
AUSTRALIAN PRODUCT INFORMATION

RESOTRANS[®]

(PRUCALOPRIDE)

FILM-COATED TABLET

1. NAME OF THE MEDICINE

Prucalopride (as succinate)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1 mg or 2 mg of prucalopride as the succinate salt.

Excipient of known effect: sugars as lactose.

For a full list of excipients, see **section 6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Film-coated tablet

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 THERAPEUTIC INDICATIONS

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

- Before RESOTRANS is considered patients must have tried at least two different types of laxatives from different classes (at the highest tolerated recommended doses) for at least six months, but have not had adequate relief from constipation.
- If treatment with RESOTRANS is not effective within four weeks, the benefit of continuing treatment should be reconsidered.

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.

Method of administration

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

Dosage adjustment

Hepatic impairment

The dose for patients with severe hepatic impairment (Child-Pugh class C) is 1 mg once daily (see **sections 4.4 Special warnings and precautions for use** and **5.2 Pharmacokinetic properties**). 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.

Renal impairment

The dose for patients with severe renal impairment not requiring dialysis (GFR < 30 mL/min/1.73m²) is 1 mg once daily (see **sections 4.3 Contraindications** and **5.2 Pharmacokinetic properties**). No dose adjustment is required for patients with mild to moderate renal impairment.

Elderly (>65 years)

Start with one 1 mg tablet once daily (see **section 5.2 Pharmacokinetic properties**); if needed the dose can be increased to 2 mg once daily.

Paediatric

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

Treatment Duration

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

Efficacy and safety of RESOTRANS has been established in double-blind placebo controlled studies for up to 12 weeks. Patients should be reassessed after 12 weeks prior to continuation of treatment with prucalopride.

Use with Laxatives

Efficacy and safety of RESOTRANS when used in combination with laxatives has not been assessed, although laxatives were used as rescue medications in the pivotal clinical trials.

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, and ulcerative colitis and toxic megacolon/megarectum
- Recent bowel surgery

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Prior to receiving RESOTRANS patients require a thorough history and examination to exclude secondary causes of constipation and to establish failure to respond adequately to at least 2 different types of laxatives from different classes for at least 6 months.

The safety and efficacy of RESOTRANS in combination with laxatives has not been assessed, although laxatives were used as rescue medications in the pivotal clinical trials.

Secondary constipation

Efficacy and safety of RESOTRANS has been demonstrated only in patients with chronic functional constipation. Efficacy and safety of RESOTRANS in patients with secondary causes of constipation including endocrine disorders, metabolic disorders and neurologic disorders have not been assessed and use in these patients is not recommended. Efficacy and safety of RESOTRANS in patients with medication-related constipation, including constipation due to opioid use as a secondary cause of constipation, has not been demonstrated and use of RESOTRANS is not recommended.

Concomitant disease

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.

Oral contraceptives

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).

Lactose

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.

Psychiatric Disorders

Suicides, suicide attempts, and suicidal ideation have been reported in clinical trials and post-market experience. A causal association between treatment with RESOTRANS and suicidal ideation and behaviour has not been established. Patients should be monitored for persistent worsening of depression or the emergence of suicidal thoughts and behaviours. Counsel the patients and their caregivers and family members to be aware of any unusual changes in mood or behaviour, and to discontinue RESOTRANS and alert the healthcare provider immediately.

Use in hepatic impairment

A lower dose is recommended for patients with severe hepatic impairment (see **section 4.2 Dose and method of administration**).

Use in renal impairment

Renal excretion is the main route of elimination of prucalopride (see **section 5.2 Pharmacokinetic properties**). A dose of 1 mg is recommended in subjects with severe renal impairment (see **section 4.2 Dose and method of administration**).

Use in the elderly

Start with one 1 mg tablet once daily (see **sections 4.2 Dose and method of administration** and **5.2 Pharmacokinetic properties**). If needed, the dose can be increased to 2 mg once daily.

