NAME OF THE MEDICINE
Prucalopride

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:

\[ \text{CH}_3\text{O} - \text{CH}_2\text{CH}_2\text{CH}_2\text{N} - \text{NH} - \text{C} - \text{O} - \text{NH}_2 \cdot \text{CH}_2\text{COOH} \]
\[ \text{O} \]
\[ \text{Cl} \]
\[ \text{CH}_2\text{COOH} \]
\[ \text{C}_{18}\text{H}_{26}\text{ClN}_3\text{O}_3\text{C}_4\text{H}_6\text{O}_4 \]

Molecular weight: 485.96

CAS Registry No: 179474-85-2

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

RESOTRANS tablets contain the following inactive ingredients:
Tablet core: lactose monohydrate, microcrystalline cellulose, magnesium stearate and colloidal silicon dioxide.
Coating: hypromellose, titanium dioxide, lactose monohydrate, macrogol 3000 and glycerol triacetate. Additionally, in the coating, the 2 mg tablet contains iron oxide red, iron oxide yellow and indigo carmine C173015.

PHarmacology
Pharmacodynamics
Pharmacotherapeutic group: Drugs acting on serotonin receptors.
Prucalopride is a dihydrobenzofurancarboxamide with enterokinetic activities. Prucalopride is a selective, high affinity serotonin (5-HT₄) receptor agonist, which likely explains its enterokinetic effects. In vitro, affinity for other receptors was detected only at concentrations exceeding its 5-HT₄ 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-HT₄ 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-HT₄ receptor antagonists illustrating that the observed effects are exerted via selective action on 5-HT₄ receptors.

Pharmacokinetics

Absorption
Prucalopride is rapidly absorbed; after a single oral dose of 2mg, \(C_{\text{max}}\) 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 (\(V_{\text{dss}}\)) 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). Renal excretion of unchanged prucalopride involves both passive filtration and active secretion. 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 DOSAGE AND ADMINISTRATION and PRECAUTIONS).

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 PRECAUTIONS - Use in Children and Adolescents).

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 1 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 1: History of constipation for Phase III pivotal studies (PRU-INT-6, PRU-USA-11, PRU-USA-13) in patients with chronic constipation - ITT population

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

*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≤0.01; 4 mg p≤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≤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.

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

**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.

**WARNINGS AND PRECAUTIONS**
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) have not been studied. 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.

**Use in Patients with Renal Impairment**
Renal excretion is the main route of elimination of prucalopride (see Pharmacokinetics). A dose of 1 mg is recommended in patients with severe renal impairment (see DOSAGE AND ADMINISTRATION).

**Use in Patients with Hepatic Impairment**
A lower dose is recommended for patients with severe hepatic impairment (see DOSAGE AND ADMINISTRATION).

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

**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, it is not recommended to use RESOTRANS during breast-feeding.

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 DOSAGE AND ADMINISTRATION and Pharmacokinetics). If needed, the dose can be increased to 2 mg once daily.

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.

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. Although RESOTRANS may be a weak substrate for P-glycoprotein (P-gp), it is not an inhibitor of P-gp at clinically relevant concentrations.

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-HT₄ receptor mediated effects of RESOTRANS.

Interactions with food have not been observed.

**Effects on Laboratory Tests**
No effects are known.

**Effects on Ability to Drive or Operate Machinery**
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 **ADVERSE EFFECTS**).

