Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

# Australian Public Assessment Report for Prucalopride

## Proprietary Product Name: Resotrans

## Sponsor: Janssen-Cilag Pty Ltd

**November 2011**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

# About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

# Contents

# Introduction to Product Submission

## Submission Details

| | |
|---|---|
| *Type of Submission* | New Chemical Entity |
| *Decision:* | Approved |
| *Date of Decision:* | 4 October 2011 |
| *Active ingredient(s):* | Prucalopride (as succinate) |
| *Product Name(s):* | Resotrans |
| *Sponsor's Name and Address:* | Janssen-Cilag Pty Ltd<br>1-5 Khartoum Rd, Macquarie Park, NSW 2113. |
| *Dose form(s):* | Tablets |
| *Strength(s):* | 1 mg and 2 mg[1] |
| *Container(s):* | Blister packs (polyamide-aluminium (Al)-Polyvinyl chloride/Al) |
| *Pack size(s):* | 7 and 28 tablets |
| *Approved Therapeutic use:* | The treatment of chronic functional constipation in adults in whom laxatives fail to provide adequate relief<br>● 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.<br>● If treatment with Resotrans is not effective within four weeks, the benefit of continuing treatment should be reconsidered. |
| *Route(s) of administration:* | Oral |
| *Dosage:* | 1 mg or 2 mg once daily |
| *ARTG Number (s)* | AUST R 176747 (1mg) and AUST R 176746 (2mg) |

## Product Background

Prucalopride is a dihydrobenzofurancarboxamide derivative and a selective agonist for serotonin receptor type 4 receptors (5-$HT_4$). It has been developed as an enterokinetic agent for the treatment of chronic constipation and is a "first in class" agent. The sponsor proposes that 5-$HT_4$ receptor stimulation induces facilitation of cholinergic as well as non cholinergic excitatory neurotransmission leading to the enterokinetic effects of prucalopride.

While prucalopride is registered in the European Union (EU) the indication there is limited to women only. The EU indication is otherwise the same as those proposed for Australia. The UK's National Institute for Health and Clinical Excellence (NICE) recommendations for use of prucalopride are:

That prucalopride should only be considered in women:

[1] Potency is expressed in terms of prucalopride free base.

- who 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 relief from constipation and
- in whom invasive treatment is being considered.

Prucalopride should only be prescribed by a clinician with experience of treating chronic constipation and who has reviewed the woman's previous course of laxatives. If treatment with prucalopride is not effective after four weeks the benefit of continuing treatment should be reconsidered.

Constipation, which can be caused by dietary changes, stress or immobility, is defined as passing abnormally delayed or infrequent dry, hardened faeces (stools), often accompanied by straining and/or pain. People with chronic constipation have no more than two spontaneous complete bowel movements per week.

Constipation may also be the consequence of an underlying condition, including irritable bowel syndrome or an underactive thyroid. In addition, some medications can cause constipation as a side effect. These include opioids (such as common codeine pain killers) and diuretics. Chronic constipation affects on average two to three times as many women as men, with prevalence rates of around 10% in women under 65 years of age in the UK. Rates are often higher (around 20%) in women over 65 years of age.

Appropriate diet and lifestyle changes should be the first step in managing constipation. If this is unsuccessful, laxatives may relieve the symptoms and restore normal bowel function. Prucalopride can be prescribed for women with long term constipation, whose condition has not responded to standard laxatives.

Prucalopride was developed by Johnson and Johnson (J&J).

Two other 5-$HT_4$ agonists have previously been registered in Australia; tegaserod and cisapride. Both were removed from the Australian Register of Therapeutic Goods (ARTG) after concerns about cardiac safety.

### Regulatory Status

Prucalopride 1 mg and 2 mg tablets are approved for marketing in the EU (since 2009) and Switzerland (since 2010). Prucalopride is also approved for marketing in Macau (since April 2011) and Peru (since June 2011). An application is currently under evaluation in New Zealand (submitted October 2010).

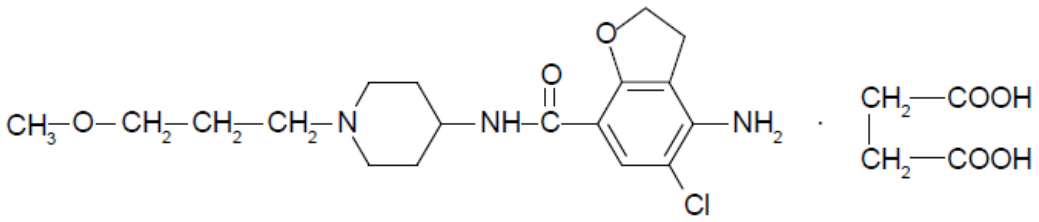
### Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

# II. Quality Findings

## Drug Substance (active ingredient)

The drug substance is a 1:1 salt of prucalopride and succinic acid with the following structure:



It has no chiral centres. It is a white powder with no known polymorphs. It has a pKa of 8.5 and an octanol/phosphate buffer (pH 12) partition coefficient (log P) of 2.2. It is freely soluble in water (16.0% w/v) but less soluble in basic solution. It is classified as BCS Class 1[2].

The limits proposed for two synthesis impurities are above the International Conference on Harmonisation (ICH) qualification threshold (see *Nonclinical findings* below).

### Drug Product

The drug product is a film coated tablet containing prucalopride succinate equivalent to 1 mg or 2 mg of prucalopride. The two strengths are not direct scales but contain the same excipients; while the content of active ingredient is doubled in the higher strength, the content of each excipient in the tablet core is increased by 11.1%. The tablets are manufactured by direct compression and packaged in Aluminium (Al)/Al blisters within cardboard cartons.

The finished product specifications were validated.

No degradants are limited above the ICH identification threshold.

The proposed shelf life of 2 years below 30°C has been satisfactorily justified.

### Biopharmaceutics

Four bioavailability studies were evaluated. They showed that:

- the absolute bioavailability of the tablets is about 92%;
- the two strengths of tablet are bioequivalent at equal dose;
- the tablets proposed for registration are bioequivalent to tablets used in clinical trials and to an oral solution of the drug;
- food has no significant effect on the rate or extent of absorption of the drug from the tablets.

### Quality Summary and Conclusions

All issues raised with the sponsor following the initial evaluation of this submission have been satisfactorily resolved. There are no objections in respect of quality to the registration of this product.

The application was considered at the 138th meeting of the Pharmaceutical Subcommittee of the Advisory Committee of Prescription medicines (ACPM). The PSC made a number of recommendations concerning the Product Information document which have been referred to the Clinical Delegate.

# III. Nonclinical Findings

### Introduction

The nonclinical studies were well presented and described. The majority of the safety pharmacology studies were not Good Laboratory Compliant (GLP) compliant; however, they were well reported and the large number of similar studies provided some assurance regarding the accuracy of the findings. Some of the early toxicity studies were conducted with the hydrochloride salt rather than the commercially used succinate salt but adequate bridging studies were conducted.

[2] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

## Pharmacology

### Mechanism of action

*In vitro* studies of prucalopride showed its high affinity for human and animal 5-$HT_4$ receptors at concentrations that are comparable to the clinical exposure. These responses were blocked by 5-$HT_4$ receptor antagonists. Prucalopride had a low affinity for other 5-HT receptor subtypes. In animal studies, prucalopride had a significant effect on propulsive motor patterns in the colon and stomach.

#### *In vitro* studies

*In vitro* studies have confirmed the high binding affinity of prucalopride in cell lines, with 50% effective concentration ($EC_{50}$) values comparable to, or lower than, the clinical exposure levels (7–20 nM). In various *in vitro* 5-$HT_4$ receptor models (such as examination of twitch contractions in guinea pig ileum; contractions in guinea pig and dog colon; relaxation in rat oesophagus, forestomach and colon; contractions in porcine stomach; relaxation of pre-contracted human colonic circular smooth muscle; and contractions in circular muscle strips from human antrum), prucalopride was effective at concentrations comparable to the clinical exposure. The metabolites of prucalopride also showed specificity to the 5-$HT_4$ receptor that was similar to prucalopride but except for the 3-hydroxy metabolite (R106569), the potency was generally lower.

#### *In vivo* studies

Prucalopride was tested in conscious dogs for its effect on colonic motility. It increased the intensity of clustered contractions in the distal colon after oral administration and the 50% effective dose ($ED_{50}$) was 0.04 mg/kg, which is equivalent to the clinical mg/kg dose. It also stimulated gastric, pyloric and duodenal motility in dogs at 0.08–0.31 mg/kg (estimated 2 to 8 fold the clinical mg/kg dose or 1 to 5 fold the clinical mg/$m^2$ dose). In rats, the results were more variable; prucalopride stimulated gastric emptying but had variable effects on gastrointestinal (GI) transit at higher doses than those needed in dogs. This is likely to be related to differences in bioavailability or metabolism since the differences were not observed in the *in vitro* studies. Prucalopride did not induce diarrhoea in dogs but it did increase the defecation frequency at 0.02–0.08 mg/kg PO (0.5 to 2 fold the clinical mg/kg dose or ≤ the clinical mg/$m^2$ dose) and enhanced the onset of $MgSO_4$-induced diarrhoea at an $ED_{50}$ 2.3 mg/kg PO (estimated as 60 fold the clinical mg/kg dose or 35 times the clinical mg/$m^2$ dose). In cats, prucalopride had contradictory results on the rate of defecation.

### Secondary pharmacodynamics

Secondary pharmacodynamic effects of prucalopride were examined in relation to cardiac 5-$HT_4$ receptors as well as in relation to non-5-$HT_4$ receptors. Prucalopride acted as a partial 5-$HT_4$ receptor agonist in the porcine and human right atrium with an $EC_{50}$ of 40 to100 nM (16–40 ng/mL, which is 2 to 5 fold the clinical exposure based on maximal serum concentration ($C_{max}$). Unlike 5-HT, prucalopride did not induce arrhythmia after administration up to 10 µM (4040 ng/mL, which is *ca* 550 times the clinical exposure). In other *in vitro* and *in vivo* studies, prucalopride did not show affinity for a wide range of receptors, ion channels or monoamine transporters; did not inhibit a range of enzymes; did not affect rat gastric or intestinal secretion; and did not have any effects in a variety of experiments using vascular, trachea and heart tissues. Prucalopride did not have any haemolytic effects on human blood at 2 mg/kg over a 30 minute period. In *in vivo* studies in rodents and dogs up to 40 mg/kg and 10 mg/kg, respectively, there was no evidence of behavioural effects or other effects (except for GI effects) which would suggest specific receptor interaction. Only at very high dose levels ($K_i$ 14 µM or 5656 ng/mL, which is *ca* 750 times the clinical exposure) was binding to dopamine receptors or antagonism at these receptors demonstrated.

### Safety pharmacology

The focus of the safety pharmacology studies was on cardiovascular effects with some examination of pulmonary function as part of the studies in dogs and pigs. These studies (except for one) were

not GLP compliant. The potential for central nervous system (CNS) and GI effects were examined in the pharmacology and repeat dose studies.

Inhibition of hERG channel activity *in vitro* was observed only at concentrations at least 280 times the clinical exposure. Other *in vitro* effects (in dog and rabbit Purkinje fibres) were only seen at 50 times the clinical exposure. There was no evidence of proarrhythmia in isolated rabbit heart or guinea pig papillary muscle. *In vivo* studies were conducted in guinea pig, rabbit, dog and pig. Cardiovascular parameters in all species showed little change; slight but reversible changes in heart rate (HR) and blood pressure (BP) were noted in guinea pigs. HR and BP changes were also noted in dogs at exposure levels 50 times those expected in patients based on $C_{max}$. In pigs, transient HR and BP increases were seen at exposures 10 times those expected in the clinic.

Pulmonary parameters were not affected by treatment in dogs and pigs at 1000 times the clinical exposure based on $C_{max}$.

### Pharmacodynamic drug interactions

The propulsion enhancing effects are linked to the effect of prucalopride at receptors located on cholinergic neurons resulting in the release of acetylcholine. Therefore, concomitant use of acetylcholinesterase inhibitors or anticholinergic compounds will potentiate or reduce the response of prucalopride, respectively. Prucalopride interaction with its receptor leads to an intracellular increase in cyclic adenosine monophosphate (cAMP) and therefore compounds that interfere with the breakdown of cAMP might also affect the response of prucalopride.

## Pharmacokinetics

Nonclinical pharmacokinetic studies were conducted in the mouse, rat, rabbit and dog to support the pharmacology and toxicity studies.

Absorption following a single dose administration was rapid in all species with time to maximal serum concentration ($T_{max}$) reached in 1–2 h and $C_{max}$ and area under the plasma concentration time curve (AUC) increasing in a dose proportional (dogs) or higher than dose proportional (rats) manner. In rats and rabbits there was evidence of first pass metabolism with low bioavailability while in dogs there was limited first pass metabolism and high bioavailability. The volume of distribution was high for all species. There was high clearance in rats (3–11 L/h/kg) and rabbits (4.4 L/h/kg) and low clearance in dogs (0.34 L/h/kg). The excretion half life ($t_{1/2}$) was rapid in rats (circa 1 h) but slower in dogs (4–7 h). The data suggests prucalopride is metabolised at different rates in rats and dogs.

Following repeat exposure, $C_{max}$ and AUC increased more than dose proportionally in mice and rats and dose proportionally in dogs. However, the $C_{max}$ and AUC values were comparable following the first and last doses in rats (6 months) and dogs (12 months) with no evidence of accumulation. In rats, exposure was higher in females than in males in studies up to 6 months. In dogs, there were no gender differences in a one month study but this was not examined in longer studies. There was no difference in the kinetics of the hydrochloride and succinate salts of prucalopride. In the 24 month carcinogenicity studies in mice and rats, there was rapid absorption and a more than dose proportional increase in $C_{max}$ and AUC but no evidence of accumulation.

Plasma protein binding was independent of drug concentration and there was no evidence of species differences. Percentage binding was 28–30% in rats, dogs and humans. Distribution was slightly higher in red blood cells than in plasma, with no species differences. Tissue distribution was to a wide range of tissues, with the highest levels in colon, glandular tissues, liver and kidney. The highest residual levels were detected in the colon.

The metabolism of prucalopride was examined in mice, rats, rabbits, dogs and humans. *In vitro*, there was extensive metabolism in the presence of mice or rat microsomes or hepatocytes but little in the presence of dog or human microsomes or hepatocytes. *In vivo*, hydroxylation was the major metabolic pathway in mice and rats, with unchanged prucalopride just <0.5% of the plasma radioactivity in rats. In rabbits, N-glucuronidation was the major metabolic pathway. In dogs and humans, the metabolism was not extensive with unchanged prucalopride being 60% of the plasma radioactivity in dogs and 84% in humans. The major metabolic pathway was O-methylation.

Urinary metabolites were compared between species rather than plasma due to inadequate detection sensitivity. Fewer metabolites are found in human urine but all of these occur in rat and dog urine.

Excretion in mice and rabbits was mainly via the urine while excretion in rats was mainly via the faeces indicative of biliary excretion. In dogs and humans, excretion was mainly via the urine (~70%), predominantly as unchanged prucalopride with some evidence of enterohepatic recirculation in dogs.

### Pharmacokinetic drug interactions

There was no evidence of induction or inhibition of cytochrome P450 enzymes by prucalopride at dose levels up to 20 mg/kg/day (>100 times the clinical exposure based on $C_{max}$) (see *Mechanistic Studies* section below).

There was some evidence from *in vitro* cultures that prucalopride may have a slight inhibitory effect on efflux proteins such as P-glycoprotein and thus reducing efflux protein mediated renal excretion. Binding was shown at 100 µM (>1000 times the clinical exposure based on $C_{max}$). While unlikely based on relative exposure, the clinical finding of an increase in plasma AUC for prucalopride co administered with ketoconazole may be relevant to this result.

### Relative exposure

The systemic bioavailability of prucalopride has been studied in a number of clinical trials. Exposure ratios shown in Tables 2 and 3 have been calculated based on the animal/human AUC values and $C_{max}$ values using data from a human single dose and 7-day oral exposure study (Report PRU-BEL-15).

**Table 2. Repeat dose toxicity and carcinogenicity studies**

| Species | Study duration (weeks) | Dose (mg/kg/day) | $C_{max}$ (ng/mL) (m/f) | $C_{max}$ Exposure ratio[a] | $AUC_{0\text{-}24\ h}$ (ng.h/mL) (m/f) | AUC Exposure ratio[a] |
|---|---|---|---|---|---|---|
| **Repeat dose toxicity studies** | | | | | | |
| Rat | 6 months | 1.25 | 12/13 | 1.6/1.7 | -/- | -/- |
| | | **5** | 229/655 | 30/88 | 785/4150 | 7/38 |
| | | 20 | 1980/4220 | 265/566 | 7910/26500 | 72/243 |
| Rat | 6 month (1 month recovery) | 5 | 230/500 | 30/67 | 540/1290 | 5/12 |
| | | **20** | 1760/2260 | 236/303 | 8130/15500 | 75/142 |
| | | 80 | 7870/10100 | 1056/1355 | 85600/124000 | 785/1137 |
| Dog | 6 months | 0.63 | 140 | 18 | 1360 | 12 |
| | | 2.5 | 695 | 93 | 6820 | 62 |
| | | **10** | 2930 | 393 | 27400 | 251 |
| Dog | 12 months | 2.5 | 545 | 73 | 5510 | 50 |
| | | **10** | 2575 | 345 | 26600 | 244 |
| | | 30 | 6536 | 877 | 62400 | 572 |
| **Carcinogenicity studies** | | | | | | |
| Mouse | 24 months | 10 | 612 | 82 | 973 | 9 |
| | | **20** | 1349 | 181 | 2913 | 27 |
| | | 80 | 6275 | 842 | 22517 | 206 |
| Neonatal mouse | 12 months | 75 | 4890 | 656 | 24600 | 225 |
| | | 150 | 10225 | 1372 | 79600 | 730 |
| | | **300** | 14000 | 1879 | 179000 | 1642 |
| Rat | 24 months | **5**(m/f) | 256 | 34 | 753 | 7 |
| | | 10(f)/ 20(m) | 1119 | 150 | 4948 | 45 |
| | | 40(f)/ 80(m) | 4887 | 656 | 44614 | 409 |

[a] Exposure ratio based on human PK study (2 mg/50 kg/day for 7 days): $C_{max}$ 7.45 ng/mL; $AUC_{0\text{-}24h}$ 7 days 109 ng.h/mL (Study no. PRU-BEL-15). NOAEL doses are bolded.

**Table 3. Embryofetal development**

| Species | Study | Dose (mg/kg/day) PO (gavage) | $C_{max}$ (ng/mL)[b] | $C_{max}$ Exposure ratio[a] | AUC $_{0-24}$ (ng·h/mL) | AUC Exposure ratio[a] |
|---|---|---|---|---|---|---|
| **Rat** | Embryofetal toxicity (R093877, PO) | 1.25<br>5<br>**20** | 35<br>427<br>2430 | 4.7<br>57<br>326 | nd<br>nd<br>nd | -<br>-<br>- |
| **Rat** | Embryofetal toxicity (R108512; PO) | 5<br>20<br>**80** | 259<br>2184<br>6986 | 34<br>293<br>937 | nd<br>11081<br>nd | <br>101<br>- |
| **Rat** | Embryofetal toxicity (R093877; SC) | 1.25<br>5<br>**20** | 138<br>587<br>2729 | 18<br>78<br>366 | nd<br>nd<br>nd | -<br>-<br>- |
| **Rabbit** | Embryofetal toxicity (R093877;PO) | 5<br>**20**<br>80 | 90<br>327<br>1211 | 12<br>44<br>162 | 238<br>1110<br>4198 | 1<br>10<br>38 |
| **Rabbit** | Embryofetal toxicity (R093877; SC) | 1.25<br>5<br>**20** | 240<br>911<br>4960 | 32<br>122<br>665 | 415<br>1540<br>8200 | 4<br>14<br>75 |

[a] Exposure ratio based on human PK study (2 mg/50 kg/day for 7 days): $C_{max}$ 7.45 ng/mL; $AUC_{0-24h}$ 7 days: 109 ng.h/mL (Study no. PRU-BEL-15). NOAEL doses are bolded. nd = Not determined

## Toxicology

### Acute toxicity

Prucalopride has moderate acute toxicity in mice and rats by the IV route. By the oral route, the acute toxicity was 2–4 fold lower in mice and >16 fold lower in rats. Signs of toxicity were indicative of CNS toxicity. By the subcutaneous (SC) route there was no evidence of acute toxicity in rats at 50 mg/kg. In dogs, there was evidence of toxicity at 50 mg/kg SC but no lethality while at 1.25 mg/kg CS there were no clinical signs of toxicity (33 fold the clinical exposure based on $C_{max}$).

### Repeat dose systemic toxicity

Repeat dose toxicity with prucalopride was examined in mice (up to 3 months), rats (up to 6 months) and dogs (up to 12 months). Studies were conducted with both the hydrochloride salt (R093877) and the succinate salt (R108512).

In mice after oral administration, there were mild liver changes at 80 and 160 mg/kg. There was also hypertrophy in the pituitary, increased development in the mammary gland and reduced cyclic activity in the genital tract which is likely to be related to increased prolactin levels.

In rats after oral administration, there were changes in bodyweight, haematology parameters, clinical chemistry parameters and organ weights noted at the higher dose levels which were mostly resolved after the recovery period. The persistent changes were those likely to be related to prolactin induction; an increase in granulocyte infiltration of the prostate, an increase in interstitial tissue in the ovaries and glandular development in the mammary glands. The NOAEL (no adverse effect level) in the 6 months (plus recovery) study was 20 mg/kg/day (76 and142 times the clinical exposure based on AUC, in males and females, respectively). There were no differences observed between the hydrochloride and succinate salts of prucalopride. After IV administration for one

month, no toxicity was observed up to 10 mg/kg/day (138 and 382 times the clinical exposure based on AUC in males and females, respectively). Similar toxicity was observed after SC administration for one month, with a NOAEL of 5 mg/kg/day (20 times the clinical exposure based on AUC).

In dogs after oral administration, there was no evidence of toxicity after one month at 20 mg/kg/day but clinical signs of CNS related toxicity were evident at 30 mg/kg/day and 40 mg/kg/day. After 6 months, 3 males given 30 mg/kg/day died. The deaths were preceded by CNS-related toxicity. Other toxicity included ocular changes, organ weight changes and some evidence of reduced cyclic activity related to prolactin levels. There were no changes in blood pressure or clear evidence of electrocardiogram (ECG) changes. The NOAEL was 10 mg/kg/day (251 times the clinical exposure based on AUC). After IV administration, no toxicity was observed at doses up to 5 mg/kg/day for one month (99 times the clinical exposure based on AUC). No toxicity was observed after SC administration at doses up to 10 mg/kg/day for one month (229 times the clinical exposure based on AUC).

In a two week study in rats with 40 mg/kg/day prucalopride with or without the degradants R149706 (2%), R103451 (1%) and R102390 (1%), there was no evidence of additional toxicity related to the presence of these degradants.

### Genotoxicity and carcinogenicity

Prucalopride at doses of 500 µg/plate and above produced a weak positive result in a reverse mutation assay in *Salmonella typhimurium* strain TA100, indicating a potential to cause point mutations. No positive result was seen in TA1537, the parent strain of TA100. There was no evidence of a positive result in other strains or in the *Escherichia coli* (*E. coli)* forward mutation assays. The possibility of oxidative damage being responsible for this result could not be conclusively determined by including an antioxidant in the assay. The positive result in TA100 does not seem to be the result of induction of the error prone SOS repair system[3] in bacteria which could result from the formation of unrepairable deoxyribonucleic acid (DNA) adducts.

In *in vitro* tests in mammalian cells there was no evidence of prucalopride induced mutations at the TK locus in mouse lymphoma cells. Nor was there any evidence of formation of chromosome aberrations in human lymphocytes. *In vivo* assays for chromosome damage (micronucleus assay) or DNA repair (rat hepatocytes) were also negative. The potential for point mutations was also tested in the lac1 gene in transgenic Big Blue mice. There was no evidence of point mutations in this system. DNA adduct formation was examined in mice and rat tissues using radioactive phosphorous ($^{32}P$) labelling of adducts and this sensitive assay gave negative results. The overall conclusion is that prucalopride does not have genotoxic potential *in vivo*.