Paediatric use

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

Effects on laboratory tests

No effects are known.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Potential of effect

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%. 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. Prucalopride is likely also secreted via another renal transporter(s). Inhibition of all transporters involved in the active secretion of prucalopride (including P-gp) may theoretically increase the exposure by up to 75%.

Reduction of effect

Because of the mechanism of action, the use of atropine-like substances may reduce the 5-HT₄ receptor mediated effects of RESOTRANS.

In vitro data indicate that prucalopride has a low interaction potential, and 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-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.

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 RESOTRANS 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.

There are no data on the effect of prucalopride on SSRIs other than paroxetine or of the effect of SSRIs on prucalopride.

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

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

Interactions with food have not been observed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There is no information on the effects of prucalopride on human fertility. There were no adverse effects on the fertility of rats treated orally or subcutaneously with prucalopride at doses up to 20 mg/kg/day, with estimated exposure about 100 times clinical exposure at the MRHD, based on AUC.

Use in pregnancy

Category B1

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. RESOTRANS is not recommended during pregnancy, and women of childbearing potential should use effective contraception during treatment with RESOTRANS.

There was no evidence of teratogenicity in rats or rabbits treated with prucalopride during the period of organogenesis at oral doses up to 80 mg/kg/day, (respective exposures about 400 times and 40 times the clinical exposure at the MRHD, based on AUC).

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.

Oral administration of prucalopride to rats from early gestation to weaning at doses up to 80 mg/kg/day was associated with slightly reduced pup survival due to maternotoxicity, with estimated exposure at least 100 times clinical exposure at the MRHD, based on AUC.

4.7 EFFECTS ON ABILITY TO DRIVE AND 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 Adverse Effects (Undesirable effects)**).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

RESOTRANS has been 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 $\geq 2\%$ of RESOTRANS-treated subjects in Phase II and III double-blind placebo-controlled studies. Population: All patients

System Organ Class Preferred Term	Placebo n (%)	RESOTRANS 0.5 mg n (%)	RESOTRANS 1 mg n (%)	RESOTRANS 2 mg n (%)	RESOTRANS 4 mg n (%)	All RESOTRANS 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)
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

RESOTRANS 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 ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($> 1/1,000$ to $< 1/100$), Rare ($> 1/10,000$ to $< 1/1,000$) and Very rare ($\leq 1/10,000$). 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, flatulence, abnormal bowel sounds

Uncommon: rectal haemorrhage

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.

RESOTRANS has been shown not to cause rebound phenomena, nor to induce dependency.

A thorough QT study was performed to evaluate the effects of RESOTRANS on the QT interval at therapeutic (2 mg) and suprathreshold doses (10 mg) 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.

Suicidal behaviour / ideation

In the double-blind clinical trials, one patient reported a suicide attempt 7 days after the end of treatment with RESOTRANS 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 RESOTRANS 2 mg or 4 mg; both discontinued RESOTRANS for at least one month prior to the event.

Cardiovascular Safety Analysis

An evaluation was performed by an independent adjudication committee of all potential major adverse cardiovascular events (MACE) across 28 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=5715) were matched to new users of polyethylene glycol 3350 (PEG) (N=29,372) 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 6.57 (95% CI: 3.90, 10.39) for RESOTRANS compared to an IR of 10.24 (95% CI: 6.97, 14.13) for PEG and the IRR for MACE was 0.64 (95% CI: 0.36, 1.14). These data do not indicate an increased risk of MACE in patients using RESOTRANS as compared with patients using PEG for chronic idiopathic constipation.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In a study in healthy volunteers, treatment with RESOTRANS 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 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 information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pharmacotherapeutic group: Drugs acting on serotonin receptors, ATC code: A03AE04.

In subjects with chronic constipation, there was a reduction in small bowel transit time, an increase in gastric emptying and more rapid colonic filling. There was an increase in the frequency of bowel motions but no significant effect on colonic transit time.

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 studies 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 RESOTRANS doses studied in each of these three studies included 2 mg and 4 mg once daily. The respective mean ages of patients in the three studies were 43.9, 48.3, and 47.9 (range 17–95) years. Patients with secondary causes of constipation including opioid use, endocrine disorders, metabolic disorders and neurologic disorders were excluded from the studies. **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.