**ADVERSE 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 2**.

**Table 2**: Chronic constipation: adverse events reported by ≥2% of prucalopride-treated subjects in Phase II and III double-blind placebo-controlled studies. Population: All patients
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Placebo n (%)</th>
<th>PRU 0.5mg n (%)</th>
<th>PRU 1mg n (%)</th>
<th>PRU 2mg n (%)</th>
<th>PRU 4mg n (%)</th>
<th>All PRU n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td></td>
<td>1369</td>
<td>110</td>
<td>308</td>
<td>938</td>
<td>1361</td>
<td>2717</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>106 (7.7)</td>
<td>7 (6.4)</td>
<td>31 (10.1)</td>
<td>157 (16.7)</td>
<td>267 (19.6)</td>
<td>462 (17.0)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td>45 (3.3)</td>
<td>5 (4.5)</td>
<td>23 (7.5)</td>
<td>111 (11.8)</td>
<td>191 (14.0)</td>
<td>330 (12.1)</td>
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<tr>
<td>Abdominal pain</td>
<td></td>
<td>128 (9.3)</td>
<td>7 (6.4)</td>
<td>22 (7.1)</td>
<td>110 (11.7)</td>
<td>142 (10.4)</td>
<td>281 (10.3)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td></td>
<td>37 (2.7)</td>
<td>4 (3.6)</td>
<td>12 (3.9)</td>
<td>40 (4.3)</td>
<td>71 (5.2)</td>
<td>127 (4.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>32 (2.3)</td>
<td>5 (4.5)</td>
<td>6 (1.9)</td>
<td>43 (4.6)</td>
<td>72 (5.3)</td>
<td>126 (4.6)</td>
</tr>
<tr>
<td>Flatulence</td>
<td></td>
<td>52 (3.8)</td>
<td>3 (2.7)</td>
<td>11 (3.6)</td>
<td>43 (4.6)</td>
<td>67 (4.9)</td>
<td>124 (4.6)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td></td>
<td>64 (4.7)</td>
<td>0 (0.0)</td>
<td>5 (1.6)</td>
<td>52 (5.5)</td>
<td>58 (4.3)</td>
<td>115 (4.2)</td>
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<tr>
<td>Dyspepsia</td>
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<td>4 (1.3)</td>
<td>23 (2.5)</td>
<td>42 (3.1)</td>
<td>71 (2.6)</td>
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<tr>
<td>Nervous system disorders</td>
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<td>212 (15.5)</td>
<td>16 (14.5)</td>
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<td>258 (27.5)</td>
<td>395 (29.0)</td>
<td>724 (26.6)</td>
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<tr>
<td>Headache</td>
<td></td>
<td>162 (11.8)</td>
<td>12 (10.9)</td>
<td>43 (14.0)</td>
<td>204 (21.7)</td>
<td>329 (24.2)</td>
<td>588 (21.6)</td>
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<tr>
<td>Dizziness</td>
<td></td>
<td>25 (1.8)</td>
<td>2 (1.8)</td>
<td>8 (2.6)</td>
<td>41 (4.4)</td>
<td>56 (4.1)</td>
<td>107 (3.9)</td>
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<tr>
<td>Infections and infestations</td>
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<td>257 (18.8)</td>
<td>15 (13.6)</td>
<td>30 (9.7)</td>
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<tr>
<td>Sinusitis</td>
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<td>40 (2.9)</td>
<td>2 (1.8)</td>
<td>4 (1.3)</td>
<td>28 (3.0)</td>
<td>42 (3.1)</td>
<td>76 (2.8)</td>
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<tr>
<td>Nasopharyngitis</td>
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<td>43 (3.1)</td>
<td>1 (0.9)</td>
<td>3 (1.0)</td>
<td>31 (3.3)</td>
<td>38 (2.8)</td>
<td>73 (2.7)</td>
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<tr>
<td>Influenza</td>
<td></td>
<td>40 (2.9)</td>
<td>1 (0.9)</td>
<td>4 (1.3)</td>
<td>33 (3.5)</td>
<td>33 (2.4)</td>
<td>71 (2.6)</td>
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<tr>
<td>Urinary tract infection</td>
<td></td>
<td>29 (2.1)</td>
<td>8 (7.3)</td>
<td>4 (1.3)</td>
<td>23 (2.5)</td>
<td>20 (1.5)</td>
<td>55 (2.0)</td>
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<tr>
<td>General disorders and administration site conditions</td>
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<td>89 (6.5)</td>
<td>6 (5.5)</td>
<td>24 (7.8)</td>
<td>90 (9.6)</td>
<td>153 (11.2)</td>
<td>273 (10.0)</td>
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<tr>
<td>Fatigue</td>
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<td>21 (1.5)</td>
<td>1 (0.9)</td>
<td>7 (2.3)</td>
<td>24 (2.6)</td>
<td>41 (3.0)</td>
<td>73 (2.7)</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
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<td>20 (6.5)</td>
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<td>31 (2.3)</td>
<td>73 (2.7)</td>
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<tr>
<td>Investigations</td>
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<td>6 (5.5)</td>
<td>10 (3.2)</td>
<td>83 (8.8)</td>
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<td>Respiratory, thoracic and mediastinal disorders</td>
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<td>4 (3.6)</td>
<td>11 (3.6)</td>
<td>52 (5.5)</td>
<td>72 (5.3)</td>
<td>139 (5.1)</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
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<td>54 (3.9)</td>
<td>3 (2.7)</td>
<td>17 (5.5)</td>
<td>41 (4.4)</td>
<td>63 (4.6)</td>
<td>124 (4.6)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
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<td>31 (2.3)</td>
<td>1 (0.9)</td>
<td>6 (1.9)</td>
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<td>Psychiatric disorders</td>
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<td>0 (0.0)</td>
<td>7 (2.3)</td>
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<td>46 (3.4)</td>
<td>95 (3.5)</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
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<td>2 (1.8)</td>
<td>5 (1.6)</td>
<td>32 (3.4)</td>
<td>48 (3.5)</td>
<td>87 (3.2)</td>
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<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td>40 (2.9)</td>
<td>5 (4.5)</td>
<td>10 (3.2)</td>
<td>32 (3.4)</td>
<td>38 (2.8)</td>
<td>85 (3.1)</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
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<td>38 (2.8)</td>
<td>3 (2.7)</td>
<td>11 (3.6)</td>
<td>37 (3.9)</td>
<td>29 (2.1)</td>
<td>80 (2.9)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>23 (1.7)</td>
<td>2 (1.8)</td>
<td>10 (3.2)</td>
<td>16 (1.7)</td>
<td>42 (3.1)</td>
<td>70 (2.6)</td>
</tr>
</tbody>
</table>

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
   Uncommon: anorexia

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

Cardiac disorders
   Uncommon: palpitations

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.

**DOSAGE AND 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 Pharmacokinetics); 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/1.73m²) 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*: The dose for patients with severe hepatic impairment (Child-Pugh class C) is 1 mg once daily (see PRECAUTIONS and Pharmacokinetics). 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.

**OVERDOSAGE**

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.

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.
PRESENTATION AND STORAGE CONDITIONS

Presentation
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:
- 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.

Storage Conditions
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.

MEDICINE CLASSIFICATION
Prescription Medicine

SPONSOR
Janssen-Cilag (New Zealand) Ltd
Auckland, NEW ZEALAND
Telephone: 0800 800 806
Date of Preparation: 02 April 2015

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