Reverse mutation assays in bacteria were conducted using prucalopride with increased levels (spiked) of degradation products (R149706, R103451, R102390) or on the degradation products themselves. A positive result was obtained with spiked prucalopride in TA100 *S. typhimurium* but not with degradation products alone. The production intermediates T001830 and T001874 were negative in bacterial forward mutation assays but positive for chromosomal aberrations in Chinese Hamster Ovary (CHO) cells (at 750 µg/mL and 150 µg/mL, respectively) without S9[4] but negative in human lymphocytes. Both were also negative in the mouse micronucleus assay. The overall conclusion is that the degradation products and production intermediates do not have genotoxic potential *in vivo*.

Carcinogenicity studies were conducted in mice and rats via gavage administration. In mice, a 12 month neonatal study was conducted at dose levels up to 300 mg/kg (split dose on days 8 and 15 of

[3] The SOS response is a global response to DNA damage in which the cell cycle is arrested and DNA repair and mutagenesis are induced. The SOS uses the RecA protein (Rad51 in eukaryotes). It is an error-prone repair system.

[4] Liver S9 fractions are subcellular fractions that contain drug metabolizing enzymes including the cytochromes P450, flavin monooxygenase and UDP glucuronyl transferases. Liver S9 fractions are a major tool for studying xenobiotic metabolism.

age *only*) and a 2 year study was conducted at doses up to 80 mg/kg/day. In the neonatal mouse study, there was no evidence of carcinogenicity at any dose level. The NOAEL was 300 mg/kg (>1600 times the clinical exposure based on AUC). In the 2 year study, there was no significant increase in treatment related individual tumours but there was a positive trend in mammary gland epithelial tumours in females, particularly adenocarcinomas, at 80 mg/kg/day. This is considered to be related to the pituitary gland hyperplasia and subsequent increased levels of prolactin and increased mammary gland development observed at this dose level. The increase in prolactin levels in mice was demonstrated in a separate 7 day mechanistic study at dose levels of 80–320 mg/kg/day (see *Mechanistic Studies* section below). The NOAEL for these tumours was 20 mg/kg/day (27 times the clinical exposure based on AUC).

In rats, the 2 year study conducted at doses up to 40 (females) or 80 (males) mg/kg/day was characterised by a wide tumour distribution including hepatocellular adenomas, mammary gland adenomas and fibroadenomas and thyroid follicular tumours in both sexes. Additionally, adrenal medullary benign phaeochromocytomas, pancreatic islet cell adenomas and pituitary adenomas were noted in males. Except for hepatocellular adenomas in males, these tumours were only reported at the highest tested doses in both sexes (hepatocellular adenomas were also noted at the mid-dose in males).

The increased tumour incidence in the mammary gland (adenomas) in both sexes and the pituitary and pancreatic (adenomas) and adrenal gland tumours in males are likely to be related to prucalopride triggered increases in prolactin levels. It was demonstrated in separate single dose and 6 month studies in rats that prucalopride increases prolactin levels when given at doses up to 160 mg/kg/day (see below). A threshold for tumour formation is expected in all cases and is supported by the lack of genotoxicity for prucalopride. The NOAEL was 20 mg/kg/day in males and 10 mg/kg/day in females (45 times the clinical exposure at the Maximum Recommended Human Dose (MRHD), based on AUC).

The increased tumour incidences in liver and thyroid are likely related to enzyme induction in the liver and subsequent thyroid hormone changes. This is supported by separate studies (1 week, 1 month and 6 month studies; see below) showing prucalopride induced increase in centrilobular hypertrophy and increased thyroid hormone triiodothyronine (T3) levels which underlies thyroid proliferation. Both effects were reversible upon cessation of treatment. The NOAEL was 5 mg/kg/day[5] (7 times the clinical exposure at the MRHD, based on AUC).

### Reproductive toxicity

Fertility was examined in Wistar rats. Embryofetal development was examined in Wistar rats and in Cunistar and Albino rabbits while pre and post natal development was examined in Wistar rats. Juvenile toxicity was examined in Wistar rats and in Beagle dogs. Autoradiography studies indicated a low level of placental transfer of prucalopride to fetal tissues, with levels in whole fetuses similar to those in maternal blood. There were no studies that examined the excretion of prucalopride into milk. There was no effect of prucalopride on fertility; pre-implantation loss was increased at 80 mg/kg, consistent with general toxicity at this dose level. The NOAEL was 20 mg/kg. Toxicokinetic exposure data were not obtained in the fertility studies. However, this dose administered to the same rat strain in the same laboratory in an embryofetal development study demonstrated a plasma exposure 100 times the clinical exposure based on AUC. A comparison of dose based on body surface area (BSA) gives a similar margin (*ca* 90)[6]. There was no evidence of teratogenicity in rats following SC or oral administration up to 20 mg/kg/day (100 times the clinical exposure based on AUC) with either the hydrochloride or succinate salt. There was also no evidence of teratogenicity in rabbits following SC or oral administration up to 20 mg/kg/day (10 times the clinical exposure based on AUC). A higher dose (80 mg/kg/day PO) was also tested in both species, eliciting some maternotoxicity in rabbits but no teratogenicity. Pre and post natal

[5] The no-effect dose for hepatocellular tumours was not exactly clear; males showed a non significant increase at 5 mg/kg/day which may nevertheless have been treatment related, while females showed small increases at ≥10 mg/kg/day.

[6] Rat dose: 20 mg/kg/day x 6 = 120 mg/m$^2$/day; human dose 2 mg/50 kg/day = 0.04 mg/kg/day x 33 = 1.32 mg/m$^2$/day.

development was examined in rats following oral administration of the succinate salt. There was no evidence of developmental toxicity but maternal toxicity was evident at 80 mg/kg/day with reduced nursing behaviour and slightly reduced pup survival at 20 mg/kg/day and 80 mg/kg/day (*ca* 100 times the clinical exposure based on AUC, at 20 mg/kg/day).

In juvenile animal toxicity studies in neonatal rats and dogs, a NOAEL of 5 mg/kg was established in both species after one month of treatment. These studies were not used in this evaluation of prucalopride, as this product is not intended for use in children at this stage.

### Pregnancy classification

The available studies in rats and rabbits provide adequate evidence that prucalopride is not teratogenic. The data also indicate that there is an adequate margin between the exposure at which fetal toxicity is first observed and the clinical exposure.

The sponsor's Product Information document suggests a B2 pregnancy classification, based on 'cases of spontaneous abortion have been observed during clinical studies'. This is not considered appropriate, however, as a B2 classification is associated with absent/inadequate animal studies and the sponsor has provided ample reproductive toxicity data from animal studies. In addition, the proposed statement indicates that the relationship between abortion and Resotrans treatment remains unknown. On the basis of the nonclinical data, a category B1 classification is recommended.

### Use in children

The sponsor does not recommend use of prucalopride in children and adolescents younger than 18 years until further data become available.

### Mechanistic Studies

A number of studies were undertaken to investigate mechanisms which might account for the increased incidence of tumours observed in the carcinogenicity studies in rats and mice. In mice, hyperprolactinaemia was clearly demonstrated in a 7 day mechanistic study at dose levels of 80–320 mg/kg/day (lower doses were not tested). With regard to the endocrine tissue tumours in rats, prucalopride was shown to significantly increase prolactin levels following single dose of prucalopride of 5 mg/kg and above. However, prolactin levels were increased only at high dose levels (160 mg/kg/day) when given over a 6 month period. The link between the rodent carcinogenicity findings and hyperprolactinaemia could have been investigated more thoroughly if prolactin measurements had been carried out regularly during the actual carcinogenicity studies. The reported interactions of prucalopride with dopamine $D_2$ receptors (see *Secondary Pharmacodynamics*) gave additional support for a prolactin mediated mechanism.

Prucalopride was also shown to increase T3 levels and increase liver and thyroid weights in 1 week, 1 month and 6 month studies at dose levels up to 160 mg/kg/day. The observed changes were reversible upon cessation of treatment.

The potential for prucalopride and three metabolites formed from O-demethylation (R129531, R107504 and R112718) to induce hepatocyte enzymes was examined *in vitro*. All were weak inducers of CYP2B and possibly CYP3A. Prucalopride was also shown not to inhibit thyroxine glucuronosyl transferase and thyroid peroxidase which modulate thyroid hormone levels.

### Local tolerance, impurities, other studies

Primary irritation in rabbits was examined following treatment with formulations containing 1.55 mg/mL of prucalopride hydrochloride via the intramuscular (IM), intravenous (IV), intraperitoneal (IP), subcutaneous (SC) or perivenous (PV) routes. No irritation was noted after IM, IV or IP routes. Hematomas were occasionally found following administration via other routes. Treatment with formulations containing 8 mg/mL of prucalopride succinate produced no irritation after administration via the IM, IV, SC, IP or PV routes but slight irritation was observed after the intra arterial (IA) route.

Three impurities have been identified in production batches of prucalopride. In an early batch of prucalopride hydrochloride, the levels of two of these were above 0.25%. Levels of these impurities

in prucalopride succinate, the commercially used salt of prucalopride, are all below 0.25%. The sponsor has requested higher specifications for two of the impurities in the product proposed for marketing. Following toxicological evaluation of animal exposure to these impurities in the submitted studies, both impurities were considered to be qualified at the level proposed by the sponsor.

Prucalopride treatment at dose levels up to 10 mg/kg did not increase ultraviolet (UV) induced phototoxicity in rats.

### Benefit–risk assessment

**Assessment of benefits:**

- Based on the pharmacology data, prucalopride is a high affinity 5-$HT_4$ receptor agonist, both *in vitro* and *in vivo*.
- Prucalopride has a low affinity for other 5-HT receptors.
- The *in vivo* data in dogs indicate that prucalopride has a positive effect on colonic motility, without inducing diarrhoea, at exposure levels comparable to the clinical exposure level.
- There was little evidence of secondary pharmacodynamic effects on cardiac 5-$HT_4$ receptors at the clinical exposure level, or any evidence of prucalopride induced arrhythmia.
- There was no evidence of treatment related effects on cardiovascular parameters or pulmonary parameters at exposure levels comparable to the clinical exposure level.
- Based on the nonclinical data, there is reasonable evidence that prucalopride will provide the benefits claimed.

***Assessment of risks:***

- There is a potential for mild effects related to the pharmacological effects of prucalopride. These include increased heart rate and blood pressure.
- There is a potential for acetylcholinesterase inhibitors or anticholinergic compounds to potentiate or reduce, respectively, the response of prucalopride. Compounds that interfere with the breakdown of cAMP may also affect the response of prucalopride.
- There is a low potential for prucalopride to inhibit efflux proteins such as P-glycoprotein and reduced renal excretion.
- There is a low potential for effects related to prolactin induction after prolonged high level exposure.
- There is potential for clinical signs of CNS related toxicity following high dose exposure.
- There is potential for tumour formation following high level, prolonged exposure.

## Nonclinical Summary and Conclusions

- Prucalopride (Resotrans) is a selective 5-$HT_4$ receptor agonist, representative of a new class of dihydrobenzofurancarboxamide compounds with potent enterokinetic activity.

- The sponsor, Jansen-Cilag Pty Ltd, has provided a significant number of nonclinical studies of the pharmacodynamics, pharmacokinetics and toxicity of prucalopride. The studies are of reasonable quality although most of the safety pharmacology studies were not GLP-compliant. However, the large number of similar studies provides some assurance regarding the accuracy of the findings.

- Primary pharmacodynamics studies were conducted both *in vitro* and *in vivo*. The *in vitro* studies confirmed the high binding affinity of prucalopride for the 5-$HT_4$ receptor in a variety of *in vitro* systems. *In vivo* studies in dogs confirm that prucalopride stimulates gastric, pyloric and duodenal motility, without inducing diarrhoea, at dose levels comparable to the clinical

exposure. The results were more variable in rats and occurred at higher dose levels. This difference is likely to be related to differing bioavailability and metabolism in the two species.

- Secondary and safety pharmacology studies concentrated on the potential effects of prucalopride on cardiac 5-$HT_4$ receptors. Prucalopride was a receptor agonist in the right atrium *in vitro* with an $EC_{50}$ 2–5 fold the clinical exposure. In the safety pharmacology studies, there was no inhibition of the hERG channel activity *in vitro* nor was there any evidence of arrhythmia in isolated heart muscle. In a number of *in vivo* studies there was little change in cardiovascular parameters other than reversible increases in HR and BP at exposures 10 fold (or greater) the clinical exposure. There were no treatment related effects on pulmonary parameters. There was no binding to dopamine receptors at clinically relevant dose levels. There is a potential pharmacodynamic drug interaction with acetylcholinesterase inhibitors or anticholinergic compounds.

- Pharmacokinetics was examined in mouse, rat, rabbit and dog. Absorption was rapid in all species with $C_{max}$ reached in 1–2 h. In rodents and rabbits, there was first pass metabolism and low bioavailability whereas in dogs there was limited first pass metabolism and high bioavailability. The volume of distribution was high is all species while clearance was high in rats and low in dogs. There was no evidence of accumulation after repeated exposure. Metabolism was extensive in rats (via hydroxylation), while in dogs and humans unchanged prucalopride made up 60% and 84% of the plasma radioactivity, respectively, with O-methylation the major metabolic pathway. Excretion in rats was mainly via faeces while urine was the major excretion route in dogs and humans. There was weak evidence for a slight inhibitory effect of prucalopride on efflux proteins.

- The general toxicity of prucalopride (both hydrochloride and succinate salts) was examined after single and repeated exposure in mice, rats and dogs. Acute oral toxicity was low, with symptoms in dogs indicative of CNS toxicity at dose levels 33 times the clinical exposure. After repeated exposure in rats, there were reversible changes in the liver, in organ weights and in haematological and clinical chemistry parameters. Persistent changes were related to increased prolactin levels as a result of hypertrophy in the pituitary (namely, granulocyte infiltration in the prostate, increased interstitial tissue in the ovaries and glandular activity in the mammary gland) at approximately 100 times the clinical exposure. In dogs there were ocular changes and prolactin related reduced oestrus cyclic activity. The NOAEL was 250 times the clinical exposure. In a two week study in rats with prucalopride and high levels of three degradants there was no evidence of additional toxicity related to the degradants.

- Genotoxicity assays produced a weak positive result for prucalopride in a reverse mutation assay in *S. typhimurium* strain TA100 but not in other bacterial strains. Reverse mutation assays in mammalian cells were negative. *In vitro* tests for chromosome aberrations were negative as were *in vivo* tests for chromosome damage, DNA repair or DNA adduct formation. The degradation products were negative in *in vitro* bacterial assays. The production intermediates were positive for chromosome aberrations in CHO cells but negative in human cells. The overall conclusion was that prucalopride, its degradation products and its production intermediates, do not have genotoxic potential.

- Carcinogenicity was examined in mice and rats. Mice were studied over 12 months in a neonatal study and over 24 month in an adult study. In the neonatal study, there was no increase in treatment related tumours up to 300 mg/kg (single split dose in first 2 weeks of age). In the 24 month study, at 80 mg/kg/day, there was no increase in treatment related individual tumours. There was however a positive trend in mammary gland adenocarcinomas considered to be related to the increased levels of prolactin following pituitary hyperplasia. The NOAEL was 27 times the clinical exposure. In rats, at 40 mg/kg/day (f) or 80 mg/kg/day (m), there was an increased tumour incidence in the liver and thyroid (related to reversible liver hypertrophy and increased T3 levels) as well as in the mammary gland, pituitary gland, pancreas and adrenal (related to increased prolactin levels). A threshold for tumour formation

is expected in all cases. The NOAEL was 7 fold (liver tumours) and 45 fold (endocrine tumours) the clinical exposure, respectively.

- Reproductive toxicity studies examined fertility, embryofetal development and pre- and postnatal development in rats and rabbits. Juvenile toxicity was also examined in rats and dogs although prucalopride will not be used in children at this stage. Placental transfer of prucalopride is expected to be low. There was no evidence of potential effects of prucalopride on fertility in rat studies. There was also no evidence of teratogenicity in adequate studies in rat and rabbit (exposures 100 times and 10 times the clinical exposure, respectively). In the pre and postnatal study there was no evidence of developmental toxicity, only reduced nursing behaviour and slightly reduced pup survival due to maternal toxicity.

- Mechanistic studies were conducted to examine the potential mechanism for tumour formation in rodents. Prucalopride was shown to significantly increase prolactin levels following a single 5 mg/kg dose. Higher dose levels were required to increase prolactin levels in repeat dose studies over 6 months. Prucalopride was also able to increase liver and thyroid weights at dose levels up to 160 mg/kg but these changes were reversible upon cessation of treatment.

- Other studies examined primary irritation and phototoxicity. Prucalopride is a slight skin irritant but does not cause phototoxicity.

### Conclusions and Recommendations

#### Nonclinical evidence for efficacy

Overall, the pharmacodynamic studies provided adequate evidence that prucalopride is an effective 5-$HT_4$ receptor agonist *in vitro*. The *in vivo* data in dogs indicate that prucalopride has a positive effect on colonic motility, without inducing diarrhoea. The effects observed in dogs would need to be verified in the clinical studies. The *in vivo* studies also indicate that the dog responds to the pharmacological effects of prucalopride at exposure levels comparable to the clinical exposure level. The dog is therefore a suitable model to examine the potential toxicity of prucalopride at higher exposures.

#### Toxicological findings impacting on safety

Overall, the toxicity studies provide little evidence of potential adverse effects associated with prucalopride. The potential for prucalopride to cause mild effects on heart rate and blood pressure need further examination in clinical studies, as does the potential for CNS related symptoms. The likelihood of other adverse effects related to the pharmacological activity of prucalopride is low. The carcinogenic potential of prucalopride has been adequately studied and the mechanism of formation of the observed tumours appropriately investigated. A threshold for tumour formation has been demonstrated, with an adequate margin between the threshold exposure level and the clinical exposure level.

#### Benefit/ risk conclusion

On the basis of the nonclinical data, the potential benefits of prucalopride outweigh the risks.

#### Recommendation

Based on the nonclinical data provided for prucalopride and evaluated in this report, the registration of prucalopride is supported.

# IV. Clinical Findings

## Introduction

The development program appears to comply with Good Clinical Practice (GCP).

## Pharmacokinetics

There were a large number of studies conducted in order to investigate the pharmacokinetics (PK) of prucalopride:

- There were eleven bioavailability studies.
- There were five *in vitro* studies pertinent to PK using human biomaterials
- There were eleven PK studies in healthy volunteers
- There were five intrinsic factor PK studies
- There were seven drug interaction studies

### Bioavailability

There were 11 bioavailability studies conducted, with the following findings:

- In Study BEL-4: $T_{max}$ was approximately 3 hours, $t_{1/2}$ was approximately 21 hours and food did not affect the bioavailability of the capsule preparation
- In Study BEL-14: prucalopride 1 mg as a tablet and as a solution were bioequivalent.
- In Study BEL-32: food did not affect the bioavailability of a 2 mg tablet of prucalopride and the absolute bioavailability of prucalopride was 93%.
- In Study BEL-33: prucalopride 2 mg as 0.2 mg/mL solution was bioequivalent with the 2 mg tablet.
- In Study BEL-12: prucalopride succinate 1 mg tablets were bioequivalent with prucalopride hydrochloride (HCl) 1 mg tablets.
- In Study BEL-29: prucalopride batch 97K05/F8 2mg tablet; prucalopride 98D20/F27 2 mg tablet and prucalopride 98D22/F25 2 mg tablet were all bioequivalent. Thus establishing bioequivalence between the formulations used in the Phase II and Phase III studies.
- In Study BEL-30: the formulations intended for marketing (Prucalopride (F24) 1 mg tablets; and Prucalopride (F25) 2 mg) were demonstrated to be bioequivalent with the 2 mg formulation used in the Phase III studies (Prucalopride (F6) 1 mg).
- In Study BEL-31: the formulations intended for marketing (Prucalopride (F25) 2 mg tablet; and Prucalopride (F26) 4 mg tablet) were demonstrated to be bioequivalent to the Phase III 4 mg tablet (Prucalopride (F2) 4 mg phase III tablet).
- In Study USA-29: the formulations intended for marketing (Prucalopride (F25) (Gurabo) 2 mg tablets; and Prucalopride (F24) (Gurabo) 1 mg tablets) were demonstrated to be bioequivalent with the 2 mg Phase III formulation (Prucalopride (F8) (Beerse) 2 mg tablets)
- In Study USA-31: the formulations intended for marketing (Prucalopride (F26) (Gurabo) 4 mg tablet; and Prucalopride (F25) (Gurabo) 2 mg tablet) were demonstrated to be bioequivalent with the 4 mg Phase III formulation (Prucalopride (F2) (Beerse) 4 mg tablet).
- Study USA-32: the formulations intended for marketing (Prucalopride (F23) (Gurabo) 0.5 mg tablet; and Prucalopride (F24) (Gurabo) 1 mg tablet) were demonstrated to be bioequivalent with the 1 mg Phase III formulation (Prucalopride (F6) (Beerse) 1 mg tablet).

### *In vitro* studies relevant to pharmacokinetics

Plasma protein binding of prucalopride was investigated *in vitro* in Study FK1913. The protein binding was around 29% in human plasma. In blood, around 66% of prucalopride was distributed to blood cells.

*In vitro* drug metabolism studies (Study FK1475) indicated that during incubation with human microsomal fractions prucalopride undergoes oxidative N-dealkylation at the piperidine nitrogen resulted in the formation of M2. Study FK1897 found that in human hepatocytes only minor or trace amounts of metabolites of prucalopride were found. In incubations with subcellular fractions of human liver there was only a very slow biotransformation of prucalopride. Study FK1900 found that azole antimycotics (ketoconazole, itraconazole and hydroxy-itraconazole) had no substantial inhibitory effect on the biotransformation of prucalopride. There were as also no clinically relevant potential interactions between prucalopride and CYP enzymes.

Study FK3219 found that prucalopride at concentrations of 100 μM exhibited slight inhibitory effects on P-gp mediated taxol transport in both Caco-2 and MDCK cell monolayers.

### Pharmacokinetic studies

In Study BEL-16, around 70% of prucalopride was excreted unchanged; 64% in urine and 6% in faeces. $T_{max}$ was 2.4 hours and $t_{1/2}$ was 26 hours. In Study BEL-3, in the IV dose range of 0.063 to 5 mg, the PK of prucalopride appeared to be dose proportional. The mean terminal $t_{1/2}$ of prucalopride was between 14 and 23 hours and up to 60 % of the dose was excreted unchanged in urine. In Study BEL-5, $T_{max}$ following SC injection was 0.5 hours and $C_{max}$ was half of that detected following an IV infusion (6.22 ng/mL and 3.0 ng/mL, respectively). Administration of 1 mg SC was bioequivalent to IV administration. In Study BEL-1, the PK of orally administered prucalopride were dose proportional in the range 0.125 to 4 mg.

Study BEL-2 found that steady state plasma concentrations were attained within three days; average steady state plasma concentrations of about 2.3, 4.6 and 8.8 ng/mL were reported after doses of 0.5 mg, 1.0 mg and 2.0 mg prucalopride, respectively. The multiple PO dose PK are dose proportional in the dose range from 0.5 to 2 mg. The accumulation ratio was between 3 and 4. At steady state, the $t_{1/2}$ of prucalopride was approximately one day and 60% of the dose was excreted unchanged in the urine. In Study USA-2, the steady state PK of prucalopride following dose escalation were similar to those following a fixed dose (4 mg) regimen. Study GBR-9, $t_{1/2}$ at Day 8 of treatment with 10 mg once daily was 24 hours. In Study GBR-10, steady state of prucalopride was obtained on the fourth day of dosing at 20 mg once daily; steady state trough and peak plasma concentrations were 27 and 88 ng/mL, respectively; and $t_{1/2}$ was 24 hours.

