one 1 mg tablet once daily (see **section 5.2**); if needed the dose can be increased to 2 mg once daily.

Children and adolescents: RESOTRANS is not recommended in children and adolescents younger than 18 years.

Patients with renal impairment: The dose for patients with severe renal impairment (GFR < 30 mL/min/1.73m^2) is 1 mg once daily (see **sections 4.3** and **5.2**). No dose adjustment is required for patients with mild to moderate renal impairment.

Patients with hepatic impairment: The dose for patients with severe hepatic impairment (Child-Pugh class C) is 1 mg once daily (see **sections 4.4** and **5.2**). No dose adjustment is required for patients with mild to moderate hepatic impairment.

Due to the specific mode of action of RESOTRANS (stimulation of propulsive motility), exceeding the daily dose of 2 mg is not expected to increase efficacy.

Treatment Duration

If the intake of once daily RESOTRANS is not effective after 4 weeks of treatment, the patient should be re-examined and the benefit of continuing treatment reconsidered.

The efficacy of RESOTRANS has been established in double-blind placebo controlled studies for up to 3 months. In case of prolonged treatment, the benefit should be reassessed at regular intervals.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Renal impairment requiring dialysis
- Intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus and active severe inflammatory conditions of the intestinal tract, such as Crohn's disease ulcerative colitis and toxic megacolon/megarectum.

4.4 Warnings and precautions

There is limited information in 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). Therefore, caution should be exercised when prescribing RESOTRANS to patients with these conditions. In particular, RESOTRANS should be used with caution in patients with a history of arrhythmias or ischaemic cardiovascular disease.

In case of severe diarrhoea, 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).

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

Special populations

Use in Patients with Renal Impairment

Renal excretion is the main route of elimination of prucalopride (see **section 5.2**). A dose of 1 mg is recommended in patients with severe renal impairment (see **section 4.2**).

Use in Patients with Hepatic Impairment

A lower dose is recommended for patients with severe hepatic impairment (see **section 4.2**).

Use in Children and Adolescents

RESOTRANS is not recommended in children and adolescents younger than 18 years.

Use in the Elderly

Elderly (>65 years): Start with one 1 mg tablet once daily (see **sections 4.2** and **5.2**)**.** If needed, the dose can be increased to 2 mg once daily.

4.5 Interactions with Other Medicines

In vitro data indicate that RESOTRANS has a low interaction potential, and therapeutic concentrations of RESOTRANS are not expected to affect the CYP-mediated metabolism of co-medicated medicinal products.

Prucalopride is a weak substrate for P-glycoprotein (P-gp). 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.

Ketoconazole (200 mg twice/day), a potent inhibitor of CYP3A4 and of P-gp, increased the area under the curve (AUC) of RESOTRANS by approximately 40%. This effect is too small to be clinically relevant and is likely attributable to inhibition of P-gp mediated renal transport. 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. RESOTRANS is likely also secreted via another renal transporter(s). Inhibition of all transporters involved in the active secretion of RESOTRANS (including P-gp) may theoretically increase the exposure by up to 75%.

Studies in healthy subjects showed that there were no clinically relevant effects of RESOTRANS on the pharmacokinetics of warfarin, digoxin, alcohol, paroxetine and oral contraceptives. A 30% increase in the plasma concentrations of erythromycin was found during prucalopride co-treatment. The mechanism for this interaction is not fully known, but the available data support that this is the consequence of the high intrinsic variability in erythromycin kinetics, rather than a direct effect of RESOTRANS.

Therapeutic doses of probenecid, cimetidine, erythromycin and paroxetine did not affect the pharmacokinetics of RESOTRANS.

RESOTRANS should be used with caution in patients receiving concomitant drugs known to cause QTc prolongation.

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

Interactions with food have not been observed.

Effects on Laboratory Tests

No effects are known.

4.6 Fertility, pregnancy & lactation

Use in Pregnancy

Category B2

Experience with RESOTRANS during pregnancy is limited. Cases of spontaneous abortion have been observed during clinical studies, although, in the presence of other risk factors, the relationship to RESOTRANS is unknown. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. RESOTRANS is not recommended during pregnancy. Women of childbearing potential should use effective contraception during treatment with RESOTRANS.