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	RESOTRANS 2 mg N=640	RESOTRANS 4 mg N=639	All RESOTRANS 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)

^a BM = bowel movement

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

The primary efficacy endpoint was the proportion (%) of subjects 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. The main secondary efficacy parameter was the proportion of patients with an average increase of ≥ 1 SCBM per week from run-in. A summary of primary efficacy data for individual pivotal studies is provided in **Table 3**. 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 over the 2 mg dose.

Table 3: Summary of Primary Efficacy Data from the PRU-INT-6, PRU-USA-11 and PRU-USA-13 Studies – ITT Population

	Placebo	RESOTRANS 2mg	RESOTRANS 4mg
PRU-INT-6	N=240	N=238	N=238
Number of patients with an average ≥ 3 SCBM per week, n/N(%)			
Run-in	2/239 (0.8)	2/236 (0.8)	3/237 (1.3)
Weeks 1-12	23/240 (9.6)	46/236 (19.5)**	56/237 (23.6)***
Number of patients with an average increase ≥ 1 SCBM per week, n/N (%)			
Weeks 1-12	49/234 (20.9)	86/226 (38.1)***	94/213 (44.1)***
PRU-USA-11	N=193	N=190	N=187
Number of patients with an average ≥ 3 SCBM per week, n/N(%)			
Run-in	0/192 (0)	2/189 (1.1)	2/187 (1.1)
Weeks 1-12	25/193 (13.0)	55/190 (28.9)***	54/187 (28.9)***
Number of patients with an average increase ≥ 1 SCBM per week, n/N (%)			
Weeks 1-12	49/189 (25.9)	89/177 (50.3)***	90/176 (51.1)***
PRU-USA-13	N=212	N=214	N=215
Number of patients with an average ≥ 3 SCBM per week, n/N(%)			
Run-in	2/212 (0.9)	1/213 (0.5)	3/215 (1.4)
Weeks 1-12	25/207 (12.1)	50/209 (23.9)**	48/204 (23.5)**
Number of patients with an average increase ≥ 1 SCBM per week, n/N (%)			
Weeks 1-12	57/207 (27.5)	89/209 (42.6)***	95/204 (46.6)***

Asterisks refer to differences vs placebo: ** $p < 0.01$; *** $p < 0.001$

Results from the analyses of proportion of patients achieving an average of ≥ 3 SCBM per week during weeks 1-4 were similar to that for the primary efficacy endpoint. Both doses were significantly superior ($p < 0.001$) to placebo in each of the three studies.

In the pooled 3 pivotal study data analyses, 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. Based on the 12 weeks pooled data, for placebo, 1 out of 8 patients responded (ie had ≥ 3 SCBM/week). For an average number of 8 patients receiving RESOTRANS 2 mg daily, one additional patient had ≥ 3 SCBM per week (ie NNT=8), indicating that for patients on RESOTRANS 2 mg, 2 out of 8 patients responded. For an average of 7 patients who received RESOTRANS 4 mg daily, one additional patient had ≥ 3 SCBM/week compared with the placebo control (ie NNT=7). For a clinically meaningful improvement of ≥ 1 SCBM/week, for placebo, 1 out of 4 patients had ≥ 1 SCBM/week. For an average of 5 patients receiving RESOTRANS 2 mg daily or 4 patients receiving RESOTRANS 4 mg daily, one additional patient had ≥ 1 SCBM/week, compared with the placebo control (ie NNTT=5 for the 2 mg daily, and NNTT=4 for the 4 mg daily).

In all three studies, RESOTRANS significantly improved the time to first bowel movement when compared with placebo. In addition, for all three studies, treatment with RESOTRANS resulted in significant improvements in a validated and disease specific set of symptom measures (PAC SYM), 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.