In Study BEL-15 the PK of prucalopride were dose proportional in the dose range 1 mg to 6 mg both following single and multiple daily dosing.

In Study BEL-9 following SC injections of prucalopride 0.5 mg, 1 mg, 2 mg and 4 mg, the PK were dose proportional with a $T_{max}$ of 0.4 to 0.9 hours and $t_{1/2}$ of 21.8 to 26.7 hours. Study BEL-10 demonstrated that after SC administration of prucalopride in the dose range 0.5 mg to 4 mg daily for 7 days, steady state plasma concentrations were attained with the fourth dose; the accumulation factor was approximately 2; and the pharmacokinetics of prucalopride were dose proportional. $T_{max}$ was 0.6 to 0.8 hours and terminal elimination $t_{1/2}$ was 22.2 to 28.8 hours.

In Study USA-6, all degrees of renal impairment resulted in a significant decrease in clearance. The PK of a single oral dose of prucalopride 2 mg in subjects with normal renal function (creatinine clearance CrCL ≥80 mL/min/1.73 $m^2$), mild renal impairment (CrCL = 50-79 mL/min/1.73 $m^2$), moderate renal impairment (CrCL = 25-49 mL/min/1.73 $m^2$) and severe renal impairment (CrCL ≤24 mL/min/1.73 $m^2$). Clearance was halved in severe renal impairment (from 18.7 L/hour to 8.5 L/hour) and the $t_{1/2}$ was doubled (from 29.9 hours to 46.9 hours). There was a resulting increase in exposure, as indicated by increases in $C_{max}$ and AUC.

In Study NED-5 investigated the PK of prucalopride in elderly subjects. In elderly subjects there was a 19% higher plasma AUC and a 28% longer $t_{1/2}$. At steady state, which was attained within 4 days, $C_{max}$ and AUC were 26% and 28% higher, respectively, in elderly subjects. The $t_{1/2}$ was similar following single and multiple doses. Urinary excretion of prucalopride was the primary route of elimination. Protein binding was similar for the two groups. True renal clearance of prucalopride exceeded CrCL by a mean (standard deviation (SD)) of 3.0 (0.7) fold in the elderly subjects and by 2.2 (0.5) fold in the young subjects, indicating tubular secretion of prucalopride in addition to filtration.

Study USA-12 indicated that the $t_{1/2}$ was shorter in children (aged 4 to 12 years) than in adults: mean (SD) 19 (3) hours. The apparent clearance was also higher: 13.6 (4.5) L/h. Protein binding and $T_{max}$ were similar to the adult population. A follow on study (Study USA-24) did not indicate any significant accumulation of prucalopride with long term dosing in children aged 2 to 12 years.

In Study RSA-1 prucalopride concentrations in breast milk were 2.7 fold higher than the plasma concentrations. The average daily amount passed to the infant was estimated to be 1.7 μg/kg.

Adjusted for body weight, this represents about 6% of the maternal dose, indicating that prucalopride exposure is about 16 times lower in the infant than in the mother. However, neonates have decreased renal function compared with older children and adults which might result in decreased clearance of prucalopride in that population relative to older children and adults.

### Drug interaction studies

The following information was obtained from drug interaction studies:

- There was no significant effect of prucalopride 2 mg upon warfarin PK, protein binding or pharmacodynamics (Study BEL-20)
- Prucalopride decreased digoxin AUC and the average and minimum plasma exposure by 10% (Study NED-11).
- Prucalopride did not affect the PK of ethanol or influence the psychomotor effects of ethanol (Study BEL-25).
- Cimetidine did not have any significant effect upon the PK of prucalopride (Study NED-7).
- Probenecid did not have any significant effect upon the pharmacokinetics of prucalopride (Study NED-7).
- Erythromycin did not have a significant effect on the pharmacokinetics of prucalopride (Study NED-14).
- Prucalopride increased the bioavailability of erythromycin by 25% (Study NED-14).
- Ketoconazole increased the bioavailability of prucalopride by 40% (Study NED-6).
- Paroxetine did not alter the PK of prucalopride (Study NED-12).
- Prucalopride did not alter the PK of paroxetine (Study NED-12).

### Population pharmacokinetic analyses

Study 07-mov-045-1011a was a population PK analysis of Phase I to III data comprising 4702 plasma concentrations of prucalopride from 1343 individuals. The study examined the covariates of age, body mass index (BMI), chronic constipation, creatinine, creatinine clearance (estimated using Cockroft-Gault formula), height, race, sex, single/multiple dose and weight. The study found that the only covariate influencing clearance was creatinine clearance. However, because the Cockroft-Gault formula uses age, weight, sex and creatinine to estimate creatinine clearance and therefore all of these individual characteristics might be taken to influence prucalopride clearance.

### Evaluator's overall conclusions on pharmacokinetics

Prucalopride had a $T_{max}$ of around 2.5 to 3 hours and a $t_{1/2}$ of around 24 hours. Food did not affect bioavailability. SC administration of 1 mg was bioequivalent with IV administration. The solution formulation was bioequivalent with a tablet formulation. The formulations used in development and those intended for marketing were bioequivalent. Prucalopride had protein binding of 29% in human plasma and 66% of prucalopride was distributed to blood cells.

A total of 70% of a prucalopride dose was excreted unchanged, 60 to 64% in urine and 6% in faeces. The PK of prucalopride appear to be dose proportional in the IV dose range 0.063 mg to 5 mg and the PO dose ranges of 0.125 to 6 mg for single dosing and 1 mg to 6 mg for multiple dosing. Steady state plasma concentrations were attained within 3 to 4 days.

Elimination is of prucalopride was primarily renal. Its renal clearance involves tubular secretion as well as filtration. At steady state, which was attained within 4 days, $C_{max}$ and AUC were 26% and 28% higher, respectively, in elderly subjects. The $t_{1/2}$ was shorter in children (aged 4 to 12 years) than in adults (mean (SD) 19 (3) hours) and the apparent clearance was higher (13.6 (4.5) L/h). All degrees of renal impairment resulted in decreased clearance, with a 50% lower clearance in subjects with severe renal impairment. Prucalopride clearance correlated with CrCL estimated by the Cockroft-Gault formula. The Cockroft-Gault formula uses age, weight, sex and creatinine to estimate creatinine clearance and therefore all of these individual characteristics can be taken to influence prucalopride clearance.

Exposure of a breast fed infant to maternal prucalopride was estimated to be about 6% of the maternal dose (adjusted for body weight) indicating that prucalopride exposure is about 16 times

lower in the infant than in the mother. However, neonates have decreased renal function compared with older children and adults which might result in decreased clearance of prucalopride in this population relative to older children and adults.

Prucalopride decreased digoxin AUC and average and minimum plasma exposure by 10%, indicating the potential for interactions involving p-glycoprotein. Ketoconazole increased the bioavailability of prucalopride by 40%, indicating the metabolic clearance of prucalopride has the potential for inhibition.

There has been insufficient investigation of which transporters are responsible for active secretion of prucalopride and the effect of inhibition of drug transporters in the kidney upon the PK of prucalopride. There has been insufficient investigation of the metabolic pathways of prucalopride and which enzymes are involved in biotransformation of prucalopride.

## Pharmacodynamics

There were 12 studies conducted to examine the pharmacodynamic (PD) effects of prucalopride in humans.

### Effect on gastrointestinal functioning in healthy subjects

Study BEL-27 indicated that co ingestion with food did not affect either the effect on bowel movements or the rate of AEs.

In Study NED-15, the PK of prucalopride were dose proportional in the 2 mg to 4 mg dose range. There was an increase in some AEs with dose: headache was reported in 12 (80%) subjects in the 2 mg group and 13 (87%) in the 4 mg group, diarrhoea in eight (53%) in the 2 mg and ten (67%) in the 4 mg; flatulence in six (40%) in the 2 mg group and gout (27%) in the 4 mg; and dizziness in four (27%) in the 2 mg group and seven (47%) in the 4 mg. At 3 hours post dose there was a significant increase in heart rate compared with placebo: mean (95% CI) difference from placebo at Day 11 of 8.3 (2.89 to 13.64) beats per minute (bpm) for 2 mg and 3.5 (1.06 to 5.87) bpm for 4 mg. There was also a significant increase in supine systolic blood pressure (SBP) in the 4 mg group: mean (95% CI) difference from placebo at Day 11 of 6.0 (2.45 to 9.55) mmHg.

In Study GBR-1 in healthy volunteers, prucalopride 1 mg and 2 mg both resulted in a decrease in colonic transit time and in an increased frequency of bowel movements compared with placebo. However, there was also an increase in the frequency of headache and nausea.

In Study GBR-2 prucalopride increased the urge to defaecate and the actual stool output; resulted in the production of looser stools; decreased oro-caecal transit time (OCTT). Total intestinal transit time (TITT) and mean colonic transit time (MCTT) also appeared to be shorter with prucalopride. Prucalopride did not affect rectal distention thresholds or anorectal electrosensory thresholds.

These findings were confirmed in Study NED-1. Results from this study also indicated a dose dependent decrease in intestinal transit time and a greater number of loose stools with prucalopride (greater effect with 2 mg than 1 mg). Anorectal manometry did not appear to be changed with prucalopride.

However, in Study NED-8 there was no significant difference in colonic transit time: mean (95% CI) COM 7.787 (7.6392 to 7.9348) for prucalopride and 7.8446 (7.7205 to 7.9688) for placebo (Note: COM = centre of mass, which was measured depending on which of eight regions of interest was the centre of mass). There were a greater mean number of bowel motions per week with prucalopride 4 mg compared with placebo.

In Study USA-7 prucalopride in the dose range 0.5 to 4 mg was investigated. All the dose levels decreased intestinal transit time in relation to placebo but there did not appear to be any differences between the dose levels. Diarrhoea, flatulence and headache appeared to be dose related and each occurred in six (50%) of the 4 mg dose group.

### Pharmacodynamic studies in subjects with constipation

Study FRA-1 was a randomised, double blind placebo controlled (4 weeks) study of prucalopride 1 mg or 2 mg once daily, followed by an open label treatment (at 2 mg prucalopride) of 24 weeks, into the effect of prucalopride on gastrointestinal transit and the colonic response to eating in patients with objective chronic idiopathic constipation. The study included 37 subjects with a history of constipation for at least 6 months. The study enrolled 33 females and four males with an age range of 18 to 68 years. The measures of intestinal transit times did not show any consistent improvement in either study group, during the blind phase or during the open label phase. At the end of double blind treatment (Week 4), the severity of constipation on the Visual Analog Scale (VAS) was decreased from baseline by 17.2 mm and 26.5 mm in the prucalopride 1 mg and 2 mg groups, respectively, compared to 5.0 mm in the placebo group. This change was however only statistically significant in the prucalopride 2 mg group ($p = 0.021$). There was no significant difference between the groups in bowel movement frequency, investigator's Global Assessment of therapeutic effect, or Investigator's assessment of severity of constipation and likely no significant difference in subject's Global Assessment of therapeutic effect.

Study NED-13 was a randomized placebo controlled cross over study of the effect of prucalopride on colonic transit and on colonic motility as measured by prolonged ambulatory colonic manometry in subjects with chronic constipation. There were eight subjects included in the study and one withdrew prior to completion. The PD data were considered to be insufficient and were not analysed.

Study NED-2 was a randomized, double blind, placebo controlled, Phase II cross over study to evaluate the effect of repeated oral dosing of prucalopride 1 mg or 2 mg, given once daily over 2 weeks, on gastrointestinal transit, anorectal manometry and safety/tolerability, in patients with chronic idiopathic constipation. The study included 28 subjects who had had constipation for at least 6 months: 25 females and three males, with an age range of 18 to 66 years. There was no significant difference in colonic transit times or anorectal physiology between prucalopride 1 mg or 2 mg and placebo. However, in the prucalopride 1 mg group there was an increase in the frequency of bowel motions in relation to placebo: least squares (LS) mean difference (standard error (SE)) 3.28 (1.28) bowel motions per week, $p=0.0282$. There was also an increase in the urge to defaecate in the 1 mg group relative to placebo: LS mean difference (SE) 2.19 (0.90); $p = 0.0351$.; a decrease in the number of bowel motions with hard/lumpy consistency: LS mean (SE) difference -31.65 (10.21); $p = 0.0113$; and a decrease in the number of bowel motions with straining: LS mean (SE) difference -31.65 (10.21); $p = 0.0113$. There was no significant difference between the prucalopride 2 mg dose and placebo.

Study USA-21 was a randomised, double blind, placebo controlled, parallel group study with prucalopride (2 mg or 4 mg) or placebo once daily for 7 days to investigate the dose related effects of prucalopride on gastrointestinal and colonic transit in subjects with functional constipation. The study included 40 subjects who had had constipation for at least 6 months: 35 females and five males, with an age range of 21 to 69 years. In the prucalopride 4 mg group there was a reduction in small bowel transit time, an increase in gastric emptying and more rapid colonic filling compared with placebo.

### Effect on QT interval

In Study GBR-9 there was no clinically relevant increase in QTc at doses of up to 10 mg. In Study GBR-10, at none of the (postdose) time points, did the mean difference for QTcF between the treatments exceed +5 ms, except on Day 13 at 2 hours postdose; mean (95% CI) +5.4 (-1.4 to +12.2) ms.

In Study M0001-C102 at steady state doses of prucalopride 2 mg and 10 mg per day there was no significant increase in QTc interval[7]. The positive control (moxifloxacin) did have a significant increase in comparison with placebo. However, there was an increase in mean heart rate (HR) with prucalopride, of up to 5.8 bpm with prucalopride 10 mg.

### Evaluator's overall conclusions on pharmacodynamics

In healthy volunteers, co ingestion with food did not influence effect. Headache, flatulence, diarrhoea and dizziness appeared to be dose related side effects. Oro-caecal transit time was reduced with prucalopride. However colonic transit time was not decreased. Stools were looser with prucalopride compared with placebo. Prucalopride did not affect rectal distention thresholds, anorectal electrosensory thresholds or anorectal manometry.

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 also an increase in the frequency of bowel motions but no effect on colonic transit time.

Two studies have been performed of the effect of prucalopride on QTc. Doses up to 10 mg as single doses and in steady state and did not have a consistent effect upon QTc. However, the doses examined were only five times the sponsor's recommended dose. The sponsor does not appear to have performed a Thorough QT Study[8].

## Efficacy

There were six Phase II and six Phase III studies conducted in subjects with chronic idiopathic constipation.

### Dose Finding and Phase II Studies

#### Study INT-1

*Methods for Study INT-1*

Study INT-1 was a multicentre, double blind placebo controlled dose finding trial to evaluate the efficacy and safety of prucalopride (R093877) in patients with chronic idiopathic constipation. The study was conducted at 22 sites in five countries: Austria, Belgium, France, Germany and The Netherlands.

The inclusion criteria included:

- Age between 18 and 70 years
- History of constipation; the patient reported the occurrence of two or more of the following criteria for at least 6 months before the selection visit :
  - two or fewer spontaneous (not preceded by the intake of a laxative agent within a period of 12 hours) bowel movements in a week.
  - lumpy (scyballae) and/or hard stools at least a quarter of the stools.
  - sensation of incomplete evacuation following at least a quarter of the stools.
  - straining at defaecation at least a quarter of the time.
- Constipation causing disability; the patient's occupational, social and recreational activities were governed by his/her constipation and efforts to attain relief.
- Normal electromyographic inhibition pattern of the external anal sphincter during straining (clinical and/or electromyographic and/or manometric evidence was acceptable).

[7] $QT_c$: The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated.

[8] FDA Guidance: E14 Clinical evaluation of QT/QTc interval prolongation and pro-arrhythmic potential for non-antiarrhytmic drugs. See http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129357.pdf

- Absence of organic abnormalities of the colon on barium enema or on total colonoscopic examination.
- Poor results with laxative treatment and diet counseling.
- Constipation of a functional, idiopathic nature.

The exclusion criteria included:

- Constipation thought to be drug induced
- Presence of secondary causes of constipation, for instance:
  - Endocrine disorders: hypopituitarism, hypothyroidism, hypercalcaemia, pseudohypoparathyroidism, pheochromocytoma, glucagon producing tumors
  - Metabolic disorders: porphyria, uraemia, hypokalaemia, amyloid neuropathy, insulin dependent diabetes mellitus.
  - Neurologic disorders: Parkinson's disease, cerebral tumours, cerebrovascular accidents, multiple sclerosis, meningocele, aganglionosis, hypoganglionosis, hyper-ganglionosis, autonomic neuropathy, spinal cord injury, Chagas disease.
- Congenital megacolon/megarectum.
- History of previous abdominal surgery other than hysterectomy, surgery for Meckel's diverticle, appendicectomy, cholecystectomy, inguinal repair, splenectomy, nephrectomy or fundoplication
- Known or suspected organic disorders of the large bowel; obstruction, carcinoma or inflammatory bowel disease
- Active proctological conditions which were thought to be responsible for constipation
- Evidence of a non relaxing pelvic floor ("anismus") as the main cause of constipation
- Clinically significant ECG abnormalities
- Known illnesses or conditions which might interfere in any way with the adequate assessment of the drug under study, such as severe cardiovascular or lung disease, neurologic or psychiatric disorders, alcoholism, cancer or Acquired Immune Deficiency Syndrome (AIDS)
- Impaired renal function; serum creatinine concentration > 180 µmol/l or CrCL ≤50 ml/min
- Presence of a serum amylase, a serum glutamic oxaloacetic transaminase (SGOT) or a serum glutamic pyruvic transaminase (SGPT) concentration of >2 times the upper limit of normal
- Clinically significant abnormalities of blood chemistry, haematology or urinalysis at selection
- Pregnancy or wish to become pregnant during the course of the study. Oral contraception, intrauterine devices, sterilization or a double barrier method (condom and contraceptive sponge or condom and vaginal suppository or condom and diaphragm) were acceptable methods of birth control. Post menopausal patients could be enrolled.
- Breast feeding
- Known use of street drugs such as marijuana and cocaine.

The study treatments were:

1. Prucalopride 0.5 mg capsule
2. Prucalopride 1.0 mg capsule
3. Prucalopride 2.0 mg capsule
4. Placebo

Treatments were administered orally, once daily. The treatment duration was for 4 weeks and it was preceded by a 4 week run in phase. Treatment allocation was by computer generated randomisation code.

The primary efficacy outcome measure was the number of days (extrapolated to a 4 week period) with constipation determined by:

- daily stool frequency,
- stool consistency,
- presence of straining and

- laxative intake.

The secondary efficacy outcome measures were:

- Percentage of days with constipation and normal bowel habit, based on subject diary
- Global evaluation of therapeutic effect and severity of constipation by the investigator (The severity of the symptoms in the last 7 days prior to each visit, was assessed on a 7 point Likert scale. The following symptoms were evaluated:

  A. *Target symptoms*: Difficulty of stool passage/straining abdominal bloating/distension/flatulence, abdominal pain/cramps, decreased frequency of defaecation, sensation of incomplete evacuation, defaecation urge, unproductive calls to stool and tenesmus.

  B. *Associated symptoms*: Nausea (with or without vomiting), anorexia, malaise, fatigue, dysmenorrhoea and/or irregular periods and difficulty in starting micturition.

  The following scoring system was applied:

  Absent, very mild, mild, moderate, marked, severe, or extremely severe.

- VAS scores on global therapeutic efficacy and on severity of constipation by the subject (The subjects were asked to record in the CRF on a 100 mm VAS:
  - The severity of his/her constipation (all visits). Extremes: 0 mm = no constipation, 100 mm = constipation could not be worse.
  - The global evaluation of the efficacy of treatment (Visits 3 and 4). Extremes: 0 mm = medication is ineffective, 100 mm = medication is very effective).
- Total gut transit time in all patients, in those with initially delayed colonic transit and in those with initially normal transit.

The safety outcome measures were: Adverse events (AEs), laboratory safety tests, vital signs and ECGs.

### *Statistical issues for Study INT-1*

Hypothesis tests were performed using the Mann Whitney U test. Within-group comparisons were done using the Wilcoxon Matched Pairs Signed Rank test (in case of comparing 2 time points) or the Friedman test (in case of more than 2 time points).

The sample size estimation assumed a 30% response to placebo and 65% response to prucalopride and determined a sample size of 31 subjects per treatment group.

### *Results for Study INT-1*

A total of 208 subjects were recruited and 174 were randomized to treatment: 45 to placebo, 46 to 0.5 mg, 43 to 1.0 mg and 40 to 2.0 mg prucalopride. There were 160 (92.0%) females and 14 (8.0%) males and the age range was 18 to 73 years. The treatment groups were similar in demographic characteristics, excepting a shorter gut transit time in the prucalopride 1.0 mg group. The treatment groups were similar in constipation history. A total of 17 subjects discontinued: two placebo, five 0.5 mg, four 1.0 mg and six 2.0 mg prucalopride. Twelve subjects discontinued because of AEs: one placebo, three 0.5 mg, three 1.0 mg and five 2.0 mg prucalopride.

At Week 4, constipation VAS severity scores in the 1.0 mg and the 2.0 mg prucalopride group (mean scores 37.4 and 33.7 respectively) were significantly lower than in the placebo group (mean score 55.2) (Mann-Whitney *U*, p=0.015 and p=0.005 respectively) (Table 4). Therapeutic effect was greater than placebo for all three prucalopride groups (Table 5).

**Table 4. Shifts from baseline of the severity scores of constipation (VAS)**

| | Week 2 | | Week 4 | | Endpoint | |
|---|---|---|---|---|---|---|
| | N | Mean | N | Mean | N | Mean |
| Placebo | 44 | -21.5 | 43 | -19.0 | 44 | -19.8 |
| R093877 0.5 mg | 44 | -22.9 | 38 | -35.2 | 44 | -33.1 |
| R093877 1.0 mg | 40 | -25.0 | 36 | -34.3 | 40 | -30.9 |
| R093877 2.0 mg | 37 | -16.7 | 34 | -39.0 | 37 | -35.0 |

[1]Mean VAS-scores: 0=no constipation, 100= could not be worse

**Table 5.Therapeutic effect (VAS)**

| | Week 2 | Week 4 | Endpoint |
|---|---|---|---|
| Placebo | 42.9 | 44.7 | 45.5 |
| R093877 0.5 mg | 58.4 | 63.3 | 63.4 |
| R093877 1.0 mg | 55.5 | 63.4 | 61.6 |
| R093877 2.0 mg | 54.7 | 67.4 | 64.8 |
| P-value[2] | 0.096 | 0.010 | 0.024 |

[1]Mean VAS-scores: 0=not effective, 100= very effective, [2] Kruskall-Wallis test for intergroup comparison.

During the double blind phase, stool frequency was greater in the prucalopride 1.0 mg and 2.0 mg groups compared with placebo (Table 6). Stool consistency was improved in the 1.0 mg and 2.0 mg groups compared with placebo (Table 7). There was no significant difference between groups in degree of straining but the proportion of stools with 'no' straining appeared to be dose-related (22.9% for placebo, 23.8% for 0.5 mg, 29.1% for 1.0 mg and 34.7% for 2.0 mg).

**Table 6. Stool frequency: totals**

| | | Run-in | | | Double-blind | | | Shift | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | p-value[2] | N | Mean | p-value | N | Mean | p-value |
| Placebo | | 44 | 4.3 | | 44 | 4.5 | | 44 | 0.2 | |
| R093877 | 0.5 mg | 46 | 3.6 | 0.142 | 46 | 5.0 | 0.493 | 46 | 1.5 | 0.006 |
| R093877 | 1.0 mg | 43 | 4.0 | 0.792 | 43 | 6.6 | 0.009 | 43 | 2.6 | 0.001 |
| R093877 | 2.0 mg | 39 | 4.1 | 0.743 | 38 | 7.5 | 0.002 | 38 | 3.5 | 0.0002 |
| K-W-test[1] | p-value | 0.501 | | | 0.004 | | | 0.0003 | | |

[1]K-W-test: Kruskall-Wallis test for intergroup comparison, [2] Mann-Whitney U-test for pairwise comparison (with placebo). Stool frequency is expressed as mean number of stools per week.