Use in Lactation

Prucalopride is excreted in breast milk. However, at therapeutic doses of RESOTRANS, no effects on the breastfed newborns/infants are anticipated. In the absence of human data in women who breastfed while taking RESOTRANS, it is not recommended to use RESOTRANS during breast-feeding.

Effects on Fertility

Animal studies indicate that there is no effect on male or female fertility.

4.7 Effects on ability to drive or use machines

No studies on the effects of RESOTRANS on the ability to drive and use machines have been performed. RESOTRANS 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 **section 4.8**).

4.8 Undesirable effects

RESOTRANS was given orally to approximately 2,700 patients with chronic constipation in controlled clinical studies. Of these patients, almost 1,000 patients received RESOTRANS at the recommended dose of 2 mg per day, while about 1,300 patients were treated with 4 mg RESOTRANS daily. Total exposure in the clinical development plan exceeded 2,600 patient years. The most frequently reported adverse reactions associated with RESOTRANS therapy are headache and gastrointestinal symptoms (abdominal pain, nausea or diarrhoea) occurring in approximately 20% of patients each. The adverse reactions occur predominantly at the start of therapy and usually disappear within a few days with continued treatment. Other adverse reactions have been reported occasionally. The majority of adverse events were mild to moderate in intensity.

Adverse events reported by more than 2.0% of the patients in the 'All prucalopride' treatment group in the Phase II and III double-blind placebo-controlled trials in patients with chronic constipation are shown in **Table 1**.

Table 1: Chronic constipation: adverse events reported by ≥ 2% of prucalopride-treated subjects in Phase II and III double-blind placebo-controlled studies. Population: All patients

System Organ Class Preferred Term	**Placebo** n (%)	**PRU 0.5mg** n (%)	**PRU 1mg** n (%)	**PRU 2mg** n (%)	**PRU 4mg** n (%)	**All PRU** n (%)
Total no. of patients	**1369**	**110**	**308**	**938**	**1361**	**2717**
Gastrointestinal disorders	**413 (30.2)**	**31 (28.2)**	**89 (28.9)**	**396 (42.2)**	**614 (45.1)**	**1130 (41.6)**
Nausea	106 (7.7)	7 (6.4)	31 (10.1)	157 (16.7)	267 (19.6)	462 (17.0)
Diarrhoea	45 (3.3)	5 (4.5)	23 (7.5)	111 (11.8)	191 (14.0)	330 (12.1)
Abdominal pain	128 (9.3)	7 (6.4)	22 (7.1)	110 (11.7)	142 (10.4)	281 (10.3)
Abdominal pain upper	37 (2.7)	4 (3.6)	12 (3.9)	40 (4.3)	71 (5.2)	127 (4.7)
Vomiting	32 (2.3)	5 (4.5)	6 (1.9)	43 (4.6)	72 (5.3)	126 (4.6)
Flatulence	52 (3.8)	3 (2.7)	11 (3.6)	43 (4.6)	67 (4.9)	124 (4.6)
Abdominal distension	64 (4.7)	0 (0.0)	5 (1.6)	52 (5.5)	58 (4.3)	115 (4.2)
Dyspepsia	29 (2.1)	2 (1.8)	4 (1.3)	23 (2.5)	42 (3.1)	71 (2.6)
Nervous system disorders	**212 (15.5)**	**16 (14.5)**	**55 (17.9)**	**258 (27.5)**	**395 (29.0)**	**724 (26.6)**
Headache	162 (11.8)	12 (10.9)	43 (14.0)	204 (21.7)	329 (24.2)	588 (21.6)
Dizziness	25 (1.8)	2 (1.8)	8 (2.6)	41 (4.4)	56 (4.1)	107 (3.9)