Other Clinical Studies

Study INT-12 was a double-blind, placebo-controlled study that evaluated the efficacy, safety and quality-of-life of RESOTRANS in 303 elderly patients (≥ 65 years) with chronic constipation. The doses studied were 1 mg, 2 mg and 4 mg. The primary efficacy endpoint was the proportion of patients with an average of ≥ 3 SCBM per week evaluated over the 4-week treatment period. The key secondary efficacy endpoint was the proportion of patients with an average increase of ≥ 1 SCBM per week. Results showed that there was a higher proportion of patients in all 3 RESOTRANS groups with ≥ 3 SCBM per week compared to placebo, although this observation was not statistically significant. The proportion of patients with an average increase of ≥ 1 SCBM per week was significantly higher for all 3 RESOTRANS treatment groups when compared to placebo. The results showed that no advantage was gained by increasing the dose beyond 1 mg.

Over 600 elderly subjects were investigated in double-blind placebo-controlled Phase II and III studies comparing the 0.5 mg, 1 mg, 2 mg and 4 mg 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.

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 2 mg, 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 ($V_{d_{ss}}$) of 567 L. 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.

Excretion

A large fraction of the active substance is excreted unchanged (about 60% of the administered dose in urine and at least 6% in faeces) via both passive filtration and active renal transporters (P-gp and BCRP). Renal excretion of unchanged prucalopride involves both passive filtration and active secretion. The plasma clearance of prucalopride averages 317 mL/min. Its terminal half-life

is about one day. Steady-state is reached within three to four days. On once daily treatment with 2 mg prucalopride, steady-state plasma concentrations fluctuate between trough and peak values of 2.5 and 7 ng/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 20 mg). Prucalopride o.d. displays time-independent kinetics during prolonged treatment.

Special populations

Population Pharmacokinetics

A population pharmacokinetic analysis showed that the apparent total clearance of prucalopride was correlated with creatinine clearance, and that there was no additional effect of age, body weight, sex or race.

Elderly

After once daily dosing of 1 mg, peak plasma concentrations and AUC of prucalopride in elderly subjects 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 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 ($Cl_{CR} \leq 24$ mL/min), plasma concentrations were 2.3 times the levels in healthy subjects (see **sections 4.2 Dose and method of administration** and **4.4 Special warnings and precautions for use**).

Hepatic Impairment

Non-renal elimination contributes 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

After a single oral dose of 0.03 mg/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 2 mg dose, while 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 the paediatric subjects was about 19 hours (range 11.6 to 26.8 hours) (see **section 4.2 Dose and method of administration**). RESOTRANS is not recommended in children or adolescents (see **section 4.4 Special warnings and precautions for use, Paediatric use**)

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The standard bacterial reverse mutation test had a weak positive result in one of the five strains at high concentrations (≥ 0.5 mg/plate). All subsequent in vivo tests on gene mutation, chromosomal damage, unscheduled DNA repair and DNA adduct induction showed negative results, which demonstrated that prucalopride did not have genotoxic potential.

Carcinogenicity

Carcinogenicity studies were conducted with oral prucalopride doses up to 80 mg/kg/day in mice, and 40 (female) and 80 (male) mg/kg/day in rats, for two years. In mice, the incidence of mammary gland adenocarcinomas was increased at 80 mg/kg/day (200 times clinical exposure at the MRHD,

based on AUC); the no-effect dose was 20 mg/kg/day (27 times clinical exposure at the MRHD, based on AUC). In rats, the high doses were associated with increased incidences of benign adrenal pheochromocytomas, pituitary adenomas, pancreatic adenomas, hepatocellular adenomas (mid & high doses) and thyroid follicular tumours (45 times clinical exposure at MRHD, based on AUC); the no adverse effect dose was 5 mg/kg/day (7 times clinical exposure at the MRHD, based on AUC). Mechanistic studies showed that hyperprolactinaemia resulted from D2 antagonism at high prucalopride concentrations likely caused the mammary, pituitary, pancreatic and adrenal tumours in both mice and rats. Prucalopride and its rat specific metabolism at high doses had hepatic enzyme induction potential that led to the liver and thyroid tumours in rats. Since no increase of plasma prolactin levels was observed in clinical studies and human prucalopride metabolism was very different from that of the rat, these tumour findings were considered to have minimum clinical relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