**Table 7. Stool consistency**

| | | Run-in | | | Double-blind | | | Shift | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | p-value[2] | N | Mean | p-value | N | Mean | p-value |
| Placebo | | 44 | 0.5 | | 44 | 0.5 | | 44 | -0.0 | |
| R093877 | 0.5 mg | 46 | 0.4 | 0.642 | 46 | 0.3 | 0.361 | 46 | -0.1 | 0.377 |
| R093877 | 1.0 mg | 43 | 0.4 | 0.769 | 43 | 0.1 | 0.008 | 43 | -0.4 | 0.012 |
| R093877 | 2.0 mg | 39 | 0.6 | 0.658 | 38 | 0.1 | 0.006 | 38 | -0.5 | 0.003 |
| K-W-test[1] | p-value | 0.756 | | | 0.006 | | | 0.004 | | |

[1]K-W-test: Kruskall-Wallis test for intergroup comparison, [2]Mann-Whitney U-test for pairwise comparison (with placebo). Data present mean consistency scores per stool calculated over all days. Values range: -2=watery, -1=pasty, 0= normal, 1=hard, 2=lumpy.

The Investigator's assessment of response did not show a difference between treatment groups. At Week 4, all the prucalopride groups showed improvement in Investigator's assessment of severity compared with placebo (p=0.043). There was a decrease in gut transit time in all three prucalopride groups compared to placebo and overall (Table 8). There was no significant difference between the treatment groups in Quality of Life (QoL) scores.

**Table 8. Gut transit time**

| | | N | Nmiss | Mean | (95% CI) | Std | Se | Median | (Min , Max) | (95% CI) | K-W-test |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Transit time (h) | | | | | | | | | | | |
| placebo | PRE | 39 | 0 | 65.2 | ( 54.46 ; 76.00) | 33.24 | 5.32 | 55.2 | ( 0 ; 139) | ( 45.6 ; 74.4) | p=0.024 |
| | POST | 41 | 0 | 73.0 | ( 59.67 ; 86.32) | 42.21 | 6.59 | 64.8 | ( 12 ; 144) | ( 45.6 ; 91.2) | p=0.001 |
| R093877(0.5mg) | PRE | 41 | 0 | 73.5 | ( 61.97 ; 85.07) | 36.59 | 5.71 | 69.6 | ( 2 ; 144) | ( 50.4 ; 93.6) | |
| | POST | 36 | 0 | 65.7 | ( 53.62 ; 77.85) | 35.81 | 5.97 | 60.0 | ( 10 ; 144) | ( 45.6 ; 79.2) | |
| R093877(1.0mg) | PRE | 34 | 0 | 48.6 | ( 37.29 ; 59.84) | 32.32 | 5.54 | 45.6 | ( 5 ; 127) | ( 26.4 ; 55.2) | |
| | POST | 36 | 0 | 39.1 | ( 29.92 ; 48.35) | 27.24 | 4.54 | 34.8 | ( 0 ; 125) | ( 24.0 ; 48.0) | |
| R093877(2.0mg) | PRE | 33 | 0 | 63.1 | ( 48.04 ; 78.21) | 42.54 | 7.41 | 55.2 | ( 0 ; 144) | ( 36.0 ; 72.0) | |
| | POST | 33 | 0 | 53.7 | ( 37.62 ; 69.87) | 45.47 | 7.91 | 48.0 | ( 0 ; 144) | ( 16.8 ; 67.2) | |

K-W-test: Kruskal-Wallis-test for intergroup comparison, p -values represent two-tailed probability. PRE=Pre-treatment, POST=Post-treatment

**Study INT-2**

*Methods for Study INT-2*

Study INT-2 was a multicentre, double blind placebo controlled dose finding trial to evaluate the efficacy and safety of prucalopride (R093877) in patients with chronic constipation. The study was conducted at 32 sites in six countries: Austria, Belgium, The Netherlands, Norway, South Africa and Sweden.

The inclusion criteria were similar to those for Study INT-1 except for:

- Normal inhibition pattern of the external anal sphincter during straining; relaxation of the m.puborectalis and a distal displacement of the rectal canal (digital examination and/or electromyographic and/or manometric evidence was acceptable)

The study treatments were:

1. Prucalopride 0.5 mg
2. Prucalopride 1.0 mg
3. Prucalopride 2.0 mg
4. Placebo

The treatments were administered twice daily PO. Treatments were presented as capsules. Treatment allocation was by computer generated randomisation code.

The outcome measures were the same as for Study INT-1 except that the primary efficacy outcome measure was not clearly defined.

*Statistical Issues for Study INT-2*

The sample size estimation assumed a response to placebo in 30% of the subjects and a response to prucalopride in 65% of the subjects and determined that 31 subjects were required in each treatment group to detect a significant difference at the 5% level, with a power of 80%.

*Results for Study INT-2*

A total of 294 subjects were screened and 253 subjects were randomised to treatment: 63 to placebo, 67 prucalopride to 0.5 mg, 62 prucalopride to 1.0 mg, 61 prucalopride to 2.0 mg. A total of 36 subjects discontinued, 8 (12.7%) in the placebo, 8 (11.9%) in the 0.5 mg twice a day (bd) group, 9 (14.5%) in the 1 mg bd group and 11 (18.0%) in the 2 mg bd group. Discontinuation due to adverse experience did not occur in any placebo subjects but in three (4.5%) in the 0.5 mg bd, six (9.7%) in the 1 mg bd and seven (11.5%) subjects in the 2 mg bd. There were 231 (91.3%) females and 22 (8.7%) males and the age range was 18 to 70 years. The treatment groups were similar in baseline characteristics and in history of constipation.

At Week 12 there was no significant difference in VAS for severity, VAS for therapeutic effect between the treatment groups and placebo (Table 9). There was a statistically significant increase in stool frequency compared to placebo for both the 1 mg and 2 mg groups ($p<0.05$) (Table 9). There was also a statistically significant improvement in stool consistency in the 2 mg group compared to placebo ($p<0.05$). There was no significant difference in straining or % of stools with complete evacuation. The combined bowel index was statistically significantly better in the 1 mg and 2 mg groups compared to placebo at Week 12 (Table 9). For the Investigator's assessments, there was no significant difference between the groups for severity but there was an improvement in clinical effect in the 2 mg group compared to placebo ($p<0.05$) (Table 9). There was a statistically and clinically significant decrease in time to first stool for all prucalopride groups compared to placebo ($p<0.01$) (Table 9).

**Table 9. Summary of efficacy data from Study INT-2.**

| Efficacy | Placebo b.i.d. (n= 63) | | | R093877 0.5mg b.i.d. (n= 67) | | | R093877 1mg b.i.d. (n= 62) | | | R093877 2mg b.i.d. (n= 61) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **I. Subject's evaluation** | | | | | | | | | | | | |
| VAS | bl[a] | $ep_4$ | $ep_{12}$ | bl | $ep_4$ | $ep_{12}$ | bl | $ep_4$ | $ep_{12}$ | bl | $ep_4$ | $ep_{12}$ |
| • severity of constipation[b] | 75.8 | 60.9 | 57.3 | 74.8 | 56.6 | 54.4 | 73.6 | 49.4 | 46.4 | 72.2 | 49.9 | 46.1 |
| • therapeutic effect.[c] | | 41.6 | 44.3 | | 44.5 | 47.4 | | 50.4 | 52.2 | | 53.3 | 53.2 |
| DIARY | RI | w 1-4 | w 1-12 | RI | w 1-4 | w 1-12 | RI | w 1-4 | w 1-12 | RI | w 1-4 | w 1-12 |
| • stools (weekly mean) | 4.5 | 5.1 | 4.8 | 4.3 | 5.9 | 5.0 | 5.1 | 6.6 * | 6.2 * | 4.6 | 7.1 *** | 6.1 ** |
| • consistency[d] (mean) | 0.5 | 0.4 | 0.4 | 0.3 | 0.2 ◊ | 0.3 | 0.2 | 0.2 ◊ | 0.1 ◊ | 0.5 | 0.1 ** | 0.2 * |
| • straining[e] (mean) | 1.2 | 1.1 | 1.1 | 1.1 | 1.0 | 1.0 | 1.1 | 1.1 | 1.0 | 1.1 | 1.0 | 1.0 |
| • % stools with incomplete evacuation[f] | 70.8 | 62.8 | 63.2 | 65.0 | 60.3 | 59.9 | 63.0 | 58.4 | 55.0 | 61.5 | 63.9 | 62.4 |
| • combined bowel index (mean)[g] | 7.6 | 6.8 | 6.6 | 6.9 ◊ | 5.9 ◊ | 6.1 | 6.8 | 5.8 * | 5.5 * | 7.4 | 5.7 * | 5.6 * |
| • weekly laxative use (mean), n | 0.5 | 0.5 | 0.5 | 0.8 * | 0.6 | 0.6 | 0.7 | 0.5 | 0.5 | 0.6 | 0.4 | 0.4 |
| **II. Investigator's evaluation** | | | | | | | | | | | | |
| | bl[a] | $ep_4$ | $ep_{12}$ | bl[a] | $ep_4$ | $ep_{12}$ | bl[a] | $ep_4$ | $ep_{12}$ | bl[a] | $ep_4$ | $ep_{12}$ |
| • severity[h] | 4.3 | 3.3 | 3.1 | 4.2 | 3.0 | 2.9 | 4.3 | 2.8 | 2.6 | 4.3 | 2.7 ◊ | 2.5 ◊ |
| • clinical effect[i] | | 0.8 | 0.8 | | 0.8 | 1.2 | | 1.0 | 1.2 ◊ | | 1.2 * | 1.4 * |
| • symptoms (associated and target): no relevant intergroup differences | | | | | | | | | | | | |
| • subjects with relief of constipation | 7.9% | | | 10.4% | | | 16.1% | | | 13.1% | | |
| **III. Measurements** | | | | | | | | | | | | |
| | pre | | post | pre | | post | pre | | post | pre | | post |
| • total transit time (mean), h | 72.1 | | 75.8 | 79.0 ◊ | | 67.8 | 70.4 | | 67.9 | 71.6 | | 60.7 |
| | RI | w 1-4 | w 1-12 | RI | w 1-4 | w 1-12 | RI | w 1-4 | w 1-12 | RI | w 1-4 | w 1-12 |
| • time between stools (mean), h:min | 45:02 | 40:46 | 48:46 | 54:46 | 41:28 | 49:52 | 57:56 | 47:13 * | 53:23 ◊ | 56:14 | 30:02 ** | 44:40 * |
| • time to first stool, (mean) h:min | | | | | | | | | | | | |
| - spontaneous | 102:00 | | | 32:37** | | | 44:26* | | | 10:08*** | | |
| - all | 32:51 | | | 15:55*** | | | 16:22** | | | 8:16*** | | |

a) bl = baseline; $ep_4$ = end point week 4; $ep_{12}$ = end point week 12 / b) 0 = no constipation; 100 = could not be worse
c) 0 = not effective; 100 = very effective / d) score from -2=watery to 2=hard / e) 0=no; 1=little; 2=lot
f) 0 = no; 1=yes / g) from 0 to 12 (the lower the better) / h) 0 = absent; 1 = very mild; 2 = mild; 3 = moderate; 4 = marked; 5 = severe; 6 = very severe / i) -3 = very much worsened; -2 = much worsened; -1 = minimally worsened; 0 = unchanged; 1 = minimally improved; 2 = much improved; 3 = very much improved

Asterisks refer to differences with placebo
Levels of significance: ◊ $p \leq 0.1$; * $p \leq 0.05$; **$p \leq 0.01$, ***$p \leq 0.001$

**Study USA-3**

*Methods for Study USA-3*

Study USA-3 was a multicentre, double blind, placebo controlled, randomised, parallel group, dose finding trial to evaluate the efficacy and safety of prucalopride in subjects with chronic constipation. The study was conducted at 26 sites in the USA. There were 212 (91.8%) females and

19 (8.2%) males and the age range was 21 to 70 years. The treatment groups were similar in demographic characteristics and in baseline findings.

The inclusion and exclusion criteria were similar to those for Study INT-2 except that constipation need only be present for 3 months instead of 6 months and the constipation was not required to cause disability.

The study treatments were:

1. Prucalopride 0.5 mg
2. Prucalopride 1.0 mg
3. Prucalopride 2.0 mg
4. Prucalopride 4.0 mg
5. Placebo

The treatments were administered once daily prior to breakfast. There was a four week double blind treatment phase, preceded by a four week run in phase.

The primary efficacy parameter was the proportion of the subjects who had had at least three or more spontaneous, complete bowel movements (SCBM)/week at the end of double blind treatment.

The secondary efficacy outcome measures were:

- Proportion of subjects with ≥3 SCBM/week
- Frequency of SCBM/week
- Frequency of non laxative induced bowel movements (BM)/week
- Frequency of BM/week
- Weekly average score of hardness of stool
- Weekly average score of straining
- Percent of bowel movements with incomplete emptying per week
- Weekly average score of bellyache
- Number of bisacodyl tablets used per week
- Number of urges to move bowels per week
- Number of days with events per week from diary data (urge to BM, BM, rescue medication taken)
- Investigator's assessments of severity of constipation
- Investigator's assessments of therapeutic effect
- Mean colonic transit time
- Subjects' evaluation of target symptoms of constipation
- Subjects' evaluation of symptoms associated with constipation
- Subject evaluation of severity of constipation during the last 2 weeks by VAS
- Subject evaluation of the efficacy of the constipation treatment during the last 2 weeks by VAS
- Medical Outcomes Study Short Form 36 (SF-36)[9],
- Psychological General Well Being (PGWB)[10]
- Constipation Specific Quality of Life (CIC-QoL)

[9] The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It measures eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and mental health. It yields scale scores for each of these eight health domains and two summary measures of physical and mental health. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. The SF-36 is available for two recall periods: standard (4-week recall) and acute (1-week recall).

[10] The PGWB Index is a 22 item health-related Quality of Life (HRQoL) questionnaire developed in USA which produces a self perceived evaluation of psychological well being expressed by a summary score.

The safety outcome measures were: AEs, physical examination, vital signs, laboratory tests and ECGs

*Statistical issues for Study USA-3*

Hypothesis tests were performed using analysis of variance (ANOVA) and analysis of co variance (ANCOVA).

The sample size calculation assumed a 30% response rate for subjects receiving placebo and 65% for those receiving any dose of prucalopride, resulting in an estimated requirement of 31 subjects in each treatment group (155 subjects in total) required to complete the double blind phase in order to detect a significant difference in response between placebo prucalopride at the two sided 5% significance level, with a power of 80%.

*Results for Study USA-3*

A total of 313 subjects were screened and 231 were randomized to treatment: 46 to placebo, 43 to 0.5 mg, 48 to 1 mg, 48 to 2 mg and 46 to 4 mg prucalopride. Twenty-nine (13%) subjects discontinued: four (9%) subjects in the placebo group, three (7%) in the 0.5 mg, seven (15%) in the 1 mg, eight (17%) in the 2 mg and seven (15%) in the 4 mg group. Three (6%) subjects in the 1 mg group, two (4%) in the 2 mg and six (13%) in the 4 mg prucalopride group discontinued because of AEs.

The proportion of responders increased with dose and was significantly more than placebo at the 2 mg and 4 mg dose levels (Table 10). At the end of the double blind phase, a response was reported for 6 (13.3%) subjects in the placebo group, 10 (24.4%) in the 0.5 mg, 11 (23.4%) in the 1 mg, 15 (32.6%) in the 2 mg ($p<0.05$) and 25 (55.6%) in the 4 mg group ($p<0.01$). Compared with placebo, softer stools, less straining, less laxative use, a greater frequency of urge to move bowels and greater frequency of bowel movement were reported in the 2 mg and 4 mg groups (Table 11). The % of bowel movements with incomplete emptying was also less in the 4 mg group. There was no significant difference between the groups in subject's assessment of severity or of efficacy (Table 10). The Investigator's assessments of severity and of therapeutic effect were improved in the 2 mg and 4 mg groups compared with placebo (Tables 12 and 13). There was no significant difference between the groups in colonic transit time. There was no significant difference between the groups in the SF-36 or PGWB results. However, for over half of the components of the CIC-QoL, the 2 mg and 4 mg dose levels were significantly better compared to placebo (Table 14). Bisacodyl usage was reported by 31 (67%) subjects in the placebo group, 21 (49%) in the 0.5 mg, 22 (46%) in the 1 mg, 32 (68%) in the 2 mg dose and 15 (33%) in the 4 mg dose group.

**Table 10. Summary of efficacy data from Study USA-2.**

| Efficacy | Placebo | R093877 0.5 mg | R093877 1 mg | R093877 2 mg | R093877 4 mg |
|---|---|---|---|---|---|
| Primary efficacy parameter | (n=45) | (n=41) | (n=47) | (n=46) | (n=45) |
| Percentage of subjects with three or more complete[1], spontaneous[2] BM/week[3] (≥3 SCBM/week) | 13.3% | 24.4% | 23.4% | 32.6%* | 55.6%** |
| Secondary efficacy parameters | | | | | |
| Frequency of complete spontaneous BM/week[4] | 0.54 | 1.50 | 1.34* | 1.83** | 2.97** |
| Frequency of spontaneous BM/week[4] | 0.95 | 2.25 | 3.07 | 2.49* | 4.34** |
| Frequency of any BM/week[4] | 0.88 | 2.22 | 2.58 | 2.44** | 3.94** |
| Hardness of stool[4,5] | -0.01 | 0.00 | -0.30* | -0.24** | -0.23* |
| Straining[4,5] | -0.09 | 0.02 | -0.12 | -0.22 | -0.29** |
| Percentage of BM with feeling of incomplete emptying /week[4,5] | -3.74 | -10.9 | -11.4 | -14.6 | -15.3* |
| Dulcolax® tablet usage/week[4,5] | -0.00 | -0.79 | -0.83** | -0.92* | -0.91** |
| Urges to move bowels/week[4] | -0.36 | 1.84 | 2.06* | 1.74 | 2.70** |
| Subject's assessment of severity of constipation[5,6] | -1.66 | -2.70 | -2.32 | -2.30 | -3.03** |
| Subject's assessment of efficacy[7] | 5.85 | 4.51 | 4.62 | 4.86 | 3.38** |

BM = bowel movements;
SCBM= non-laxative induced, complete, bowel movements;
[1] Complete = accompanied by a feeling of complete emptying;
[2] Spontaneous = non-laxative induced;
[3] Based on all double blind diary data;
[4] Mean change from baseline, based on all double-blind diary data;
[5] Negative value reflects improved score;
[6] Mean change from baseline, based on double-blind endpoint data.;
[7] Mean VAS score (cm), based on double-blind endpoint data.

Asterisks refer to two-sided p-value vs. placebo; levels of significance: * p≤0.05; **p≤0.01; ***p≤0.001

**Table 11. Summary of other constipation-related diary parameters in the Intention to Treat Population (ITT)**

| | Placebo | | R093877 0.5 mg | | R093877 1 mg | | R093877 2 mg | | R093877 4 mg | | Overall |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Mean Diff. | Mean | Mean Diff. | Mean | Mean Diff. | Mean | Mean Diff. | Mean | Mean Diff. | p-value |
| Hardness of stool[1] | | | | | | | | | | | |
| Baseline | 3.24 | | 3.02 | | 3.23 | | 3.07 | | 3.08 | | 0.517 |
| DB Endpoint | 3.36 | 0.08 | 3.16 | 0.14 | 3.03 | -0.20 | 3.05 | -0.03 | 3.12 | 0.03 | 0.238 |
| All DB | 3.23 | -0.01 | 3.02 | 0.00 | 2.93 | -0.30* | 2.83 | -0.24** | 2.85 | -0.23* | 0.009 |
| Straining[2] | | | | | | | | | | | |
| Baseline | 1.16 | | 0.97 | | 1.01 | | 1.03 | | 1.06 | | 0.466 |
| DB Endpoint | 1.13 | -0.02 | 1.04 | 0.10 | 0.99 | -0.04 | 0.82 | -0.23 | 0.88 | -0.18 | 0.083 |
| All DB | 1.07 | -0.09 | 0.97 | 0.02 | 0.89 | -0.12 | 0.81 | -0.22 | 0.77 | -0.29** | 0.004 |
| Percentage of BM with feeling of incomplete emptying | | | | | | | | | | | |
| Baseline | 70.7 | | 75.3 | | 71.7 | | 71.7 | | 63.6 | | 0.267 |
| DB Endpoint | 67.0 | -4.32 | 62.7 | -12.0 | 61.0 | -11.8 | 55.6 | -16.5 | 49.2 | -13.6 | 0.346f |
| All DB | 67.0 | -3.74 | 64.3 | -10.9 | 60.4 | -11.4 | 57.1 | -14.6 | 48.3 | -15.3* | 0.044 |
| Frequency of Dulcolax tablet usage/week | | | | | | | | | | | |
| Baseline | 1.61 | | 1.88 | | 1.62 | | 2.23 | | 1.52 | | 0.322 |
| DB Endpoint | 1.71 | 0.10 | 1.00 | -0.88 | 0.60 | -1.02* | 1.47 | -0.76 | 0.61 | -0.92 | 0.075 |
| All DB | 1.61 | -0.00 | 1.09 | -0.79 | 0.78 | -0.83** | 1.31 | -0.92* | 0.61 | -0.91** | 0.005 |
| Frequency of urges to move bowels/week | | | | | | | | | | | |
| Baseline | 9.01 | | 6.25 | | 9.16 | | 7.40 | | 9.53 | | 0.033 |
| DB Endpoint | 8.20 | -0.69 | 7.55 | 1.31 | 10.94 | 1.76 | 8.79 | 1.29 | 11.63 | 2.40* | 0.046 |
| All DB | 8.65 | -0.36 | 8.08 | 1.84 | 11.22 | 2.06* | 9.14 | 1.74 | 12.23 | 2.70** | 0.004 |
| Number of days with urges to move bowels/week | | | | | | | | | | | |
| Baseline | 4.24 | | 3.44 | | 4.27 | | 3.65 | | 4.41 | | 0.011 |
| DB Endpoint | 4.16 | -0.08 | 4.53 | 1.09 | 5.37 | 1.10** | 4.51 | 0.86 | 5.41 | 1.00** | 0.004 |
| All DB | 4.21 | -0.02 | 4.53 | 1.09* | 5.36 | 1.09** | 4.58 | 0.93* | 5.65 | 1.25** | <0.001 |
| Number of days with BM/week | | | | | | | | | | | |
| Baseline | 2.98 | | 2.60 | | 2.78 | | 2.50 | | 2.74 | | 0.377 |
| DB Endpoint | 3.58 | 0.60 | 3.93 | 1.33 | 4.18 | 1.40 | 3.68 | 1.18 | 4.71 | 1.97 | 0.011 |
| All DB | 3.44 | 0.46 | 3.98 | 1.38* | 4.25 | 1.47** | 3.98 | 1.48** | 4.79 | 2.05** | <0.001 |
| Number of days taking Dulcolax/week | | | | | | | | | | | |
| Baseline | 0.73 | | 0.80 | | 0.69 | | 1.02 | | 0.63 | | 0.131 |
| DB Endpoint | 0.71 | -0.02 | 0.41 | -0.39 | 0.30 | -0.39* | 0.58 | -0.44 | 0.25 | -0.37* | 0.074 |
| All DB | 0.70 | -0.02 | 0.42 | -0.38* | 0.36 | -0.33** | 0.57 | -0.45* | 0.25 | -0.38** | 0.002 |

Displays: EFF.1E through EFF.1K

BM=bowel movements; DB=double-blind phase

1Hardness evaluation: watery=1; loose=2; normal=3; hard=4; very hard=5

[2] Straining evaluation: no=0; a little=1; a lot=2

* Two-sided p-value vs placebo ≤0.05

** Two-sided p-value vs placebo ≤0.01

**Table 12. Summary of investigator assessment of severity of constipation in the ITT**

| | Placebo | | R093877 0.5 mg | | R093877 1 mg | | R093877 2 mg | | R093877 4 mg | | Overall p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Mean Diff. | Mean | Mean Diff. | Mean | Mean Diff. | Mean | Mean Diff. | Mean | Mean Diff. | |
| DB | | | | | | | | | | | |
| Baseline | 3.96 | | 4.22 | | 4.13 | | 4.35 | | 4.11 | | 0.202 |
| DB Week 2 | 3.37 | -0.60 | 2.78 | -1.45 | 2.32 | -1.84** | 2.53 | -1.80** | 2.03 | -2.05** | <0.001 |
| DB Week 4 | 3.17 | -0.76 | 2.48 | -1.75 | 2.64 | -1.54 | 2.73 | -1.59 | 2.00 | -2.11** | 0.010 |
| End Point | 3.18 | -0.80 | 2.51 | -1.71 | 2.53 | -1.60 | 2.85 | -1.50 | 1.95 | -2.13** | 0.008 |
| RO | | | | | | | | | | | |
| RO Week 4 | 3.56 | -0.37 | 3.75 | -0.45 | 3.47 | -0.63 | 4.05 | -0.28 | 3.81 | -0.30 | 0.467 |
| End Point | 3.56 | -0.37 | 3.75 | -0.45 | 3.47 | -0.63 | 4.05 | -0.28 | 3.86 | -0.26 | 0.410 |

DB=double-blind; RO=run-out Source: Display EFF.2A

Severity of constipation evaluation: absent=0; very mild=1; mild=2; moderate=3; marked=4; severe=5; very severe=6.