System Organ Class Preferred Term	Placebo n (%)	PRU 0.5mg n (%)	PRU 1mg n (%)	PRU 2mg n (%)	PRU 4mg n (%)	All PRU n (%)
Infections and infestations	**257 (18.8)**	**15 (13.6)**	**30 (9.7)**	**196 (20.9)**	**254 (18.7)**	**495 (18.2)**
Sinusitis	40 (2.9)	2 (1.8)	4 (1.3)	28 (3.0)	42 (3.1)	76 (2.8)
Nasopharyngitis	43 (3.1)	1 (0.9)	3 (1.0)	31 (3.3)	38 (2.8)	73 (2.7)
Influenza	40 (2.9)	1 (0.9)	4 (1.3)	33 (3.5)	33 (2.4)	71 (2.6)
Urinary tract infection	29 (2.1)	8 (7.3)	4 (1.3)	23 (2.5)	20 (1.5)	55 (2.0)
General disorders and administration site conditions	**89 (6.5)**	**6 (5.5)**	**24 (7.8)**	**90 (9.6)**	**153 (11.2)**	**273 (10.0)**
Fatigue	21 (1.5)	1 (0.9)	7 (2.3)	24 (2.6)	41 (3.0)	73 (2.7)
Musculoskeletal and connective tissue disorders	**118 (8.6)**	**6 (5.5)**	**20 (6.5)**	**106 (11.3)**	**110 (8.1)**	**242 (8.9)**
Back pain	39 (2.8)	1 (0.9)	11 (3.6)	30 (3.2)	31 (2.3)	73 (2.7)
Investigations	**100 (7.3)**	**6 (5.5)**	**10 (3.2)**	**83 (8.8)**	**105 (7.7)**	**204 (7.5)**
Respiratory, thoracic and mediastinal disorders	**73 (5.3)**	**4 (3.6)**	**11 (3.6)**	**52 (5.5)**	**72 (5.3)**	**139 (5.1)**
Skin and subcutaneous tissue disorders	**54 (3.9)**	**3 (2.7)**	**17 (5.5)**	**41 (4.4)**	**63 (4.6)**	**124 (4.6)**
Renal and urinary disorders	**31 (2.3)**	**1 (0.9)**	**6 (1.9)**	**37 (3.9)**	**56 (4.1)**	**100 (3.7)**
Psychiatric disorders	**51 (3.7)**	**0 (0.0)**	**7 (2.3)**	**42 (4.5)**	**46 (3.4)**	**95 (3.5)**
Metabolism and nutrition disorders	**20 (1.5)**	**2 (1.8)**	**5 (1.6)**	**32 (3.4)**	**48 (3.5)**	**87 (3.2)**
Injury, poisoning and procedural complications	**40 (2.9)**	**5 (4.5)**	**10 (3.2)**	**32 (3.4)**	**38 (2.8)**	**85 (3.1)**
Reproductive system and breast disorders	**38 (2.8)**	**3 (2.7)**	**11 (3.6)**	**37 (3.9)**	**29 (2.1)**	**80 (2.9)**
Cardiac disorders	**23 (1.7)**	**2 (1.8)**	**10 (3.2)**	**16 (1.7)**	**42 (3.1)**	**70 (2.6)**
Note: AEs reported any time during treatment or within 5 days of end of treatment are included						

A total of 564 elderly patients (≥65 years) with chronic constipation were treated with RESOTRANS in double-blind studies, with a total exposure of 63 person-years. Most patients in the Phase II/III double-blind placebo-controlled studies were younger than 65 years. The incidence of adverse events in the < 65 years old group was 71.2% (1534 out of 2153 patients) in the prucalopride group, and 61.6% (712 out of 1155) in the placebo group. In the group of patients older than 65 years, the incidence of adverse events in the RESOTRANS group was 58.7% (331 out of 564) and in the placebo group 52.8% (113 out of 214). Similar to the younger age group, the most common adverse events with RESOTRANS treatment among the elderly (>65 years) groups were gastrointestinal disorders and headache. No clinically meaningful increase of adverse events was observed in RESOTRANS treated groups as compared to placebo group.

The following adverse reactions were reported in controlled clinical studies at the recommended dose of 2 mg with frequencies corresponding to Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000) and Very rare (≤ 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are calculated based on the placebo-controlled clinical study data.