RESOTRANS tablets contain the following inactive ingredients:

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Magnesium stearate
Colloidal anhydrous silica

Coating

1 mg: Opadry II complete film coating system 33G28707 WHITE (ARTG PI No 107234)
2 mg: Opadry II complete film coating system 33G34847 PINK (ARTG PI No 107235)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

RESOTRANS tablets should be kept out of reach of children. Store below 30°C. Protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Both strengths of RESOTRANS film-coated tablets are available in PA/Al/PVC/Al blisters containing 7 tablets. Each pack contains 7 or 28 film-coated tablets.

Not all pack sizes are marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

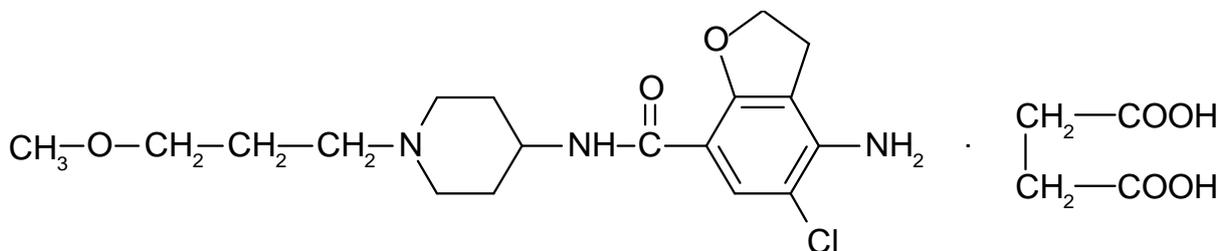
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Prucalopride succinate is a white to almost white powder.

The chemical name for prucalopride is 4-amino-5-chloro-2,3-dihydro-N-[1-(3-methoxypropyl)-4-piperidinyl]-7-benzofurancarboxamide butanedioate (1:1). Prucalopride has the following chemical structure:



Molecular weight: 485.96

CAS number

179474-85-2

Solubility

In organic media, prucalopride succinate is soluble in *N,N*-dimethylformamide, sulfinylbismethane and *N,N*-dimethylacetamide and sparingly soluble in methanol. In aqueous media, prucalopride succinate is freely soluble in acidic aqueous media. However, this solubility decreases with increasing pH.

Dissociation Constant

The pKa for the piperidine moiety of prucalopride succinate is 8.5, determined at 20°C by potentiometric titration of an aqueous solution of prucalopride succinate. The pKa for the amino moiety of prucalopride succinate is less than 3, determined at 20°C by spectrometric measurements of solutions of prucalopride succinate in water at different pH-values.

Partition Coefficient

The partition coefficients are determined at 20°C between *n*-octanol and aqueous buffered solutions. The partition coefficient P is defined as the ratio of the equilibrium concentrations of a single molecular species in a two-phase system of *n*-octanol and an aqueous buffered solution. The results for partition coefficient P are shown in **Table 4**.

Table 4: Partition coefficient P

Aqueous solution	buffered	Partition coefficient P	Log P	pH solution of
Phosphate-NaOH solution		1.78 X 10 ²	2.25	12.0

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine

8. SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd
Macquarie Park NSW 2113 Australia
Telephone: 1800 226 334

NZ Office: Auckland New Zealand
Telephone: 0800 800 806

9. DATE OF FIRST APPROVAL

7 October 2011

10 DATE OF REVISION

5 July 2021

Summary table of changes

Section changed	Summary of new information
1	editorial change to the active ingredient
2	Inclusion of excipient with known effect
6.1	Editorial changes to the excipient
6.5	Editorial changes to the pack size
6.7	Added Prucalopride succinate appearance from Section 2.

RESOTRANS[®] is a registered trademark of Ortho-McNeil-Janssen Pharmaceuticals, Inc. for prucalopride oral tablets.