* Two-sided p-value versus placebo ≤0.05.

** Two-sided p-value versus placebo ≤0.01.

**Table 13. Summary of investigator assessment of therapeutic effect in the ITT**

| | Placebo | R093877 0.5 mg | R093877 1 mg | R093877 2 mg | R093877 4 mg | Overall p-value |
|---|---|---|---|---|---|---|
| DB Endpoint (n) | 44 | 41 | 45 | 46** | 40* | 0.051 |
| Very much improved (n [%]) | 6 (14) | 9 (22) | 9 (20) | 9 (20) | 9 (23) | |
| Much improved | 3 (7) | 9 (22) | 11 (24) | 13 (28) | 13 (33) | |
| Minimally improved | 10 (23) | 8 (20) | 10 (22) | 11 (24) | 8 (20) | |
| Unchanged | 23 (52) | 11 (27) | 9 (20) | 11 (24) | 4 (10) | |
| Minimally worsened | 2 (5) | 4 (10) | 5 (11) | 1 (2) | 5 (13) | |
| Much worsened | 0 | 0 | 1 (2) | 1 (2) | 1 (3) | |
| Very much worsened | 0 | 0 | 0 | 0 | 0 | |
| RO Endpoint (n) | 43 | 40 | 43 | 43** | 43* | 0.052 |
| Very much improved (n [%]) | 1 (2) | 4 (10) | 2 (5) | 1 (2) | 1 (2) | |
| Much improved | 3 (7) | 1 (3) | 3 (7) | 2 (5) | 7 (16) | |
| Minimally improved | 7 (16) | 3 (8) | 7 (16) | 4 (9) | 2 (5) | |
| Unchanged | 21 (49) | 12 (30) | 12 (28) | 9 (21) | 6 (14) | |
| Minimally worsened | 7 (16) | 8 (20) | 6 (14) | 11 (26) | 10 (23) | |
| Much worsened | 4 (9) | 10 (25) | 11 (26) | 16 (37) | 13 (30) | |
| Very much worsened | 0 | 2 (5) | 2 (5) | 0 | 4 (9) | |

Source: Display EFF.2B

* Two-sided p-value vs placebo at ≤0.05 (Van-Elteren test controlled by centre)

** Two-sided p-value vs placebo at ≤0.01 (Van-Elteren test controlled by centre)

**Table 14. Results for CIC-QOL compared to placebo at the double blind endpoint**

| CIC-QOL variable | R093877 0.5 mg | R093877 1 mg | R093877 2 mg | R093877 4 mg |
|---|---|---|---|---|
| Felt bloated to point of bursting | | | ** | ** |
| Felt heavy | | | | * |
| Had painful spasms due to medicine | | | | * |
| Felt physical discomfort | | | ** | ** |
| Been able to wear clothes you want | | | * | |
| Embarrassed to be w/people | | | | * |
| Careful about what you ate | * | | | * |
| Been irritable | | | | * |
| Worried about unable to open bowels (i.e., worried about being unable to open their bowels) | | | * | |
| More bothered unable to move bowel | | | | * |
| Satisfied with how often open bowels | | | ** | ** |
| Satisfied with regularity open bowels | | | ** | ** |
| Satisfied with intestinal transit | | | ** | ** |
| Satisfied with treatment | | * | * | * |

Source: Display A.QOL5

* Two-sided p-value vs placebo at ≤0.05 (Van-Elteren test controlled by centre)
** Two-sided p-value vs placebo at ≤0.01 (Van-Elteren test controlled by centre)

**Study BEL-6**

*Methods for Study BEL-6*

Study BEL-6 was a single centre, double blind placebo controlled trial to evaluate the efficacy and safety of prucalopride in patients with severe chronic constipation. The study was conducted at a single centre in Belgium.

The inclusion and exclusion criteria were similar to those for Study INT-1.

The study treatments were:

1. Prucalopride 4 mg
2. Placebo

Treatments were administered PO once daily.

The primary efficacy outcome measure was the number of patients with a 25% or greater improvement of a composite bowel index consisting of the following elements:

· Stool frequency,

· Stool consistency,

· Degree of straining,

· Frequency of laxative intake, and

· Frequency of sensation of incomplete evacuation.

The secondary efficacy outcome measures were:

· Percentage of days with constipation
· Number of patients with relief of constipation, defined as:
  - an average of ≥3 stools/week
  - straining at defaecation less than a quarter of the time
  - lumpy (scyballae) and/or hard stools less than a quarter of the stools
  - sensation of incomplete evacuation following less than a quarter of the stools.

- Percentage of unproductive trips to the toilet (difference between daily number of urge episodes minus number of stools passed)
- Percentage of days with laxative induced stools
- Percentage of days with spontaneous stools
- Mean stool frequency
- Mean score for consistency of stools
- Mean score for straining
- Mean time between 2 consecutive stools
- Longest/shortest time between two consecutive stools.
- Global evaluation of therapeutic effect and severity of constipation by the investigator
- VAS scores on global therapeutic efficacy and on severity of constipation by the patient
- Total gut transit time
- % faecal water contents

The safety outcome measures were AEs, vital signs and laboratory tests.

### *Statistical Issues for Study BEL-6*

Hypothesis tests were performed using the Mann-Whitney U test for continuous and ordinal categorical variables and the Chi square test for nominal categorical variables.

The sample size calculation assumed a response rate of 30% to placebo and 70% to prucalopride and estimated that 25 patients would be required in each group to complete the double blind phase in order to detect a significant difference between the two treatment groups at a 5% level of significance and with a power of 75%.

### *Results for Study BEL-6*

A total of 55 subjects entered the study and 53 were randomised: 27 to prucalopride and 26 to placebo. There were 52 (98.1%) females and one (1.9%) male and the age range was 17 to 70 years. The treatment groups were similar in demographic characteristics. One subject in each group discontinued.

The Subject's VAS score for efficacy of treatment was significantly better for prucalopride 4 mg than for placebo: mean (SE) score 52.7 (6.63) for prucalopride 4 mg and 24.3 (6.80) for placebo; p = 0.006 (Table 15). However, at end of study none of the other efficacy variables demonstrated a statistically significant benefit for prucalopride 4 mg. At end of study there was no significant difference between prucalopride and placebo in mean scores for stool frequency, stool consistency, straining, incomplete evacuation or bowel index (Table 15). There was no significant difference in Investigator's global clinical impression of severity, evaluation of change or in response rate (Table 15). There was no significant difference in faecal water content or total gut transit time. Mean time to first stool was decreased in the prucalopride group compared to placebo: 13:42 hrs compared to 75:39 hrs in the placebo group (p = 0.027).

**Table 15. Summary of efficacy results for Study BEL-6.**

| Efficacy | R093877 4 mg (n=27) | | | Placebo (n=26) | | |
|---|---|---|---|---|---|---|
| I. Patient's evaluation | | | | | | |
| a) VAS | Baseline | Day 14 | Day 28 | Baseline | Day 14 | Day 28 |
| • severity (VAS, 0=no constipation-100=couldn't be worse) | 86.8 | 71.5* | 71.7 | 87.8 | 80.4 | 75.0 |
| • efficacy (VAS, 0= not effective - 100= very effective) | | 43.1 | 54.3** | | 27.5 | 25.4 |
| b) DIARY (spontaneous stools) | Run-In | Treatment | | Run-In | Treatment | |
| • stool frequency (weekly mean) | 1.89 | 4.23 | | 2.04 | 3.52 | |
| • stool consistency (mean) (1) | 0.49 | 0.09 | | 0.42 | 0.49 | |
| • straining (mean) (2) | 1.58 | 1.24 | | 1.42 | 1.37 | |
| • incomplete evacuation (mean %) (3) | 78.7 | 64.2 | | 65.5 | 58.5 | |
| • combined bowel habit index (mean) (4) | 7.8 | 6.6 | | 8.0 | 7.6 | |
| • Relief of constipation (% patients) | 11.1 | 37.0 | | 11.5 | 19.2 | |

| II. Investigator's evaluation | R093877 4 mg (n=27) | | | Placebo (n=26) | | |
|---|---|---|---|---|---|---|
| | Baseline | Day 14 | Day 28 | Baseline | Day 14 | Day 28 |
| • symptoms (mean total) (5) | | | | | | |
| - target | 34.7 | | 27.3 | 34.2 | | 29.0 |
| - associated | 10.6 | | 10.4 | 11.0 | | 10.4 |
| • clinical global impression | | | | | | |
| - severity of constipation (mean) | 5.1 | 3.9* | 3.7 | 5.3 | 4.6 | 4.1 |
| - change (mean) (6) | | 1.2* | 1.2 | | 0.5 | 0.8 |
| III. Measurements | | | | | | |
| | Run-In | Treatment | | Run-In | Treatment | |
| • total gut transit time (mean h:min) | 92:42 | 82:38 | | 80:17 | 85:39 | |
| • faecal water content (mean % dry weight) | 33.4 | 27.8 | | 31.6 | 32.0 | |

Asterisks refer to differences with placebo. Levels of significance: * $p \leq 0.05$; ** $p \leq 0.01$, *** $p \leq 0.001$
(1) from -2= watery to 2= lumpy. (2) from 2= much to 0= none. (3) proportion of spontaneous stools associated with a feeling of incomplete evacuation. (4) from 0 -12 (the lower the better). (5)from 1=absent to 7=very severe. (6) from -3=very much worsened to 3=very much improved.

**Study GBR-4**

*Methods for Study GBR-4*

Study GBR-4 was a single centre, randomised, double blind, placebo controlled, parallel group, Phase II trial to investigate prucalopride 1 mg once daily for 4 weeks in female patients with chronic idiopathic constipation. The study was conducted at a single centre in the UK.

The inclusion criteria included:

- Female subjects of 18 years or over.
- History of chronic constipation for at least 6 months, characterised by either two or fewer spontaneous (without using laxatives) bowel movements in a week or straining at defaecation at least a quarter of the time
- Within 20% of her body weight as specified in the Metropolitan Life Insurance Company's 1983 Height and Weight Table 2
- Healthy on the basis of a pre trial physical examination, medical history, anamnesis, ECG and biochemistry, haematology and urinalysis

The exclusion criteria included:

- Use of disallowed concomitant medication (psychotropics, prokinetics, antibiotics, narcotic analgesics and laxatives [excluding bisacodyl]).
- Subjects who had undergone surgery for their constipation.
- Subjects with faecal impaction.
- Subjects suffering from different types or causes of constipation other than idiopathic constipation that is, presence of secondary causes such as endocrine disorders, metabolic disorders and neurologic disorders.
- Subjects with a megacolon/megarectum.
- Subjects with external rectal prolapsed.
- History of previous abdominal surgery (other than hysterectomy, surgery for Meckel's diverticle, appendectomy, cholecystectomy, inguinal hernia repair, splenectomy, nephrectomy or fundoplication) thought to be the primary cause of constipation
- Known or suspected organic disorders of the large bowel that is, obstruction, carcinoma or inflammatory bowel disease. If complaints of constipation were of recent onset, that is, had been present for less than one year and the subject was 40 years or older, results of a Barium enema or of colonoscopic examination were required
- Subjects with solitary rectal ulcer (this had to be excluded by rigid sigmoidoscopic examination at the first visit)
- Subjects with active proctological conditions thought to be responsible for the constipation.
- Subjects with known illnesses or conditions such as: severe cardiovascular or lung disease, neurologic or psychiatric disorders (including substance abuse/dependence but with the exception of nicotine), alcoholism, cancer or AIDS and other gastrointestinal or endocrine disorders.
- Subjects receiving, or who had received, care for an eating disorder.
- Subjects with impaired renal function; serum creatinine concentration ≥180 mol/L or CrCL ≤50 ml/min
- Subjects with a serum amylase, SGOT, or SGPT concentration of >2 times the normal limit.
- Pregnancy or wish to become pregnant in the course of the trial. Lack of an acceptable birth control method.
- Breast-feeding.
- History or suspicion of alcohol or drug abuse.

The study treatments were:

1. Prucalopride 1 mg
2. Placebo

Treatments were administered orally, once daily. Treatment allocation was according to a pre-prepared randomisation code. If the subject had not passed any stools for three or more consecutive days, bisacodyl was allowed as rescue medication.

The primary efficacy outcome measure was whole gut transit time.

## The secondary efficacy outcome measures were:

- Oro-caecal transit time
- Anorectal physiology values as changes from baseline:
  - resting pressure (cm H2O)
  - sensory function: threshold volume (ml) or initial sensation
  - sensory function: urgency volume (ml) or feeling of urgency
  - sensory function: maximum tolerated volume (ml)
  - anorectal mucosal electric stimulation rectum: electric sensory threshold (A)
  - anorectal mucosal electric stimulation mid anal canal: electric sensory threshold (A)
- Subjects' evaluations:
  - Severity of constipation (VAS) at screening, baseline, Week 2, Week 4 and at the endpoint.

- Severity of the most troublesome symptom related to the gut, as noted at the first visit (6 point scale), at screening, baseline, Week 2, Week 4 and at the end point.
- Severity of the most troublesome constipation symptom in general (6 point scale) at screening, baseline, Week 2, Week 4 and at the end point.
- Therapeutic efficacy (VAS) at Week 4 and end point (no analysis on change from baseline possible).

· Investigators evaluations: Global evaluation of therapeutic efficacy (5-point scale) at the last visit.
· QoL surveys:
- SF-36
- CIC QoL
- HAD (Hospital Anxiety and Depression) scale
· Bowel Habit Diary:
  - Percentage of days with an urge to defecate.
  - Average weekly stool frequency.
  - Average score of stool consistency.
  - Percentage of stools with straining.
  - Percentage of days with abdominal pain/discomfort.
  - Time to first stool.
  - Average time between two consecutive stools.
  - Percentage of days with laxative use.

The safety outcome measures were AEs, vital signs and clinical laboratory tests.

*Statistical Issues for Study GBR-4*

Hypothesis tests were performed using ANOVA, ANCOVA, Generalized Wilcoxon test, Kaplan-Meier product limit estimates, stratified randomization and Cochran-Mantel-Haenszel tests.

The sample size calculation used data obtained from Study INT-1. From that study mean shifts of whole gut transit time of +9 hours occurred with placebo and -14 hours with prucalopride 1 mg. The standard deviation was approximately 32 hours. The estimated sample size was 33 subjects per treatment group in order to detect a difference of 23 hours with a standard deviation of 26.7 at the 5% level of significance (two tailed) with 80% power. Assuming a dropout rate of 20%, 40 subjects per treatment arm would be required.

*Results for Study GBR-4*

A total of 77subjects were randomised to treatment: 39 to prucalopride 1 mg and 38 to placebo. Three subjects discontinued and were excluded from the Intention to Treat (ITT) population analysis: two in the prucalopride 1 mg group due to AEs and one in the placebo group was lost to follow up. All subjects were female and the age range was 19 to 66 years. The treatment groups were similar in demographic characteristics.

For the ITT analysis, there was no significant difference between the treatment groups in whole gut transit time. However, mean oro-caecal transit time was significantly shorter in the prucalopride 1 mg group: 54.2 minutes compared with 71.9 minutes in the placebo p <0.001 (Table 16).

**Table 16. Oro-caecal transit (ITT and OP population)**

| Time | Placebo | | | Prucalopride | | | p-value[a)] | p-value[a)] |
|---|---|---|---|---|---|---|---|---|
| | N | Mean time (min) | Change from BL | N | Mean time (min) | Change from BL | | |
| INTENT-TO-TREAT POPULATION | | | | | | | | |
| Baseline | 37 | 70.8 | | 37 | 75.9 | | 0.415 | |
| End point | 36 | 71.9 | 0.6 | 36 | 54.2 | -21.7 | 0.004 | <0.001 |

For anorectal physiology, there were statistically significant changes for feeling of urgency, volume of air, maximum tolerated volume of air and rectal sensory threshold; but the clinical significance of these changes was not apparent (Table 17). For the subject evaluations, there was lesser severity

of constipation at endpoint in the prucalopride 1 mg group: 38.6 compared with 68.6, p <0.001 (Table 18); and greater effect of treatment: 64.5 compared with 20.6, p <0.001.

**Table 17. Ano-rectal physiology (ITT and OP population)**

| Time | Placebo | | | Prucalopride | | | p-value[a)] | p-value[a)] |
|---|---|---|---|---|---|---|---|---|
| | N | Mean value | Change from BL | N | Mean value | Change from BL | | |
| **INTENT-TO-TREAT POPULATION** | | | | | | | | |
| **Motor function: mean resting pressure (cm $H_2O$)** | | | | | | | | |
| Baseline | 37 | 89.8 | | 37 | 86.3 | | 0.621 | |
| End point | 36 | 92.3 | 1.7 | 36 | 90.0 | 3.5 | 0.765 | 0.400 |
| **Sensory function: mean initial sensation volume of air (ml)** | | | | | | | | |
| Baseline | 37 | 47.8 | | 37 | 56.3 | | 0.170 | |
| End point | 36 | 50.1 | 1.9 | 36 | 54.3 | -1.8 | 0.438 | 0.273 |
| **Sensory function: mean feeling of urgency volume of air (ml)** | | | | | | | | |
| Baseline | 37 | 104.7 | | 37 | 112.7 | | 0.411 | |
| End point | 36 | 108.8 | 2.8 | 36 | 104.6 | -7.9 | 0.623 | 0.010 |
| **Sensory function: maximum tolerated volume of air, mean (ml)** | | | | | | | | |
| Baseline | 37 | 199.3 | | 37 | 194.2 | | 0.694 | |
| End point | 36 | 208.5 | 6.3 | 36 | 177.6 | -15.9 | 0.025 | <0.001 |
| **Electric stimulation: mean rectal sensory threshold (mA)** | | | | | | | | |
| Baseline | 37 | 19.6 | | 37 | 20.2 | | 0.746 | |
| End point | 36 | 20.1 | 0.7 | 36 | 19.0 | -1.3 | 0.566 | 0.001 |
| **Electric stimulation: mean anal sensory threshold (mA)** | | | | | | | | |
| Baseline | 37 | 7.3 | | 37 | 8.7 | | 0.097 | |
| End point | 36 | 7.3 | 0.1 | 36 | 8.4 | -0.3 | 0.175 | 0.099 |

**Table 18. Symptoms (ITT and OP population)**

| Time | Placebo | | | Prucalopride | | | p-value[a)] | p-value[a)] |
|---|---|---|---|---|---|---|---|---|
| | N | Mean value | Change from BL | N | Mean value | Change from BL | | |
| **INTENT-TO-TREAT POPULATION** | | | | | | | | |
| **Severity of constipation (VAS)** | | | | | | | | |
| Baseline | 37 | 71.4 | | 37 | 65.9 | | 0.391 | |
| End point | 37 | 68.6 | -2.8 | 37 | 38.6 | -27.3 | <0.001 | 0.001 |
| **Effect of treatment (VAS)** | | | | | | | | |
| Week 2 | 36 | 17.9 | | 37 | 56.1 | | <0.001 | |
| End point | 37 | 20.6 | NAP[b)] | 37 | 64.5 | NAP | <0.001 | NAP |

a) p-value on changes from baseline: test for no difference between treatments from ANCOVA model with factor(s) treatment, baseline number of markers (Type III SS).

b) NAP = not applicable as there was no baseline

Symptom severity improved in the prucalopride 1 mg group relative to placebo (Table 19). The investigator rated the therapeutic effect as 'very good', 'good' or 'moderate' in 29 (80.6%) subjects in the prucalopride 1 mg group and 11 (30.6%) in the placebo (p<0.001). For diary symptoms in the prucalopride 1 mg group there was a clinically and statistically significant increase in the urge to defaecate and in the frequency of bowel movements (p <0.001) but not in any of the other symptoms relative to placebo (Table 20).