Metabolism and nutrition disorders
Common: decreased appetite

Nervous system disorders
Very common: headache
Common: dizziness
Uncommon: tremors, migraine

Cardiac disorders
Uncommon: palpitations

Ear and labyrinth disorders
Uncommon: vertigo

Gastrointestinal disorders
Very common: nausea, diarrhoea, abdominal pain
Common: vomiting, dyspepsia, rectal haemorrhage, flatulence, abnormal bowel sounds

Renal and urinary disorders
Common: polyuria

General disorders and administration site conditions
Common: fatigue
Uncommon: fever, malaise

After the first day of treatment, the most common adverse reactions were reported in similar frequencies (incidence less than 1% difference between RESOTRANS and placebo) during RESOTRANS therapy as during placebo, with the exception of nausea and diarrhoea that still occurred more frequently during RESOTRANS therapy, but less pronounced (difference in incidence between RESOTRANS and placebo between 1 and 3%).

Palpitations were reported in 0.7% of the placebo patients, 1.0% of the 1 mg RESOTRANS patients, 0.7% of the 2 mg RESOTRANS patients and 1.9% of the 4 mg RESOTRANS patients. The majority of patients continued using RESOTRANS. As with any new symptom, patients should discuss the new onset of palpitations with their physician.

Cardiovascular Safety Analysis

An evaluation was performed by an independent adjudication committee of all potential major adverse cardiovascular events (MACE) across 27 completed double-blind and open-label clinical studies for RESOTRANS in adult patients with chronic idiopathic constipation. The standardized incidence rate (IR) per 1000 subject-years for MACE for RESOTRANS was compared with the IR for placebo. The total exposure in the double-blind studies was 565.2 subject-years in the RESOTRANS group, 384 subject-years in the placebo group and 2769 subject-years in the double-blind and open-label clinical studies. The IR for MACE was 3.5 (2 subjects out of 3366) in the double-blind RESOTRANS group, 5.2 (2 subjects out of 2019) in the placebo group, and 3.3 (9 subjects out of 4472) for RESOTRANS in the combined double-blind and open-label clinical studies. The data do not indicate an increased risk of MACE attributable to RESOTRANS when compared to placebo.

Observational Cardiovascular Cohort Study

The overall (CV) safety of RESOTRANS was assessed in an observational population-based cohort study using European healthcare databases. New users of RESOTRANS (N=5717) were matched to new users of polyethylene glycol 3350 (PEG) (N=29,388) to determine the standardized incidence rate (IR) and the adjusted incidence rate ratio (IRR) per 1,000 person-years for MACE. In this cohort study, the pooled, standardized IR for MACE was 6.59 (95% CI: 3.90, 10.41) for RESOTRANS compared to an IR of 10.32 (7.04, 14.22) for PEG and the IRR for MACE was 0.64 (95% CI: 0.36, 1.13). These data do not indicate an increased risk of MACE in patients using RESOTRANS as compared with patients using PEG for chronic idiopathic constipation.

4.9 Overdose

In a study in healthy subjects, treatment with RESOTRANS was well tolerated when given in an up-titrating scheme up to 20mg 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 diarrhoea. Specific treatment is not available for RESOTRANS overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Extensive fluid loss by diarrhoea or vomiting may require correction of electrolyte disturbances.

For advice on the management of overdosage, please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for constipation, ATC code: A06AX05

Mechanism of actions

Prucalopride is a dihydrobenzofurancarboxamide with enterokinetic activities. Prucalopride is a selective, high affinity serotonin (5-HT_4) receptor agonist, which likely explains its enterokinetic effects. *In vitro*, affinity for other receptors was detected only at concentrations exceeding its 5-HT_4 receptor affinity by at least 150-fold. In rats *in vivo*, prucalopride at doses above 5mg/kg (at and above 30-70 times the clinical exposure) induced hyperprolactinaemia caused by an antagonistic action at the D2 receptor.

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.