**Table 19. Severity of main symptom/most troublesome symptom (ITT and OP population)**

| ITT-population | | | Severity of the main symptom: score, n | | | | | | p-value CMH *) |
|---|---|---|---|---|---|---|---|---|---|
| Group | Visit | N | Absent | Very mild | Mild | Moderate | Severe | Could not be worse | |
| Placebo | Screening | 37 | 1 | 0 | 0 | 4 | 22 | 10 | |
| | Baseline | 37 | 1 | 1 | 1 | 7 | 18 | 9 | |
| | Week 2 | 36 | 0 | 0 | 6 | 6 | 17 | 7 | |
| | Week 4 | 36 | 0 | 2 | 4 | 10 | 13 | 7 | |
| | End point | 37 | 0 | 2 | 4 | 10 | 13 | 8 | |
| Prucalopride | Screening | 37 | 0 | 0 | 0 | 7 | 20 | 10 | 0.881 |
| | Baseline | 37 | 0 | 2 | 5 | 9 | 16 | 5 | 0.168 |
| | Week 2 | 37 | 1 | 2 | 10 | 13 | 9 | 2 | 0.002 |
| | Week 4 | 35 | 3 | 7 | 8 | 10 | 7 | 0 | <0.001 |
| | End point | 37 | 3 | 7 | 9 | 11 | 7 | 0 | <0.001 |

| ITT-population | | | Severity of the most troublesome symptom: score, n | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | Screening | 35 | 4 | 0 | 1 | 12 | 17 | 1 | |
| | Baseline | 36 | 5 | 1 | 6 | 7 | 14 | 3 | |
| | Week 2 | 33 | 3 | 1 | 2 | 11 | 11 | 5 | |
| | Week 4 | 34 | 4 | 3 | 2 | 11 | 10 | 4 | |
| | End point | 35 | 4 | 3 | 2 | 11 | 10 | 5 | |
| Prucalopride | Screening | 37 | 5 | 0 | 0 | 15 | 13 | 4 | 0.927 |
| | Baseline | 37 | 5 | 0 | 3 | 14 | 11 | 4 | 0.726 |
| | Week 2 | 37 | 8 | 4 | 5 | 15 | 5 | 0 | 0.002 |
| | Week 4 | 35 | 10 | 3 | 8 | 10 | 4 | 0 | 0.004 |
| | End point | 37 | 10 | 3 | 9 | 11 | 4 | 0 | 0.003 |

**Table 20. Diary parameters: values at run-in (RI) and end point (EP) and changes from run-in at end point (_RI) – ITT population**

| ITT population – Spontaneous bowel movements | | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Time** | **Placebo** | | **Prucalopride** | | **Overall comparison** |
| | | N | Mean (SE) | N | Mean (SE) | p-value |
| Average weekly frequency of urge to defaecate | RI | 36 | 5.1 (0.69) | 37 | 5.6 (0.90) | 0.727 |
| | EP | 36 | 4.6 (0.60) | 37 | 7.3 (1.00) | 0.020 |
| | ΔRI | 36 | -0.6 (0.44) | 37 | 1.8 (0.47) | <0.001 |
| Average weekly frequency of bowel movements | RI | 36 | 5.7 (0.73) | 37 | 5.9 (0.96) | 0.886 |
| | EP | 36 | 4.9 (0.56) | 37 | 8.0 (1.00) | 0.008 |
| | ΔRI | 36 | -0.8 (0.55) | 37 | 2.1 (0.55) | <0.001 |
| Average weekly frequency of abdominal pain | RI | 36 | 4.0 (0.50) | 37 | 3.7 (0.70) | 0.758 |
| | EP | 36 | 3.5 (0.54) | 37 | 3.1 (0.69) | 0.688 |
| | ΔRI | 36 | -0.5 (0.42) | 37 | -0.5 (0.76) | 0.925 |
| Average weekly frequency of abdominal bloating | RI | 36 | 3.9 (0.43) | 37 | 4.0 (0.72) | 0.931 |
| | EP | 36 | 3.7 (0.55) | 37 | 2.7 (0.48) | 0.176 |
| | ΔRI | 36 | -0.2 (0.44) | 37 | -1.2 (0.66) | 0.184 |
| Average score of consistency | RI | 34 | 0.7 (0.15) | 35 | 0.7 (0.14) | 0.807 |
| | EP | 34 | 0.3 (0.18) | 36 | 0.2 (0.15) | 0.588 |
| | ΔRI | 34 | -0.3 (0.15) | 36 | -0.6 (0.18) | 0.180 |
| % of stools with normal consistency | RI | 34 | 20.8 (4.00) | 35 | 16.9 (3.48) | 0.466 |
| | EP | 34 | 24.5 (5.96) | 36 | 32.7 (5.21) | 0.312 |
| | ΔRI | 34 | 3.4 (6.19) | 36 | 15.0 (4.83) | 0.147 |
| % of stools with hard/lumpy consistency | RI | 34 | 59.8 (5.58) | 35 | 62.7 (5.27) | 0.703 |
| | EP | 34 | 46.0 (6.83) | 36 | 37.7 (6.25) | 0.381 |
| | ΔRI | 34 | -11.0 (6.34) | 36 | -27.6 (6.57) | 0.074 |
| Average score of straining | RI | 34 | 2.0 (0.17) | 35 | 1.8 (0.16) | 0.340 |
| | EP | 34 | 1.8 (0.17) | 36 | 1.4 (0.14) | 0.087 |
| | ΔRI | 34 | -0.1 (0.23) | 36 | -0.5 (0.14) | 0.214 |
| % of bowel movements with no straining | RI | 34 | 11.3 (3.54) | 35 | 11.1 (3.65) | 0.991 |
| | EP | 34 | 9.6 (3.85) | 36 | 18.0 (4.30) | 0.156 |
| | ΔRI | 34 | -1.7 (3.99) | 36 | 9.5 (5.24) | 0.092 |
| Weekly average number of days with abdominal pain | RI | 36 | 4.4 (0.44) | 37 | 4.0 (0.38) | 0.530 |
| | EP | 36 | 3.8 (0.46) | 37 | 3.1 (0.48) | 0.340 |
| | ΔRI | 36 | -0.7 (0.40) | 37 | -1.1 (0.38) | 0.537 |
| Weekly average number of days with abdominal bloating | RI | 36 | 4.6 (0.42) | 37 | 4.3 (0.40) | 0.591 |
| | EP | 36 | 4.1 (0.49) | 37 | 2.9 (0.44) | 0.095 |
| | ΔRI | 36 | -0.7 (0.41) | 37 | -1.3 (0.42) | 0.263 |
| Average time between two consecutive stools (h) | RI | 23 | 24.9 (2.26) | 15 | 20.9 (2.78) | 0.346 |
| | EP | 12 | 19.8 (2.01) | 20 | 16.8 (1.75) | 0.243 |
| | ΔRI | 12 | -7.4 (3.54) | 20 | -13.7 (5.10) | 0.399 |

RI = run-in; EP = end point; ΔRI = change from run-in at end point

In the prucalopride group, there was an increase in the mean frequency of bowel movement: 8.3 compared with 5.4 in the placebo group p <0.001; and in the frequency of spontaneous bowel movements: 8.0 compared with 4.9 in the placebo group p <0.001. Time to first bowel motion was shorter in the prucalopride group. In the ITT population there were no significant differences between the groups in the SF-36 or in the HAD. However, for the total CIC score there were significant improvement in the prucalopride 1 mg group, p <0.001.

### Study USA-26

Study USA-26 was a multicentre, randomised, double blind, dose escalation safety study in three cohorts of elderly patients with constipation who were living in a nursing facility. The study was conducted at 18 centres in the US. The study included:

- Male and female patients at least 65 years of age (no upper age limit).

- History of constipation; the patient should have received any treatment for constipation at any time during the 4 weeks (28 days) preceding entry into the study, including fibre/bulk forming supplements.
- The patient had to live in a nursing facility.

The study treatments were:

1. Prucalopride 0.5 mg
2. Prucalopride 1 mg
3. Prucalopride 2 mg
4. Placebo

The treatments were administered once daily for four weeks.

The outcome measures were:

- Patient's Global Assessment of severity of constipation and efficacy of treatment
- Patient's symptom assessment (Patient Assessment of Constipation Symptom Questionnaire [PAC-SYM]), healthcare utilisation (record of constipation treatment)
- Patient's evaluation of satisfaction with his/her bowel function and treatment (Patient Assessment of Constipation– Quality of Life Questionnaire [PAC-QoL])

The safety outcome measures were: AEs, vital signs, laboratory tests, physical examination, ECG and Holter monitor. No formal sample size calculation was performed and the primary efficacy outcome measure was not defined.

A total of 100 subjects were randomised and 89 received treatment: 18 to placebo, 21 to prucalopride 0.5 mg, 24 to prucalopride 1 mg and 26 to prucalopride 2 mg. Twelve subjects discontinued: four (22%) placebo, three (14.3%) prucalopride 0.5 mg, three (12.5%) prucalopride 1 mg and two (7.7%) prucalopride 2 mg. Of the treated subjects, 65 (73.0%) were female, 24 (27.0%) were male and the age range was 65 to 98 years. The treatment groups were similar in demographic characteristics. There was no significant difference between the treatment groups in any of the outcome variables. Treatment effect did not appear to increase with dose (Tables 21 and 22). Patient satisfaction appeared to improve in the prucalopride groups but there was no significant difference between treatments.

**Table 21. Distribution of Severity of Constipation Evaluations**

| Severity of constipation, n (%) | PLA | PRU 0.5 mg | PRU 1 mg | PRU 2 mg |
|---|---|---|---|---|
| Day 1 | N=18 | N=21 | N=24 | N=26 |
| Absent | 1 (5.6) | 4 (19.0) | 3 (12.5) | 4 (15.4) |
| Mild | 4 (22.2) | 6 (28.6) | 6 (25.0) | 6 (23.1) |
| Moderate | 7 (38.9) | 10 (47.6) | 10 (41.7) | 8 (30.8) |
| Severe | 5 (27.8) | 1 (4.8) | 4 (16.7) | 8 (30.8) |
| Very severe | 1 (5.6) | 0 | 1 (4.2) | 0 |
| Day 14 | N=14 | N=21 | N=21 | N=22 |
| Absent | 2 (14.3) | 9 (42.9) | 5 (23.8) | 5 (22.7) |
| Mild | 5 (35.7) | 6 (28.6) | 9 (42.9) | 10 (45.5) |
| Moderate | 3 (21.4) | 5 (23.8) | 5 (23.8) | 4 (18.2) |
| Severe | 3 (21.4) | 0 | 1 (4.8) | 2 (9.1) |
| Very severe | 1 (7.1) | 1 (4.8) | 1 (4.8) | 1 (4.5) |
| Day 28 | N=14 | N=18 | N=21 | N=23 |
| Absent | 4 (28.6) | 7 (38.9) | 11 (52.4) | 5 (21.7) |
| Mild | 2 (14.3) | 5 (27.8) | 7 (33.3) | 11 (47.8) |
| Moderate | 4 (28.6) | 5 (27.8) | 3 (14.3) | 5 (21.7) |
| Severe | 3 (21.4) | 1 (5.6) | 0 | 2 (8.7) |
| Very severe | 1 (7.1) | 0 | 0 | 0 |

**Table 22. Distribution of Efficacy of Treatment Evaluations**

| Efficacy of treatment, n (%) | PLA | PRU 0.5 mg | PRU 1 mg | PRU 2 mg |
|---|---|---|---|---|
| Day 14 | N=14 | N=21 | N=21 | N=22 |
| Not at all effective | 3 (21.4) | 2 (9.5) | 0 | 3 (13.6) |
| A little bit effective | 4 (28.6) | 1 (4.8) | 4 (19.0) | 2 (9.1) |
| Moderately effective | 6 (42.9) | 6 (28.6) | 7 (33.3) | 9 (40.9) |
| Quite a bit effective | 0 | 9 (42.9) | 5 (23.8) | 7 (31.8) |
| Extremely effective | 1 (7.1) | 3 (14.3) | 5 (23.8) | 1 (4.5) |
| Day 28 | N=14 | N=18 | N=21 | N=23 |
| Not at all effective | 2 (14.3) | 2 (11.1) | 1 (4.8) | 1 (4.3) |
| A little bit effective | 7 (50.0) | 2 (11.1) | 4 (19.0) | 5 (21.7) |
| Moderately effective | 0 | 7 (38.9) | 5 (23.8) | 8 (34.8) |
| Quite a bit effective | 3 (21.4) | 4 (22.2) | 5 (23.8) | 8 (34.8) |
| Extremely effective | 2 (14.3) | 3 (16.7) | 6 (28.6) | 1 (4.3) |

## Placebo Controlled Efficacy Studies

### Study INT-6

*Methods for Study INT-6*

Study INT-6 was a multicentre, parallel-group, two phase study (two week drug free run in phase followed by a randomised, 12 week, double blind, placebo controlled treatment phase). The study was conducted at 65 centres in eight countries: Australia (7), Belgium (5), Canada (11), The Netherlands (11), Norway (4), South Africa (8), Sweden (8) and UK (11).

The inclusion criteria included:

- Male and non-pregnant, non-breast feeding female outpatients at least 18 years of age.
- History of constipation; the patient reported having on average two or fewer spontaneous bowel movements per week that resulted in a feeling of complete evacuation as well as the occurrence of one or more of the following for at least 6 months before the selection visit:
  - very hard (little balls) and/or hard stools at least a quarter of the stools
  - sensation of incomplete evacuation following at least a quarter of the stools
  - straining at defaecation at least a quarter of the time

  Patients who never had spontaneous bowel movements were considered to be constipated and were eligible for the study
- Constipation that was not induced by secondary causes of constipation

The exclusion criteria included:

- Patients in whom constipation was thought to be drug induced, or who were using any disallowed medication (Agents that influence the bowel habit such as anticholinergics [not including antihistamines], opioids, spasmolytics, prokinetics and tricyclic antidepressants, laxatives [except for bisacodyl])
- Patients suffering from secondary causes of chronic constipation; for example:
  - *Endocrine disorders*: insulin-dependent diabetes mellitus, hypopituitarism, hypothyroidism, hypercalcaemia, pseudohypopara thyroidism, pheochromocytoma, or glucagon producing tumours
  - *Metabolic disorders*: porphyria, uraemia, hypokalaemia or amyloid neuropathy
  - *Neurologic disorders*: Parkinson's disease, cerebral tumours, cerebrovascular accidents, multiple sclerosis, meningocele, aganglionosis, hypoganglionosis, hyper ganglionosis, autonomic neuropathy, spinal cord injury, Chagas' disease or major depression
- Presence of a megacolon/megarectum or a diagnosis of pseudo-obstruction.
- Constipation as a result of surgery.
- Known or suspected organic disorders of the large bowel (that is, obstruction, carcinoma, or inflammatory bowel disease). Results of a barium enema or of a colonoscopic examination performed within the last 12 months were needed to rule out organic disorders. A colonoscopic examination performed within the last three years was acceptable if the

examination was performed for an evaluation of constipation and there was no history or evidence of weight loss, anaemia or rectal bleeding. Patients with polyps discovered by colonoscopy that were untreated (by polypectomy) were to be excluded.
- Presence of severe and clinically uncontrolled cardiovascular, liver or lung disease, neurologic or psychiatric disorders (including active alcohol or drug abuse), cancer or AIDS and other gastrointestinal or endocrine disorders.
- Impaired renal function; serum creatinine concentration >180 µmol/L
- Clinically significant abnormalities of haematology, urinalysis, or blood chemistry.
- Females of child-bearing potential without adequate contraceptive protection.

The study treatments were:

1. Prucalopride 2 mg
2. Prucalopride 4 mg
3. Placebo

Treatments were administered PO once daily after breakfast for 12 weeks. This was preceded by a two week drug free run in phase. Treatment allocation was according to a pre prepared randomisation code. Rescue therapy with bisacodyl was allowed if the patient did not have had a bowel movement for three or more consecutive days throughout the study.

The primary efficacy outcome measure was the proportion (%) of patients with an average of three or more SCBM per week.

The secondary efficacy outcome measures were:

- Proportion (%) of patients with an average increase of >1 SCBM/week compared to the run-in period
- Average number of SCBM/week
- Average number of SBM/week
- Average number of all BM/week
- Consistency per BM
- Straining per BM
- BM with a sensation of complete evacuation per week
- Bisacodyl (Dulcolax®) tablets/enema used per week
- Average time to first BM, SBM and SCBM after intake of the study medication on Days 1, 29 and 57
- Patient's Global Assessment on efficacy of treatment (5 point scales; 0=none, 4=extremely effective)
- Patient's Global Assessment on severity of constipation (5 point scales; 0=none, 4=very severe)
- Patient's symptom assessment on all of the 12 items within the PAC-SYM (5 point scales; 0=none, 4=very severe)
- Patient's symptom assessment on the three PAC-SYM subscales: stool symptoms (5 items), abdominal symptoms (4 items) and rectal symptoms (3 items)
- Patient's assessment of severity on each of the 12 items within the PAC-SYM (5-point scales; 0=none, 4=very severe)
- PAC-QoL
- SF-36

The safety outcome measures were: AEs, laboratory tests, vital signs, physical examination and ECGs.

### *Statistical Issues for Study INT-6*

Hypothesis tests were performed using paired t test, two way ANOVA, two way ANCOVA, Dunnett's test, Cochran-Mantel-Haenszel test, logistic regression model, Kaplan-Meier curves, log rank test, Van Elteren test, Pearson correlation and Cronbach's alpha.

The sample size calculation used data from previous studies for the prucalopride 2 mg dose level that indicated a 15% response rate for placebo and 30% for prucalopride. Adjusting for

multiplicity (two between treatment comparisons), 188 subjects per treatment group would be required to detect a significant difference in response rates, with a power of 90% and a two sided, Type I error rate of 2.5%. Given a dropout rate of 5%, 198 subjects were required per treatment group.

*Results for Study INT-6*

A total of 865 subjects were screened and of these 720 were randomised and 716 received treatment: 238 received 2 mg, 238 received 4 mg prucalopride and 240 received placebo. Three subjects with no efficacy data were excluded from the ITT population. In the treated population there were 650 (90.8%) females, 66 (9.2%) males and the age range was 18 to 89 years. The treatment groups were similar in demographic and baseline characteristics.

For the primary efficacy outcome measure, both the 2 mg and 4 mg prucalopride doses were superior to placebo. The number (proportion) achieving an average of ≥3 SCBM per week was 46 (19.5%) for prucalopride 2 mg, p≤0.01, 56 (23.6%) for 4 mg and 23 (9.6%) for placebo, p ≤0.001 (Table 23).

For the secondary outcome measures the two doses of prucalopride, 2 mg and 4 mg resulted in a higher proportion of subjects with:

- ≥1 SCBM per week: 86 (38.1%) for 2 mg, 94 (44.1%) for 4 mg and 49 (20.9%) for placebo, p ≤0.001.
- ≥1 SBM per week: 145 (64.2%) for 2 mg, 144 (67.6%) for 4 mg and 89 (38.0%) for placebo, p ≤0.001.
- ≥1 BM per week: 137 (60.6%) of 227 subjects for 2 mg, 132 (62.0%) of 213 for 4 mg and 90 (38.5%) of 235 for placebo, p ≤0.001.

Prucalopride 2 mg and 4 mg resulted in:

- a higher mean number of SCBM per week: mean (mean change) 1.6 (1.2) for prucalopride 2 mg, 1.9 (1.4) for prucalopride 4 mg and 1.0 (0.5) for placebo, p ≤0.001 (Table 23) and
- a higher percentage of stools with normal consistency: 40.0 (17.4%) for prucalopride 2 mg, p≤0.05, 41.6 (16.6%) for prucalopride 4 mg, p ≤0.01 and 33.7 (12.6%) for placebo (Table 23).

There was a higher percentage of BM with no straining in the prucalopride 4 mg group: mean (mean change) 19.6 (1.3%) compared with 15.0 (-3.3) in the placebo p ≤0.05. At Week 12 patient assessments of efficacy and severity were superior and there were lower scores for PAC-SYM for both the prucalopride doses compared to placebo (Table 23). PAC-QoL scores were superior for both prucalopride doses but there was no significant difference for SF-36. The average number of days per week with bisacodyl use was 0.4 for prucalopride 2 mg, 0.5 for prucalopride 4 mg and 0.8 for placebo, p ≤0.001.

**Table 23. Summary of efficacy data from Study INT-6**

| | PLA | PRU 2 mg | PRU 4 mg |
|---|---|---|---|
| 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)*** |
| Weeks 1-4 | 25/240 (10.4) | 56/236 (23.7)*** | 63/237 (26.6)*** |
| 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)*** |
| Weeks 1-4 | 49/235 (20.9) | 93/227 (41.0)*** | 99/215 (46.0)*** |
| Number of patients with an average increase ≥1 SBM per week, n/N (%) | | | |
| Weeks 1-12 | 89/234 (38.0) | 145/226 (64.2)*** | 144/213 (67.6)*** |
| Weeks 1-4 | 93/235 (39.6) | 164/227 (72.2)*** | 162/215 (75.3)*** |
| Average SCBM per week, mean (mean change) | | | |
| Run-in | 0.4 (-) | 0.4 (-) | 0.5 (-) |
| Weeks 1-12 | 1.0 (0.5) | 1.6 (1.2)*** | 1.9 (1.4)*** |
| Weeks 1-4 | 0.9 (0.5) | 1.7 (1.4)*** | 2.0 (1.5)*** |
| Percentage of BM with normal consistency, mean (mean change) | | | |
| Run-in | 21.4 (-) | 23.2 (-) | 23.9 (-) |
| Weeks 1-12 | 33.7 (12.6) | 40.0 (17.4)* | 41.6 (16.6)** |
| Weeks 1-4 | 32.0 (10.9) | 36.1 (13.4) | 39.9 (15.1)** |
| Percentage of BM with no straining, mean (mean change) | | | |
| Run-in | 17.8 (-) | 15.5 (-) | 17.9 (-) |
| Weeks 1-12 | 14.8 (-3.5) | 16.4 (1.0) | 19.6 (1.3)* |
| Weeks 1-4 | 15.0 (-3.3) | 18.8 (3.4)** | 22.1 (3.8)*** |
| Time to onset of first movement, median | | | |
| First SCBM after Day 1 dose, hh:mm | 493:00 | 113:00*** | 49:27*** |
| Number of patients rating treatment quite a bit or extremely effective, n/N (%) | | | |
| Week 4 | 36/227 (15.9) | 65/215 (30.3)*** | 72/209 (34.4)*** |
| Week 12 | 39/209 (18.7) | 71/205 (34.6)*** | 65/180 (36.1)*** |
| Patient assessment on constipation severity[a], mean (mean change) | | | |
| Baseline | 2.74 (-) | 2.66 (-) | 2.72 (-) |
| Week 4 | 2.36 (-0.39) | 1.84 (-0.82)*** | 1.87 (-0.88)*** |
| Week 12 | 2.39 (-0.31) | 1.90 (-0.76)*** | 1.82 (-0.92)*** |
| Overall PAC-SYM symptoms score, mean (mean change) | | | |
| Baseline | 2.06 (-) | 2.12 (-) | 2.00 (-) |
| Week 4 | 1.73 (-0.34) | 1.46 (-0.67)*** | 1.34 (-0.64)*** |
| Week 12 | 1.69 (-0.37) | 1.44 (-0.66)*** | 1.29 (-0.71)*** |
| Improvement ≥1 overall PAC-SYM score from baseline, n/N (%) | | | |
| Week 4 | 41/226 (18.1) | 77/216 (35.6)*** | 61/208 (29.3)** |
| Week 12 | 47/208 (22.6) | 70/205 (34.1)** | 65/178 (36.5)*** |
| PAC-SYM Stool symptoms score, mean (mean change) | | | |
| Baseline | 2.47 (-) | 2.56 (-) | 2.45 (-) |
| Week 4 | 2.10 (-0.37) | 1.83 (-0.74)*** | 1.75 (-0.67)*** |
| Week 12 | 2.08 (-0.40) | 1.75 (-0.78)*** | 1.69 (-0.77)*** |
| PAC-SYM Abdominal symptoms score, mean (mean change) | | | |
| Baseline | 2.12 (-) | 2.20 (-) | 2.04 (-) |
| Week 4 | 1.81 (-0.31) | 1.47 (-0.73)*** | 1.31 (-0.72)*** |
| Week 12 | 1.72 (-0.40) | 1.53 (-0.66)* | 1.26 (-0.77)*** |
| PAC-SYM Rectal symptoms score, mean (mean change) | | | |
| Baseline | 1.29 (-) | 1.27 (-) | 1.20 (-) |
| Week 4 | 0.99 (-0.30) | 0.84 (-0.45)[§] | 0.69 (-0.51)** |
| Week 12 | 1.01 (-0.26) | 0.82 (-0.44)* | 0.67 (-0.54)*** |

Asterisks refer to differences with placebo. Levels of significance: § p≤0.10; * p≤0.05; ** p≤0.01; *** p≤0.001
PAC-SYM: Patient Assessment of Constipation – Symptoms questionnaire

**Study USA-11**

*Methods for Study USA-11*

Study USA-11 was identical in design to Study INT-6. The study was conducted at 38 sites in the US.

*Results for Study USA-11*

A total of 832 subjects were screened and out of these 628 were randomised and 620 received treatment: 207 received prucalopride 2 mg, 204 received prucalopride 4 mg and 209 received placebo. There were 545 (87.9%) females, 75 (12.1%) males and the age range was 18 to 85 years. The treatment groups were similar in demographic and baseline characteristics. Fifty subjects from two sites were excluded from the ITT population because of errors in the conduct of the study. The number (%) subjects included in the ITT analysis was 190 (91.8%) from the prucalopride 2 mg treated population, 187 (91.7%) from the prucalopride 4 mg population and 193 (92.3%) from the placebo group.

The efficacy results were similar to those for Study INT-6. For the primary efficacy outcome measure both prucalopride doses were superior to placebo. The number (proportion) achieving an average of ≥3 SCBM per week was 55 (28.9%) for prucalopride 2 mg, 54 (28.9%) for prucalopride 4 mg and 25 (13.0%) for placebo, p ≤0.001 (Table 24).