Clinical trials

The efficacy of RESOTRANS was established in three multicentre, randomised, double-blind, 12-week placebo-controlled studies in subjects with chronic constipation (n=1,279 on RESOTRANS, 1,124 females, 155 males) namely PRU-INT-6, PRU-USA-11 and PRU-USA-13. The RESOTRANS doses studied in each of these three studies included 2 mg and 4 mg dosing once daily. **Table 2** provides a summary of the constipation history (prior to study enrolment) demonstrating that the patients enrolled were chronically constipated. Over 70% of patients had ≤1 SBM at baseline and more than 80% indicated that prior therapy was inadequate. The primary efficacy endpoint was the proportion (%) of patients that reached normalisation of bowel movements defined as an average of three or more spontaneous, complete bowel movements (SCBM) per week over the 12-week treatment period. 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 RESOTRANS that reached an average of ≥ 3 SCBM per week was 27.8% (week 4) and 23.6% (week 12), versus 10.5% (week 4) and 11.3% (week 12) on placebo. 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 RESOTRANS versus 23.4% (week 4) and 24.6% (week 12) of placebo patients.

In all three studies, treatment with RESOTRANS also resulted in significant 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. A significant benefit on a number of Quality of Life measures, such as degree of satisfaction with treatment and with bowel habits, physical and psychosocial discomfort and worries and concerns, was also observed at both the 4 and 12 week assessment time points.

Table 2: History of constipation for Phase III pivotal studies (PRU-INT-6, PRU-USA-11, PRU-USA-13) in patients with chronic constipation - ITT population

Parameter	Placebo N=645	PRU* 2 mg N=640	PRU 4 mg N=639	All PRU N=1,279
Duration of constipation, years				
Mean (SE)	20.44 (0.616)	19.84 (0.622)	20.18 (0.643)	20.01 (0.447)
Median (min;max)	20 (0.5 ; 77)	16 (0.5 ; 70)	17 (0.3 ; 82)	16 (0.3 ; 82)
Average freq./week spontaneous bowel movement over previous 6 months, n (%)				
No spontaneous BM[a]	259 (40.2)	251 (39.2)	262 (41.0)	513 (40.1)
>0 and ≤1	224 (34.7)	224 (35.0)	206 (32.2)	430 (33.6)
>1 and ≤3	153 (23.7)	153 (23.9)	155 (24.3)	308 (24.1)
>3	9 (1.4)	12 (1.9)	16 (2.5)	28 (2.2)
Subject main complaint, n (%)				
Infrequent defaecation	185 (28.7)	202 (31.6)	184 (28.8)	386 (30.2)
Abdominal bloating	163 (25.3)	152 (23.8)	159 (24.9)	311 (24.3)
Abdominal pain	98 (15.2)	102 (15.9)	85 (13.3)	187 (14.6)
Feeling not completely empty	95 (14.7)	83 (13.0)	97 (15.2)	180 (14.1)
Straining	68 (10.5)	65 (10.2)	80 (12.5)	145 (11.3)
Hard stools	36 (5.6)	36 (5.6)	34 (5.3)	70 (5.5)
Laxative taken[b], n (%)				
No	89 (13.8)	92 (14.4)	98 (15.3)	190 (14.9)
Yes	556 (86.2)	548 (85.6)	541 (84.7)	1089 (85.1)
Overall therapeutic effect, n (%)				
Adequate	106 (17.0)	115 (18.5)	100 (16.2)	215 (17.4)
Inadequate	516 (83.0)	507 (81.5)	517 (83.8)	1024 (82.6)

*PRU = Prucalopride

[a] BM = bowel movement

[b] many patients had also been treated with diet and bulking agents

PRU-INT-6

Study PRU-INT-6 was a multicentre, randomised, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy, safety, and effect on quality of life of RESOTRANS 2 and 4 mg including 716 male and female patients (mean age 43.9 [17−89] years) with chronic constipation. The study consisted of 2 phases: a 2-week drug-free run-in phase followed by a randomised, 12-week, double-blind, placebo-controlled treatment phase. The trial population had long standing chronic constipation with a mean duration of 17.6 years (1−79 years).