**Table 24. Summary of efficacy data from Study USA-11**

| ITT Population | PLA N=193 | PRU 2 mg N=190 | PRU 4 mg 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)*** |
| Weeks 1-4 | 19/193 (9.8) | 61/190 (32.1)*** | 70/187 (37.4)*** |
| 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)*** |
| Weeks 1-4 | 46/189 (24.3) | 100/177 (56.5)*** | 104/177 (58.8)*** |
| Number of patients with an average increase ≥1 SBM per week, n/N (%) | | | |
| Weeks 1-12 | 71/189 (37.6) | 132/177 (74.6)*** | 115/176 (65.3)*** |
| Weeks 1-4 | 87/189 (46.0) | 149/177 (84.2)*** | 142/177 (80.2)*** |
| Average SCBM per week, mean (mean change) | | | |
| Run-in | 0.4 (-) | 0.5 (-) | 0.5 (-) |
| Weeks 1-12 | 1.3 (0.8) | 2.3 (1.9)*** | 2.4 (1.9)*** |
| Weeks 1-4 | 1.1 (0.7) | 2.5 (2.1)*** | 2.8 (2.3)*** |
| Percentage of BM with normal consistency, mean (mean change) | | | |
| Run-in | 22.7 (-) | 23.8 (-) | 24.1 (-) |
| Weeks 1-12 | 35.1 (12.4) | 48.1 (23.5)*** | 47.6 (23.1)*** |
| Weeks 1-4 | 34.4 (11.8) | 44.9 (20.3)*** | 45.3 (20.9)*** |
| Percentage of BM with no straining, mean (mean change) | | | |
| Run-in | 23.4 (-) | 23.3 (-) | 21.1 (-) |
| Weeks 1-12 | 23.8 (0.0) | 23.1 (-0.7) | 24.6 (3.5) |
| Weeks 1-4 | 21.9 (-1.8) | 23.7 (-0.1) | 26.7 (5.4)* |
| Number of bisacodyl (Dulcolax®) tablets taken/week, mean (mean change) | | | |
| Run-in | 2.2 (-) | 1.9 (-) | 1.8 (-) |
| Weeks 1-12 | 2.0 (-0.0) | 0.9 (-1.1)*** | 1.1 (-0.7)*** |
| Weeks 1-4 | 1.9 (-0.2) | 0.9 (-1.1)*** | 0.9 (-0.9)*** |
| Number of days with laxative use (bisacodyl [Dulcolax®] or enema)/week, mean (mean change) | | | |
| Run-in | 1.0 (-) | 0.9 (-) | 0.8 (-) |
| Weeks 1-12 | 0.9 (-0.0) | 0.5 (-0.5)*** | 0.5 (-0.3)*** |
| Weeks 1-4 | 0.9 (-0.1) | 0.4 (-0.5)*** | 0.4 (-0.4)*** |
| Time to onset of first movement, median | | | |
| First SCBM after Day 1 dose, hh:mm | 297:00 | 32:30*** | 25:06*** |
| Number of patients rating treatment quite a bit or extremely effective, n/N (%) | | | |
| Week 4 | 21/175 (12.0) | 62/172 (36.0)*** | 66/172 (38.4)*** |
| Week 12 | 32/163 (19.6) | 53/155 (34.2)*** | 58/159 (36.5)*** |
| Patient assessment on constipation severity[a], mean (mean change) | | | |
| Baseline | 2.77 (-) | 2.65 (-) | 2.65 (-) |
| Week 4 | 2.38 (-0.36) | 1.69 (-0.97)*** | 1.60 (-1.05)*** |
| Week 12 | 2.26 (-0.45) | 1.82 (-0.81)*** | 1.89 (-0.78)** |

[a] None/absent=0; mild=1; moderate=2; severe=3; very severe=4

Table 24 continued on the next page.

**Table 24 continued. Summary of efficacy data from Study USA-11**

| ITT Population | PLA N=193 | PRU 2 mg N=190 | PRU 4 mg N=187 |
|---|---|---|---|
| Overall PAC-SYM symptoms score, mean (mean change) | | | |
| Baseline | 1.97 (-) | 1.93 (-) | 1.90 (-) |
| Week 4 | 1.57 (-0.38) | 1.26 (-0.65)*** | 1.22 (-0.71)*** |
| Week 12 | 1.49 (-0.46) | 1.26 (-0.63)* | 1.21 (-0.70)** |
| Improvement ≥1 overall PAC-SYM score from baseline, n/N (%) | | | |
| Week 4 | 26/172 (15.1) | 54/172 (31.4)*** | 59/169 (34.9)*** |
| Week 12 | 37/160 (23.1) | 48/154 (31.2) | 53/158 (33.5) |
| PAC-SYM Stool symptoms score, mean (mean change) | | | |
| Baseline | 2.52 (-) | 2.41 (-) | 2.53 (-) |
| Week 4 | 2.14 (-0.39) | 1.69 (-0.70)*** | 1.73 (-0.83)*** |
| Week 12 | 1.98 (-0.54) | 1.73 (-0.63) | 1.74 (-0.81)* |
| PAC-SYM Abdominal symptoms score, mean (mean change) | | | |
| Baseline | 1.98 (-) | 1.91 (-) | 1.77 (-) |
| Week 4 | 1.54 (-0.38) | 1.16 (-0.75)*** | 1.06 (-0.75)*** |
| Week 12 | 1.51 (-0.44) | 1.15 (-0.74)*** | 0.99 (-0.78)*** |
| PAC-SYM Rectal symptoms score, mean (mean change) | | | |
| Baseline | 1.02 (-) | 1.18 (-) | 1.01 (-) |
| Week 4 | 0.63 (-0.37) | 0.71 (-0.45) | 0.58 (-0.45) |
| Week 12 | 0.63 (-0.37) | 0.63 (-0.49) | 0.62 (-0.39) |

Asterisks refer to differences with placebo. Levels of significance: * p≤0.05; ** p≤0.01; *** p≤0.001
PAC-SYM: Patient Assessment of Constipation – Symptoms questionnaire

For the secondary outcome measures:

Prucalopride 2 mg and 4 mg resulted in a higher proportion of subjects with an increase of:

- ≥1 SCBM per week: 89 (50.3%) for 2 mg, 90 (51.1%) for 4 mg and 49 (25.9%) for placebo, p ≤0.001 (Table 24).
- ≥1 SBM per week: 132 (74.6%) for 2 mg, 115 (65.3%) for 4 mg and 71 (37.6%) for placebo, p ≤0.001.
- ≥1 BM per week: 110 (62.1%) of 177 subjects for 2 mg, 118 (67.0%) of 176 for 4 mg and 80 (42.3%) of 189 for placebo, p ≤0.001.

Prucalopride 2 mg and 4 mg resulted in

- a higher mean number of SCBM per week: mean (mean change) 2.3 (1.9) for prucalopride 2 mg, 2.4 (1.9) for prucalopride 4 mg and 1.3 (0.8) for placebo, p ≤0.001 (Table 24) and
- a higher percentage of stools with normal consistency: mean (mean change) 48.1 (23.5) for prucalopride 2 mg, 47.6 (23.1) for 4 mg and 35.1 (12.4) for placebo, p ≤0.001 (Table 24).

There was no significant difference between the treatment groups in percentage of BM with no straining. The average number of days per week with bisacodyl use was 0.5 for prucalopride 2 mg, 0.5 for prucalopride 4 mg and 0.9 for placebo, p ≤0.001. At Week 12, patient assessments of efficacy and severity were superior for prucalopride compared to placebo, p ≤0.01. There were significant differences at Week 12 for PAC-SYM total scores for both prucalopride doses, p ≤0.05; and also for PAC-SYM abdominal scores, p ≤0.001 (Table 24). PAC-QoL scores were superior for both prucalopride doses but there was no significant difference for SF-36, except for the SF-36 physical score for the 4 mg dose at 12 weeks, p ≤0.05.

**Study USA-13**

*Methods for Study USA-13*

Study USA-13 was identical in design to Study INT-6 and Study USA-11. The study was conducted at 41 sites in the US.

*Results for Study USA-13*

A total of 880 subjects were screened of which 651 were randomised and 641 received treatment: 214 received prucalopride 2 mg, 215 received 4 mg and 212 received placebo. All subjects that received treatment were included in the ITT population. There were 555 (86.6%) female subjects, 86 (13.4%) male and the age range was 18 to 95 years. The treatment groups were similar in demographic and baseline characteristics.

The efficacy results were similar to those for Study INT-6 and Study USA-11. For the primary efficacy outcome measure, both prucalopride 2 mg and 4 mg were superior to placebo. The number (proportion) achieving an average of ≥3 SCBM per week was 50 (23.9%) for prucalopride 2 mg, 48 (23.5%) for 4 mg and 25 (12.1%) for placebo, p ≤0.01.

For the secondary outcome measures:

Prucalopride 2 mg and 4 mg resulted in a higher proportion of subjects with an increase of:

- ≥1 SCBM per week: 89 (42.6%) for 2 mg, 95 (46.6%) for 4 mg and 57 (27.5%) for placebo, p ≤0.001.
- ≥1 SBM per week: 131 (62.7%) for 2 mg, 149 (73.0%) for 4 mg and 83 (40.1%) for placebo, p ≤0.001.
- ≥1 BM per week: 123 (58.9%) of 209 subjects for 2 mg, 132 (64.7%) of 204 for 4 mg and 83 (40.1%) of 207 for placebo, p ≤0.001.

Prucalopride 2 mg and 4 mg resulted in

- a higher mean number of SCBM per week: mean (mean change) 1.9 (1.5) for prucalopride 2 mg, 2.0 (1.5) for prucalopride 4 mg and 1.2 (0.8) for placebo, p ≤0.001 and
- a higher percentage of stools with normal consistency: 41.7 (19.5%) for prucalopride 2 mg, p≤0.01, 46.4 (20.1%) for 4 mg, p ≤0.001 and 35.7 (12.4%) for placebo.

There was a higher percentage of BM with no straining in the prucalopride groups: mean (mean change) 26.6 (3.9) for prucalopride 2 mg, 27.3 (1.2) for 4 mg and 19.0 (-1.4) for placebo, p ≤0.01. At Week 12, patient assessments of efficacy and severity were generally superior and there were lower scores for PAC-SYM for both prucalopride doses compared to placebo, except for the rectal symptoms score. PAC-QoL scores were superior for both prucalopride doses but there was no significant difference for SF-36, except for the SR-36 mental status score for prucalopride in comparison with placebo, p ≤0.05. The average number of days per week with bisacodyl use was 0.6 for prucalopride 2 mg, p ≤0.05, 0.5 for prucalopride 4 mg, p ≤0.001 and 0.7 for placebo.

**Study USA-25**

*Methods for Study USA-25*

Study USA-25 was a multicentre, parallel group, two phase study (a two week drug free run-in phase was followed by a randomised, four week, double blind, placebo controlled treatment phase) in order to compare dose titration to prucalopride 4 mg with fixed dose prucalopride 4 mg. The study was conducted at 13 centres in the US.

The inclusion and exclusion criteria were the same as for Study INT-6, USA-11 and USA-13.

The study treatments were:

1. Prucalopride commenced at a dose of 1 mg and titrated to a maximum dose of 4 mg with two day intervals between dose increments of 1 mg.
2. Prucalopride 4 mg fixed dose.
3. Placebo

Treatments were administered PO once daily prior to breakfast. Treatment allocation was according to a pre prepared randomisation code.

The primary efficacy outcome measure was the proportion (%) of patients with an average ≥3 SCBM/week. The secondary efficacy outcome measures were:

- Proportion (%) of patients with an average increase of >1 SCBM/week.

- Average number of SCBM/week.
- Average number of SBM/week.
- Average number of all BM/week.
- Consistency per BM.
- Straining per BM.
- BM with a sensation of complete evacuation per week.
- Bisacodyl (Dulcolax®) tablets/enema used per week.
- Time to first BM, SBM and SCBM after intake of the study medication on Day 1.
- Patient's Global Assessment on efficacy of treatment (5 point scales; 0=none, 4=extremely effective)
- Patient's Global Assessment on severity of constipation (5 point scales; 0=none, 4=very severe)
- Patient's symptom assessment on all of the 12 items within the PAC-SYM (5 point scales; 0=none, 4=very severe) (PAC-SYM total score);
- Patient's symptom assessment on the 3 PAC-SYM subscales: stool symptoms (5 items), abdominal symptoms (4 items) and rectal symptoms (3 items)
- Patient's assessment of severity on each of the 12 items within the PAC-SYM (5-point scales; 0=none, 4=very severe)

The safety outcome measures were AEs, laboratory tests, vital signs and ECGs.

### *Statistical Issues for Study USA-25*

Hypothesis tests were performed using paired t test, ANOVA, Holm's stepwise procedure, Dunnett's test, Cochran-Mantel-Haenszel test, Kaplan-Meier curves, log rank test, Van Elteren test, Pearson correlation, Cronbach's alpha and Fisher's exact test.

The sample size calculation was based on AE rates as the outcome measure. Assuming 5% versus 20% difference in AE incidence rates during the first week, a sample size of 93 randomised patients per treatment group would provide 90% power to detect a with a significance level of 5%. Assuming that 5% of patients will discontinue before completing the first week of the study, 98 randomised patients per treatment group were required.

### *Results for Study USA-25*

A total of 755 subjects were screened and of these some 347 were randomised and 342 received treatment: 113 in the titrated group, 112 in the 4 mg group and 117 in the placebo group. All the treated subjects were included in the ITT population. There were 293 (85.7%) females, 49 (14.3%) males and the age range was 18 to 85 years. The treatment groups were similar in demographic and baseline characteristics.

For the primary efficacy outcome measure, both titrated prucalopride and prucalopride 4 mg fixed dose were superior to placebo. The number (proportion) achieving an average of ≥3 SCBM per week was 46 (42.2%) for titrated, 36 (34.6%) for 4 mg and 15 (12.9%) for placebo, p ≤0.001.

For the secondary outcome measures:

Prucalopride titrated and 4 mg resulted in a higher proportion of subjects with an increase of:

- ≥1 SCBM per week: 66 (60.6%) for titrated, p ≤0.001, 53 (51.0%) for 4 mg, p ≤0.05 and 40 (34.5%) for placebo.
- ≥1 SBM per week: 83 (76.1%) for titrated, 71 (68.3%) for 4 mg and 53 (45.7%) for placebo, p ≤0.001.
- ≥1 BM per week: 80 (73.4%) of 109 subjects for titrated, 68 (65.4%) of 104 for 4 mg and 47 (40.5%) of 116 for placebo, p ≤0.001.

Prucalopride titrated and 4 mg fixed dose resulted in a higher mean number of SCBM per week: mean (mean change) 3.0 (2.4) for titrated prucalopride, 2.7 (2.1) for prucalopride 4 mg fixed dose and 1.3 (0.8) for placebo, p ≤0.001. There was no significant difference between placebo and titrated prucalopride or prucalopride 4 mg fixed dose in percentage of stools with normal consistency. There was a higher percentage of BM with no straining in the prucalopride groups: mean (mean change) 29.3 (13.3) for titrated prucalopride, p ≤0.001, 28.4 (6.4) for 4 mg fixed dose, p ≤0.05 and 21.0 (1.5) for placebo. The time to onset of first SCBM was shorter in the prucalopride

groups. Compared to placebo, prucalopride patient assessments of efficacy and severity were superior and there were generally lower scores for PAC-SYM for both prucalopride regimens except for the rectal symptoms score for prucalopride 4 mg.

**Study USA-28**

*Methods for Study USA-28*

Study USA-28 was a multicentre, randomised, parallel-group, two-period, double blind, placebo controlled study (two week drug free run in phase was followed by a randomised, four week, double blind, placebo controlled treatment phase, a drug free washout period of at least 2 weeks and a second four week double blind treatment period) in order to test the efficacy of prucalopride with re treatment. The study was conducted at 33 centres in the US.

The inclusion and exclusion criteria were the same as for Study INT-6, USA-11, USA-13 and USA-25.

The study treatments were:

1. Prucalopride 4 mg
2. Placebo

Treatments were administered PO once daily. If the patient did not have had a bowel movement for 3 or more consecutive days, bisacodyl (Dulcolax®) was allowed as rescue medication

The efficacy and safety outcome measures were the same as for Study USA-25.

*Statistical Issues for Study USA-28*

Hypothesis tests were performed at the end of both Phase I and Phase II using the paired t test, ANOVA, ANCOVA, Cochran- Mantel-Haenszel test, log rank test and Van Elteren tests.

The sample size calculation was performed for the primary efficacy outcome measure. Based on results from previous studies (Studies INT-6, USA-11 and USA-13), the response rate was taken to be 15% for the placebo group and 30% for prucalopride 4 mg. To have a power of 90% and two sided Type I error rate of 5%, 159 randomised patients per treatment group with data in the second treatment period were required. Since prucalopride had to be superior to placebo at both time points, no adjustment for multiplicity was necessary. Assuming a discontinuation rate prior to the start of the second treatment period of 15% and that 75% of patients would re qualify as being constipated at the end of the washout period, 250 (=159/.85/.75) patients per treatment group were required.

*Results for Study USA-28*

A total of 719 subjects were screened of which 516 were randomised and 510 received treatment: 253 received prucalopride 4 mg and 257 received placebo. There were 228 subjects in the prucalopride group and 242 in the placebo at the beginning of Phase II; 203 subjects in the prucalopride and 214 subjects in the placebo completed. In the treated population there were 456 (89.4%) females, 54 (10.6%) males and the age range was 18 to 89 years. The treatment groups were similar in demographic and baseline characteristics.

**For the primary efficacy outcome measure, prucalopride 4 mg was superior to placebo at the end of the both treatment phases (Table 25). The number (proportion) achieving an average of ≥3 SCBM per week for Phase II was 68 (36.0%) for prucalopride 4 mg and 23 (11.2%) for placebo, p ≤0.001 (Table 25). Table 25. Summary of efficacy data from Study USA-28**

| EA Population | PLA | | PRU 4 mg | |
|---|---|---|---|---|
| | Treatment I N=205 | Treatment II N=205 | Treatment I N=189 | Treatment II N=189 |
| Number of patients with an average ≥3 SCBM per week, n/N (%) | | | | |
| Run-in/washout | 0/205 (0) | 1/203 (0.5) | 1/189 (0.5) | 0/189 (0) |
| Weeks 1-4 | 22/205 (10.7) | 23/205 (11.2) | 73/189 (38.6)*** | 68/189 (36.0)*** |
| Number of patients with an average increase ≥1 SCBM per week, n/N (%) | | | | |
| Weeks 1-4 vs. run-in | 47/205 (22.9) | 55/205 (26.8) | 114/189 (60.3)*** | 96/189 (50.8)*** |
| Weeks 1-4 vs. washout | - | 45/205 (22.0) | - | 97/189 (51.3)*** |
| Number of patients with an average increase ≥1 SBM per week, n/N (%) | | | | |
| Weeks 1-4 vs. run-in | 80/205 (39.0) | 85/205 (41.5) | 157/189 (83.1)*** | 129/189 (68.3)*** |
| Weeks 1-4 vs. washout | - | 68/205 (33.2) | - | 136/189 (72.0)*** |
| Average SCBM per week, mean (mean change) | | | | |
| Run-in/washout | 0.4 (-) | 0.4 (-) | 0.5 (-) | 0.4 (-) |
| Weeks 1-4 vs. run-in | 1.0 (0.6) | 1.1 (0.7) | 2.8 (2.3)*** | 2.5 (2.0)*** |
| Weeks 1-4 vs. washout | - | 1.1 (0.6) | - | 2.5 (2.1)*** |
| Percentage of BM with normal consistency, mean (mean change) | | | | |
| Run-in/washout | 24.6 (-) | 28.5 (-) | 21.2 (-) | 26.7 (-) |
| Weeks 1-4 | 34.0 (9.4) | 37.8 (8.7) | 43.5 (22.3)*** | 44.6 (17.9)*** |
| Percentage of BM with no straining, mean (mean change) | | | | |
| Run-in/washout | 22.2 (-) | 18.2 (-) | 21.6 (-) | 22.0 (-) |
| Weeks 1-4 | 21.5 (-0.7) | 20.7 (2.7) | 28.4 (6.8)*** | 24.0 (2.1) |
| Time to onset of first movement, median; hh:mm | | | | |
| First SCBM after Day 1 dose | 383:00 | 315:00 | 22:40*** | 57:00*** |
| Average bisacodyl (Dulcolax®) tablets per week, mean (mean change) | | | | |
| Run-in/washout | 1.8 (-) | 2.0 (-) | 1.8 (-) | 2.2 (-) |
| Weeks 1-4 | 1.8 (0.0) | 1.8 (-0.3) | 0.8 (-1.0)*** | 1.0 (-1.1)*** |
| Number of patients rating treatment quite a bit or extremely effective, n/N (%) | | | | |
| Week 4 | 29/205 (14.1) | 23/192 (12.0) | 77/188 (41.0)*** | 78/186 (41.9)*** |
| Patient assessment on constipation severity[a], mean (mean change) | | | | |
| Baseline I/II | 2.68 (-) | 2.71 (-) | 2.80 (-) | 2.88 (-) |
| Week 4 | 2.46 (-0.21) | 2.28 (-0.45) | 1.64 (-1.16)*** | 1.83 (-1.05)*** |
| Overall PAC-SYM symptoms score, mean (mean change) | | | | |
| Baseline I/II | 1.94 (-) | 1.75 (-) | 1.96 (-) | 1.77 (-) |
| Week 4 | 1.52 (-0.41) | 1.48 (-0.29) | 1.12 (-0.83)*** | 1.14 (-0.64)*** |
| Improvement ≥1 overall PAC-SYM score from baseline, n/N (%) | | | | |
| Week 4 | 41/205 (20.0) | 26/192 (13.5) | 80/187 (42.8)*** | 64/185 (34.6)*** |
| PAC-SYM Stool symptoms score, mean (mean change) | | | | |
| Baseline I/II | 2.46 (-) | 2.28 (-) | 2.41 (-) | 2.27 (-) |
| Week 4 | 2.06 (-0.40) | 2.02 (-0.29) | 1.54 (-0.87)*** | 1.59 (-0.68)*** |
| PAC-SYM Abdominal symptoms score, mean (mean change) | | | | |
| Baseline I/II | 1.89 (-) | 1.70 (-) | 1.95 (-) | 1.74 (-) |
| Week 4 | 1.47 (-0.42) | 1.37 (-0.35) | 1.00 (-0.95)*** | 1.01 (-0.75)*** |
| PAC-SYM Rectal symptoms score, mean (mean change) | | | | |
| Baseline I/II | 1.12 (-) | 0.92 (-) | 1.23 (-) | 1.01 (-) |
| Week 4 | 0.70 (-0.42) | 0.74 (-0.20) | 0.60 (-0.62) | 0.57 (-0.44)* |

Asterisks refer to differences with placebo. Levels of significance: * p≤0.05; *** p≤0.001
[a] None/absent=0; mild=1; moderate=2; severe=3; very severe=4
PAC-SYM: Patient Assessment of Constipation – Symptoms questionnaire

For the secondary outcome measures:

Prucalopride 4 mg resulted in a higher proportion of subjects with an increase of:

- ≥1 SCBM per week: 96 (50.8%) for prucalopride and 55 (26.8%) for placebo, p ≤0.001 (Table 25) and
- ≥1 SBM per week: 129 (68.3%) for prucalopride, 85 (41.5%) for placebo, p ≤0.001.
- ≥1 BM per week: 123 (65.1%) of 189 subjects for prucalopride and 69 (33.7%) of 205 for placebo, p ≤0.001.

Prucalopride 4 mg resulted in a higher mean number of SCBM per week: mean (mean change) 2.5 (2.0) for prucalopride and 1.1 (0.6) for placebo, p ≤0.001 (Table 25). The percentage of stools with normal consistency was higher in the prucalopride group: mean (mean change) 44.6 (17.9) for prucalopride and 37.8 (8.7) for placebo, p ≤0.001 (Table 25). There was no significant difference between the groups in the percentage of BM with no straining (Table 25). The time to onset of first SCBM was shorter in the prucalopride groups and there was less bisacodyl use (Table 25). Compared to placebo, patient assessments of efficacy and severity were superior and there were lower scores for PAC-SYM for prucalopride 4 mg (Table 25).