The primary efficacy parameter was the proportion of patients with an average of ≥3 SCBM per week. Over the 12-week treatment period, 19.5% and 23.6% of patients in the RESOTRANS 2 and 4 mg groups, respectively, had ≥3 SCBM per week, as compared with 9.6% of placebo-treated patients (2 mg $p \leq 0.01$; 4 mg $p \leq 0.001$). Over Weeks 1 through 4, 23.7% and 26.6% of patients in the RESOTRANS 2 and 4 mg groups, respectively, had ≥3 SCBM per week compared with 10.4% of placebo-treated patients ($p \leq 0.001$, in both cases).

For the main secondary parameter (the proportion of patients with an average increase of ≥1 SCBM per week from run-in), significant improvements were seen for both RESOTRANS 2 and 4 mg treatment groups compared with placebo. Over the 12-week treatment period, the

proportion of patients with an average increase of ≥1 SCBM per week was 38.1% and 44.1% in the 2 and 4 mg groups, respectively, compared with 20.9% of placebo patients (p≤0.001, in both cases). Over Weeks 1 through 4, 41% and 46% of patients in the RESOTRANS 2 and 4 mg groups, respectively, had an increase of ≥1 SCBM per week, compared with 20.9% of placebo patients (p≤0.001, in both cases).

RESOTRANS significantly improved the time to first bowel movement when compared with placebo. The median time required to have the first SCBM in the RESOTRANS 2 and 4 mg groups was 113 and 49.5 hours after the first dose, respectively, compared with 493 hours in the placebo group (p≤0.001, in both cases).

PRU-USA-11

Study PRU-USA-11 was a multicentre, randomised, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy, safety, and effect on quality of life of 2 and 4 mg RESOTRANS including 570 male and female patients (mean age 48.3 [18−85] years) with chronic constipation. The study consisted of 2 phases: a 2-week drug-free run-in phase followed by a randomised, 12-week, double-blind,placebo-controlled treatment phase. The trial population had long-standing chronic constipation, with a mean duration of 21.1 years (1−79 years).

The primary efficacy parameter was the proportion of patients with an average of ≥3 SCBM per week. Over the 12-week treatment period, 28.9% of patients in the RESOTRANS 2 and 4 mg groups had ≥3 SCBM per week as compared with 13% of placebo-treated patients (p≤0.001, in both cases). Over Weeks 1 through 4, 32.1% and 37.4% of patients in the RESOTRANS 2 and 4 mg groups, respectively, had ≥3 SCBM per week compared with 9.8% of placebo-treated patients (p≤0.001, in both cases).

For the main secondary parameter (the proportion of patients with an average increase of ≥1 SCBM per week from run-in), significant improvements were seen for both the RESOTRANS 2 and 4 mg treatment groups compared with placebo. Over the 12-week treatment period, the proportion of patients with an average increase of ≥1 SCBM per week was 50.3% and 51.1% in the 2 and 4 mg groups, respectively, compared with 25.9% of placebo patients (p≤0.001, in both cases). Over Weeks 1 through 4, 56.5% and 58.8% of patients in the RESOTRANS 2 and 4 mg groups, respectively, had an increase of ≥1 SCBM per week, compared with 24.3% of placebo patients (p≤0.001, in both cases).

RESOTRANS significantly improved the time to first bowel movement when compared with placebo. The median time required to have the first SCBM in the RESOTRANS 2 and 4 mg groups was 32.5 and 25 hours after the first dose, respectively, compared with 297 hours in the placebo group (p≤0.001, in both cases).

PRU-USA-13

Study PRU-USA-13 was a multicentre, randomised, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy, safety, and effect on quality of life of 2 and 4 mg RESOTRANS including 641 male and female patients (mean age 47.9 [18−95] years) with chronic constipation. The study consisted of 2 phases: a 2-week drug-free run-in phase followed by a randomised, 12-week, double-blind, placebo-controlled treatment phase. The trial population had long-standing chronic constipation, with a mean duration of 22 years (1−82 years).

The primary efficacy parameter was the proportion of patients with an average of ≥3 SCBM per week. Over the 12-week treatment period, 23.4% and 22.3% of patients in the RESOTRANS 2 and 4 mg groups, respectively, had ≥3 SCBM per week as compared with 11.8% of placebo-treated patients (p≤0.01, in both cases). Over Weeks 1 through 4, 29.2% and 28.9% of patients in the prucalopride 2 and 4 mg groups, respectively, had ≥3 SCBM per week compared with 11.5% of placebo-treated patients (p≤0.001, in both cases).

For the main secondary parameter (the proportion of patients with an average increase of ≥1 SCBM per week from run-in), significant improvements were seen for both the RESOTRANS 2 and the 4 mg treatment groups compared with placebo. Over the 12-week treatment period, the

proportion of patients with an average increase of ≥1 SCBM per week was 42.6% and 46.6% in the 2 and 4 mg groups, respectively, compared with 27.5% of placebo patients (p≤0.001, in both cases). Over Weeks 1 through 4, 48.8% and 51.5% of patients in the RESOTRANS 2 and 4 mg groups, respectively, had an increase of ≥1 SCBM per week, compared with 25.5% of placebo patients (p≤0.001, in both cases).

RESOTRANS significantly improved the time to first bowel movement when compared with placebo. The median time required to have the first SCBM in the RESOTRANS 2 and 4 mg groups was 55 and 46 hours after the first dose, respectively, compared with 311 hours in the placebo group (p≤0.001, in both cases).

Over 600 elderly subjects were investigated in double-blind placebo-controlled Phase II and III studies comparing the 1mg, 2mg and 4mg doses of RESOTRANS with placebo. Results demonstrated that the 1 mg daily dose is the lowest effective dose in achieving the primary endpoint of ≥ 3 SCBM per week and the secondary endpoint of increase ≥ 1 SCBM per week.

It has been shown that RESOTRANS does not cause rebound phenomena or induce dependency. A thorough double-blind QT study was performed to evaluate the effects of RESOTRANS on the QT interval at therapeutic (2mg) and supratherapeutic doses (10mg) and compared with the effects of placebo and a positive control. This study did not show significant differences between RESOTRANS and placebo at either dose, based on mean QT measurements and outlier analysis. This confirmed the results of two placebo controlled QT studies. In double blind clinical studies, the incidence of QT-related adverse events and ventricular arrhythmias was low and comparable to placebo.

Data from open label studies up to 2.6 years offer some evidence for longer-term safety and efficacy; however, no placebo controlled efficacy data for treatments longer than 12 weeks duration are available.

5.2 Pharmacokinetic properties

Absorption

Prucalopride is rapidly absorbed; after a single oral dose of 2mg, C_{max} was attained in 2-3 hours. The absolute oral bioavailability is >90%. Concomitant intake of food does not influence the oral bioavailability of prucalopride.

Distribution

Prucalopride is extensively distributed and has a steady-state volume of distribution (Vd_{ss}) of 567 litres. The plasma protein binding of prucalopride is about 30%.

Metabolism

Metabolism is not the major route of elimination of prucalopride. *In vitro*, human liver metabolism of prucalopride is very slow and only minor amounts of metabolites are found. In an oral dose study with radiolabelled prucalopride in man, small amounts of eight metabolites were recovered in urine and faeces. The major metabolite (R107504, formed by O-demethylation and oxidation of the resulting alcohol function to a carboxylic acid) accounted for less than 4% of the dose. Unchanged active substance made up about 85% of the total radioactivity in plasma and only R107504 was a minor plasma metabolite.

Elimination

In healthy subjects a large fraction of the active substance is excreted unchanged (about 60% of the administered dose in urine and approximately 6% in faeces) via both passive filtration and active renal transporters (P-gp and BCRP). The plasma clearance of prucalopride averages 317mL/min. Its terminal half-life is about one day. Steady-state is reached within three to four days. On once daily treatment with 2mg prucalopride steady-state plasma concentrations

fluctuate between trough and peak values of 2.5 and 7ng/mL, respectively. The accumulation ratio after once daily dosing ranged from 1.9 to 2.3. The pharmacokinetics of prucalopride is dose-proportional within and beyond the therapeutic range (tested up to 20mg). Once daily prucalopride displays time-independent kinetics during prolonged treatment.

Special Populations

Population Pharmacokinetics

A population pharmacokinetic analysis based on combined data from Phase I, II, and III studies showed that the apparent total clearance of prucalopride correlated with creatinine clearance, but not with age, body weight, gender, or race.

Elderly

After once daily dosing of 1 mg, peak plasma concentrations and AUC of prucalopride in elderly patients were 26% to 28% higher than in young adults. This effect can be attributed to a diminished renal function in the elderly.

Renal Impairment

Compared to subjects with normal renal function, plasma concentrations of prucalopride after a single 2mg dose were on average 25% and 51% higher in subjects with mild (Cl_{CR} 50-79mL/min/1.73m^2) and moderate (Cl_{CR} 25-49mL/min/1.73m^2) renal impairment, respectively. In subjects with severe renal impairment (Cl_{CR} ≤ 24mL/min/1.73m^2), plasma concentrations were 2.3 times the levels in healthy subjects (see **sections 4.2** and **4.4**).

Hepatic Impairment

Non-renal elimination contributes up to about 35% of total elimination. After a single oral dose of 2mg, C_{max} and AUC of prucalopride were on average 10-20% higher in patients with moderate and severe hepatic impairment than in subjects with normal hepatic function.

Paediatric Population

After a single oral dose of 0.03mg/kg in paediatric patients aged between 4 and 12 years, C_{max} of prucalopride was comparable to the C_{max} in adults after a single 2mg dose. Unbound Area Under the Curve (AUC) was 30-40% lower than after 2mg in adults. Unbound exposure was similar over the whole age-range (4-12 years). The average terminal half-life in paediatric patients was about 19 hours (range 11.6 to 26.8 hours). RESOTRANS is not recommended in children or adolescents (see **section 4.4 - Use in Children and Adolescents**).

5.3 Preclinical safety data

Carcinogenicity

Non-clinical data reveal no special hazard for humans based on conventional studies of carcinogenic potential.

Genotoxicity

Non-clinical data reveal no special hazard for humans based on conventional studies of genotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate

Microcrystalline cellulose

Magnesium stearate

Colloidal silicon dioxide.

Coating:

Hypromellose

Titanium dioxide

Lactose monohydrate

Macrogol 3000

Glycerol triacetate.

Additionally, in the coating, the 2 mg tablet contains iron oxide red, iron oxide yellow and indigo carmine C173015.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

RESOTRANS tablets should be kept out of reach of children. Store below 30°C. Store in the original blister pack in order to protect from moisture.

6.5 Nature and content of container

Both strengths of RESOTRANS film-coated tablets are available in aluminium/aluminium perforated unit dose blisters containing 7 tablets. Each pack contains 28 film-coated tablets

6.6 Special precautions for disposal

No special requirements

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Janssen-Cilag (New Zealand) Ltd

Auckland, NEW ZEALAND

Telephone: 0800 800 806

Fax: (09) 588 1398

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9. DATE OF FIRST APPROVAL

26 April 2012

10. DATE OF REVISION OF THE TEXT

23 October 2018

RESOTRANS is a registered trademark of Ortho-McNeil-Janssen Pharmaceutical, Inc. for prucalopride oral tablets.

Summary table of changes

Section changes	Summary of new information
All	- datasheet reformat
4.4	- add clarifying text regarding patients with severe and clinically unstable concomitant disease - that limited data is available.
4.5 & 5.2	- specify interaction information (e.g., mechanism of excretion, effects on other transporters).
4.6	- editorial update/clarification.
4.8	- update/add adverse events observed in clinical trials based on a reanalysis of the integrated safety information - add new data on the cardiovascular safety from an independent adjudication of all potential major adverse cardiovascular events (MACE) from clinical studies with prucalopride. - add new data from an observational cardiovascular cohort study