**Study INT-12**

*Methods for Study INT-12*

Study INT-12 was a multicentre, parallel group, two phase study (two week drug free run-in followed by a randomised four week, double blind, placebo controlled treatment phase) in elderly subjects with chronic constipation. The study was conducted at 48 centres in seven countries: Austria (2), Canada (9), Germany (7), The Netherlands (11), Norway (2) and South Africa (4) and UK (13).

The inclusion and exclusion criteria were the same as for Study INT-6, USA-11, USA-13, USA-25 and USA-28; except that the age criterion was ≥ 65 years of age and an additional exclusion criterion of:

- patients with the main complaint of abdominal pain.

The study treatments were:

1. Prucalopride 1 mg
2. Prucalopride 2 mg
3. Prucalopride 4 mg
4. Placebo

Treatment administration was PO once daily before breakfast. Treatment allocation was by pre prepared code. If the patient had not had a BM for three or more consecutive days throughout the study, he/she was allowed to take bisacodyl (Dulcolax®) as rescue medication.

The efficacy and safety outcome measures were the same as for INT-6, USA-11 and USA-13.

*Statistical Issues for Study INT-12*

Hypothesis tests were performed using paired t test, ANCOVA, Dunnett's test, Cochran-Mantel-Haenzel test, logistic regression, Kaplan-Meier curves, log rank test, Van Elteren test, Pearson correlation and Cronbach's alpha.

The sample size calculation was performed for the primary efficacy outcome measure. From Studies INT-1, INT-2 and USA-3 response rate was taken to be 15% for the placebo group, about 30% for the 2 mg prucalopride group and 50% for the 4 mg prucalopride group. To have a power of 80% with a two sided Type I error rate of 1.67% (taking account for 3 comparisons), a difference of 15% response on placebo and 40% on a prucalopride dose could be detected with 64 patients per treatment group.

*Results for Study INT-12*

A total of 461 subjects were screened and of these 303 were randomised and 303 received treatment. Three subjects in the 4 mg were not included in the ITT group because of early withdrawal leaving 300 subjects in the ITT group: 76 in the prucalopride 1 mg, 75 in the 2 mg, 79 in the 4 mg and 70 in the placebo group. In the treated group, there were 211 (69.6%) females, 92 (30.4%) males and the age range was 64 to 95 years. There was some imbalance in the gender

distribution of the treatment groups but apart from this the treatment groups were similar in demographic and baseline characteristics.

For the primary efficacy outcome measure, although the response rate for the prucalopride groups was approximately twice that for placebo, the difference was not statistically significant. The number (proportion) achieving an average of ≥3 SCBM per week was 30 (39.5%) for prucalopride 1 mg, 24 (32.0%) for prucalopride 2 mg, 25 (31.6%) for 4 mg and 14 (20.0%) for placebo.

Prucalopride 1 mg, 2 mg and 4 mg resulted in a higher proportion of subjects with an increase of ≥1 SCBM per week: 44 (61.1%) for 1 mg, 41 (56.9%) for 2 mg, 37 (50.7%) for 4 mg and 22 (33.8%) for placebo, p ≤0.05. There was no significant difference between the groups in the proportion of subjects with an increase of ≥1 SBM per week. The prucalopride 1 mg group had a higher proportion of subjects with an increase of ≥1 BM per week: 45 (62.5%) prucalopride 1 mg and 21 (32.3%) for placebo, p ≤0.05.

Prucalopride 1 mg, 2 mg and 4 mg resulted in a higher mean number of SCBM per week: mean (mean change) 2.7 (1.9) for prucalopride 1 mg, 2.4 (1.7) for prucalopride 2 mg, 2.4 (1.8) for prucalopride 4 mg and 1.7 (0.6) for placebo, p ≤0.05. There were a higher percentage of stools with normal consistency in the prucalopride 1 mg and 4 mg groups: 49.4 (16.4%) for prucalopride 1 mg and 37.1 (7.3%) for placebo, p ≤0.05 (46.7 (9.0%) for the 4 mg dose). There was a higher percentage of BM with no straining in the prucalopride groups: mean (mean change) 26.4 (7.8) for prucalopride 1 mg, 26.7 (7.0) for 4 mg and 13.9 (-4.7) for placebo, p ≤0.05.

At Week 12, patient assessments of efficacy and severity were superior and there were lower scores for PAC-SYM total scores and stool symptom scores for the prucalopride 1 mg and 4 mg doses as compared to placebo. Compared with placebo, PAC-QoL scores were superior for the prucalopride 1 mg dose (except for psychosocial discomfort score) p ≤0.05.

### Efficacy Data for Other Indications

The sponsor also provided reports from an additional 12 studies conducted for alternative indications in their current Australian submission. There were seven double blind placebo controlled trials of oral prucalopride:

- Study BEL-18: multiple sclerosis (MS)
- Study DEN-2: spinal cord injury
- Study GBR-7: chronic pseudo-obstruction
- Study USA-8: opioid induced constipation in cancer patients
- Study USA-14: opioid induced constipation in cancer patients
- Study INT-8: opioid induced constipation in non-cancer patients
- Study USA-27: opioid induced constipation

There were two long term open label follow on studies:

- Study INT-9 follow on from Studies DEN-2 and BEL-18
- Study INT-17 follow on from Studies INT-8 and INT-14

There were two studies of different formulations and indications:

- Study GER-1: IV prucalopride after major abdominal surgery
- Study USA-5: SC prucalopride after colonic surgery

There was one taste masking test:

- Study BEL 19

One study, Study INT-8 provided limited efficacy data relevant to the present application. Study INT-8 was a double blind, placebo controlled trial to evaluate the efficacy and safety of prucalopride in subjects with chronic non cancer pain, suffering from opioid induced constipation.

The study included:

- male or non-pregnant female at least 18 years of age;
- with opioid induced constipation;
- chronic pain of any aetiology except cancer pain;
- taking a minimum total daily dose of opioids;
- expected to stay on the same dose of opioids for at least 6 weeks;
- if taking laxatives, laxative use was stopped.

The study treatments were:

- Prucalopride 2 mg;
- Prucalopride 4 mg
- Placebo.

The study treatments were taken PO once daily for 4 weeks.

The outcome measures were:

- stool frequency,
- constipation symptoms,
- subject scales,
- Investigator Global Assessment,
- PAC-SYM
- PAC-QoL.

A total of 196 subjects were randomised: 66 to 2 mg, 64 to 4 mg and 66 to placebo. There were 120 females, 76 males and the age range was 21 to 86 years. In the 4 mg group there was no increase in the number of SCBM but there was an increase in BM frequency ($p < 0.05$) compared to placebo. There was a decrease in straining in the 4 mg group ($p < 0.05$). There was no significant difference for PAC-SYM, PAC-QoL or SF-36. The 2 mg dose was not significantly different to placebo.

### Evaluator's Overall Conclusions on Clinical Efficacy

In Study INT-1 and Study INT-2, both 1 mg and 2 mg taken once daily were superior to placebo with no difference between doses and no difference between once and twice daily dosing. These studies excluded the 0.5 mg dose level from further development. In Study USA-3 there was an increase in treatment effect up to the 4 mg dose level, statistically significant effects for the 2 mg and 4 mg dose levels but no significant difference noted at the 0.5 mg and 1 mg dose levels. Study BEL-6 investigated the 4 mg dose level and found statistically and clinically significant benefit compared to placebo.

Study GBR-4 found mean oro-caecal transit time was significantly shorter in the prucalopride 1 mg group compared with the placebo group and noted a statistically and clinically significant benefit for the 1 mg dose compared with placebo. Study USA-26 found no significant difference between prucalopride at doses up to 2 mg daily with placebo in subjects aged over 65 years but this study appears to have been underpowered.

Study INT-6, Study USA-11 and USA-13 demonstrated that both the 2 mg and 4 mg dose levels were superior to placebo but there was no apparent difference in efficacy between the dose levels. The studies were identical in design.

Study USA-25 indicated that titration of a treatment dose from 1 mg to 4 mg had no greater efficacy than commencing at 4 mg.

Study USA-28 demonstrated that prucalopride at the 4 mg dose level retained efficacy with retreatment (after a period of time without treatment).

Study INT-12 demonstrated that for subjects ≥65 years age, prucalopride 1 mg once daily was superior to placebo and there was no additional benefit of increasing this dose to 2 mg or 4 mg.

The current Australian submission did not contain convincing efficacy data for any indication other that chronic idiopathic constipation. The inclusion and exclusion criteria for the pivotal studies excluded subjects with constipation secondary to drugs or to any other medical condition.

The current Australian submission did not contain any data comparing prucalopride with any other active treatment. There were no comparator controlled Phase III efficacy studies. Hence, it is not known how effective prucalopride is in comparison with commonly used treatments for constipation. In addition, the current Australian submission did not contain any data with regard to prucalopride used in combination with other medical treatments for constipation.

The placebo controlled trials were up to 12 weeks in duration. Hence, long term efficacy of prucalopride has not been demonstrated in an appropriately designed study.

## Safety

### Introduction

Safety data were provided from the PK, PD, Phase II and Phase III studies. The safety data from the PK and PD studies were limited. The safety data from the Phase II and Phase III studies are more extensive and are discussed in the following sections.

In addition, there were eight studies included in the current Australian submission that reported data from open label follow on studies or open label open access schemes. There appeared to be a total of 2990 subjects in these studies but some subjects may have been included in more than one study. Follow up was predominantly for 24 months but a small number of subjects could have been followed up for up to 2 years.

The additional 12 studies performed for different indications/formulations contained some safety data but did not indicate any additional safety concerns.

### Patient Exposure

For the indication of chronic constipation, there were 2717 subjects exposed to prucalopride in Phase II and III double blind studies and 2595 exposed in open label long term follow up studies. A total of 71 subjects were exposed prucalopride for 90 days in the Phase II and III double blind studies. A further 869 subjects were exposed for one year in the open label follow up studies. More females than males have been exposed: a total of 2294 females and 301 males were exposed to prucalopride in the long term follow up studies, with exposure for one year in 782 females and 87 males. A total of 564 subjects aged 65 years and over were exposed to prucalopride in double blind randomised controlled trials. However few subjects with renal impairment and none with hepatic or cardiac impairment, were exposed to prucalopride during double blind placebo controlled trials.

### Adverse Events

#### Treatment Emergent AEs

In Study INT-1, treatment emergent AEs (TEAEs) were reported in 11 (25%) subjects in the placebo group, 11 (23.9%) subjects in the prucalopride 0.5 mg, 20 (46.5%) subjects in the 1.0 mg and 19 (47.5%) subjects in the 2.0 mg group. The frequency of abdominal pain, headache and diarrhoea increased with dose (Table 26). There were no between group differences in ECGs or vital signs.

**Table 26. Summary of safety data.**

| Safety (n=174) | Placebo (n=45) | | R093877 0.5 mg (n=46) | | R093877 1.0 mg (n=43) | | R093877 2.0 mg (n=40) | |
|---|---|---|---|---|---|---|---|---|
| Adverse events (AE): Nr. of patients for the most frequently reported AE's during the double-blind period: | | | | | | | | |
| - abdominal pain | 3 | | 1 | | 4 | | 10 | |
| - headache | 3 | | 2 | | 1 | | 7 | |
| - diarrhoea | 0 | | 0 | | 5 | | 2 | |
| - nausea | 1 | | 1 | | 3 | | 2 | |
| - vertigo | 2 | | 0 | | 1 | | 2 | |
| - viral infection | 3 | | 1 | | 0 | | 1 | |
| No. of patients (%) with one or more AE | 11 (25.0) | | 11 (23.9) | | 20 (46.5) | | 19 (47.5) | |
| No. (%) of deaths | 0 (0.0) | | 0 (0.0) | | 0 (0.0) | | 0 (0.0) | |
| No. of patients (%) with one or more other serious AE | 1 (2.2) | | 1 (2.2) | | 3 (7.0) | | 0 (0.0) | |
| No. of patients (%) treatment stopped due to AE | 1 (2.2) | | 3 (6.5) | | 3 (7.0) | | 5 (12.5) | |
| Clinical laboratory parameters | No consistent or clinically relevant changes | | | | | | | |
| Other safety observations<br>• Vital signs and physical findings | no intergroup differences | | | | | | | |
| | Bl | Wk4 | Bl | Wk4 | Bl | Wk4 | Bl | Wk4 |
| • ECG (QRS),ms | 80.5 | 80.5 | 83.5 | 82.0 | 79.7 | 80.3 | 77.8 | 83.0 |
| • Cardiovascular tests | | | | | | | | |
| - HR (mean baseline/week 4) (bpm) | 73.3 | 72.3 | 74.1 | 73.8 | 75.7 | 75.2 | 71.7 | 73.9 |
| - DBP(mean baseline/week 4) (mmHg) | 76.5 | 76.0 | 75.8 | 78.4 | 77.9 | 77.2 | 76.6 | 77.3 |
| - SBP (mean baseline/week 4) (mmHg) | 120.4 | 119.3 | 122.9 | 125.3 | 121.1 | 121.4 | 124.1 | 125.8 |

In Study INT-2, TEAEs were reported in 25 (41%) subjects in the placebo group, 32 (49%) subjects in the prucalopride 0.5 mg bd, 40 (65%) subjects in the 1.0 mg bd and 41 (68%) subjects in the 2.0 mg bd (Table 27). Headache was reported more frequently in the prucalopride groups: three (4.9%) placebo subjects, ten (15.4%) prucalopride 0.5 mg bd subjects, eight (12.9%) 1.0 mg bd subjects and seven (11.7%) 2.0 mg bd subjects. There were no significant changes in ECG parameters or vital signs.

**Table 27. Summary of safety data from Study INT-2**

| **Safety**<br>(n = number of subjects with data) | Placebo<br>b.i.d.<br>(n= 63) | R093877<br>0.5mg<br>b.i.d.<br>(n= 67) | R093877<br>1mg<br>b.i.d.<br>(n= 62) | R093877<br>2mg<br>b.i.d.<br>(n= 61) |
|---|---|---|---|---|
| **Adverse events (AE)**<br>Most frequently reported AE during treatment | | | | |
| • headache | 4.9% | 15.4% | 12.9% | 11.7% |
| • abdominal pain | 8.2% | 1.5% | 16.1% | 18.3% |
| • nausea | 4.9% | 9.2% | 11.3% | 13.3% |
| • diarrhoea | 3.3% | 3.1% | 8.1% | 13.3% |
| • viral infection | 3.3% | 7.7% | 6.5% | 3.3% |
| No. (%) with one or more AE during treatment | 25 (41) | 32 (49) | 40 (65) | 41 (68) |
| No. of deaths | 0 | 0 | 0 | 0 |
| No.with one or more other serious AE | 2 | 3 | 6 | 3 |
| No. treatment stopped due to AE | 0 | 3 | 6 | 7 |
| **Clinical laboratory parameters** | no clinically relevant changes | | | |
| **Vital signs and physical findings** | no clinically relevant changes | | | |
| **ECG and cardiovascular parameters** | | | | |
| • ECG ($BL/EP_{12}$), (QRS-interval), mean, ms | 83.4/83.0 | 84.9/79.7 | 84.6/75.3 | 77.6/81.5 |
| • HR ($BL/EP_{12}$), mean, bpm | 73.7/70.9 | 71.4/71.0 | 71.0/72.6 | 71.5/69.4 |
| • DBP ($BL/EP_{12}$), mean, mmHg | 75.6/77.2 | 73.9/73.3 | 76.2/78.1 | 76.0/75.1 |
| • SBP ($BL/EP_{12}$), mean, mmHg | 120.8/121.4 | 118.2/119.8 | 119.7/122.4 | 120.0/116.7 |

In Study USA-3, TEAEs were reported in 37 (80%) subjects in the placebo group, 27 (63%) subjects in the 0.5 mg group, 40 (83%) subjects in the 1 mg group, 37 (77%) subjects in the 2 mg group and 37 (80%) subjects in the 4 mg group. The most frequently reported AEs were abdominal pain, diarrhoea, nausea and headache (Table 28).

**Table 28. Summary of safety data from Study USA-2**

| Safety | Placebo (n=46) | R093877 0.5 mg (n=43) | R093877 1 mg (n=48) | R093877 2 mg (n=48) | R093877 4 mg (n=46) |
|---|---|---|---|---|---|
| **Adverse events (AE)** | | | | | |
| Most frequently reported AE (≥10%): | | | | | |
| Abdominal pain (n [%]) | 12 (26) | 10 (23) | 13 (27) | 14 (29) | 15 (33) |
| Diarrhoea | 0 | 4 (9) | 6 (13) | 10 (21) | 11 (24) |
| Nausea | 4 (9) | 3 (7) | 7 (15) | 13 (27) | 10(22) |
| Headache | 8 (17) | 5 (12) | 9 (19) | 9 (19) | 9 (20) |
| Flatulence | 13 (28) | 3 (7) | 4 (8) | 7 (15) | 7 (15) |
| Vomiting | 0 | 3 (7) | 1 (2) | 5 (10) | 4 (9) |
| Constipation | 5 (11) | 2 (5) | 2 (4) | 7 (15) | 2 (4) |
| Sinusitis | 3 (7) | 3 (7) | 5 (10) | 2 (4) | 2 (4) |
| No. (%) with one or more AE: | 37 (80) | 27 (63) | 40 (83) | 37 (77) | 37 (80) |
| No. (%) of deaths: | 0 | 0 | 0 | 0 | 0 |
| No. (%) with one or more other serious AE: | 1 (2) | 0 | 1 (2) | 0 | 0 |
| No. (%) treatment stopped due to AE: | 0 | 0 | 3 (6) | 2 (4) | 6 (13) |
| • Laboratory tests | No treatment-related effect on any clinical chemistry value was observed. Mean cholesterol levels were slightly elevated in the R093877 0.5-mg dose at the end of Weeks 2 and 4 of the double-blind phase, compared to baseline. No clinically relevant trend was observed in any haematology parameter. | | | | |
| •Vital signs | Pulse rates were significantly increased in the R093877 2-mg and 4-mg groups, compared to placebo, at the end of the DB phase and at the end of the trial. Neither these changes nor other changes in vital signs were clinically significant. | | | | |
| • ECG | Compared with placebo, mean RR-interval values decreased for all R093877 groups at the end of Week 2 of the double-blind phase and at endpoint which were not considered clinically relevant. Additionally, there were no other clinically relevant trends observed. | | | | |

In Study BEL-6, TEAEs were reported in 24 (88.9%) subjects in the prucalopride 4 mg group and 12 (46.2%) subjects in the placebo group (Table 29). In the prucalopride 4 mg group, headache, nausea, palpitations and abdominal pain were reported more frequently than in the placebo (Table 30).

**Table 29. Summary of safety data from study BEL-6**

| **Safety** (intent-to-treat population, n=53) | R093877 (n=27) | | Placebo (n=26) | |
|---|---|---|---|---|
| Most frequently reported adverse events (AE) during treatment (N (%)): | | | | |
| - headache | 14 (51.9) | | 5 (19.2) | |
| - nausea | 11 (40.7) | | 2 (7.7) | |
| No. of patients (%) with one or more AE | 24 (88.9) | | 12 (46.2) | |
| No. (%) of deaths | 0 | | 0 | |
| No. (%) with one or more other serious AE | 0 | | 0 | |
| No. (%) treatment stopped due to AE | 3 | | 0 | |
| Clinical laboratory parameters | No consistent or clinically relevant changes | | | |
| Other safety observations | | | | |
| • Vital signs and physical findings | no intergroup differences | | | |
| • ECG (QRS),ms | no intergroup differences | | | |
| • Cardiovascular tests (mean) | Baseline | End point | Baseline | End point |
| - HR | 79.3 | 78.6* | 73.6 | 72.7 |
| - DBP | 80.2 | 78.2 | 78.9 | 76.1 |
| - SBP | 122.3 | 119.2 | 115.6 | 115.0 |

Asterisks refer to differences with placebo. Levels of significance: * $p \leq 0.05$; ** $p \leq 0.01$, *** $p \leq 0.001$

**Table 30. Most frequent AEs**

| | | Treatment | | | |
|---|---|---|---|---|---|
| | | Placebo | | R093877 | |
| | **Adverse event** | **N** | **%** | **N** | **%** |
| 1 | **Headache** | 5 | 19.2 | 14 | 51.9 |
| 2 | **Nausea** | 2 | 7.7 | 11 | 40.7 |
| 3 | **Palpitation** | 0 | 0 | 5 | 18.5 |
| 4 | **Abdominal pain** | 3 | 11.5 | 5 | 18.5 |
| 5 | **Micturition frequency** | 1 | 3.8 | 4 | 14.8 |
| | **Fatigue** | 1 | 3.8 | 4 | 14.8 |
| | **Diarrhoea** | 0 | 0 | 4 | 14.8 |
| | **Anorexia** | 0 | 0 | 4 | 14.8 |

In Study GBR-4, TEAEs were reported in 30 (76.9%) subjects in the prucalopride 1 mg group and 25 (65.8%) subjects in the placebo (Table 31). As with previous studies, headache, abdominal pain, nausea and flatulence were the most common AEs. Dysmenorrhoea occurred more frequently in the prucalopride 1 mg group (four (10.3%) subjects) compared with placebo, one (2.6%).

**Table 31.Adverse events reported in ≥10% of the subjects in any group**

| | Pla (n=38) | Pru (n=39) |
|---|---|---|
| **WHO-system organ class**<br>WHO-preferred term | | |
| Total no. (%) with adverse event | 25 (65.8) | 30 (76.9) |
| **Gastro-intestinal system disorders** | **16 (42.1)** | **23 (59.0)** |
| abdominal pain | 16 (42.1) | 13 (33.3) |
| nausea | 6 (15.8) | 8 (20.5) |
| flatulence | 4 (10.5) | 8 (20.5) |
| diarrhoea | 0 (0) | 4 (10.3) |
| **Centr. & periph. nervous system** | **16 (42.1)** | **20 (51.3)** |
| headache | 16 (42.1) | 19 (48.7) |
| dizziness | 1 (2.6) | 5 (12.8) |
| **Body as a whole – general disorders** | **8 (21.1)** | **9 (23.1)** |
| back pain | 5 (13.2) | 5 (12.8) |
| **Reproductive disorders, female** | **2 (5.3)** | **6 (15.4)** |
| dysmenorrhoea | 1 (2.6) | 4 (10.3) |

In Study USA-26, TEAEs were reported in 9 (50.0%) subjects in the placebo group, 18 (85.7%) subjects in the prucalopride 0.5 mg, 17 (70.8%) subjects in the 1 mg and 18 (69.2%) subjects in the 2 mg. The proportion of subjects with diarrhoea increased with dose (Table 32). Headache was not as prominent as an AE as in previous studies.

**Table 32. AEs for Study USA-26**

| WHO system organ class [a,b]<br>WHO preferred term[c] | PLA<br>N=18 | PRU 0.5 mg<br>N=21 | PRU 1 mg<br>N=24 | PRU 2 mg<br>N=26 |
|---|---|---|---|---|
| Total no. patients with AE(s), n (%) | 9 (50.0) | 18 (85.7) | 17 (70.8) | 18 (69.2) |
| Gastro-intestinal system disorders | 5 (27.8) | 6 (28.6) | 8 (33.3) | 9 (34.6) |
| Diarrhoea | 0 | 1 (4.8) | 3 (12.5) | 4 (15.4) |
| Nausea | 0 | 2 (9.5) | 2 (8.3) | 2 (7.7) |
| Vomiting | 1 (5.6) | 1 (4.8) | 2 (8.3) | 2 (7.7) |
| Melaena | 1 (5.6) | 1 (4.8) | 1 (4.2) | 2 (7.7) |
| Flatulence | 0 | 0 | 0 | 2 (7.7) |
| Abdominal pain | 2 (11.1) | 0 | 2 (8.3) | 0 |
| Dyspepsia | 0 | 2 (9.5) | 0 | 0 |
| Haemorrhoids | 0 | 0 | 0 | 2 (7.7) |
| Urinary system disorders | 3 (16.7) | 8 (38.1) | 4 (16.7) | 3 (11.5) |
| Urinary tract infection | 3 (16.7) | 7 (33.3) | 1 (4.2) | 1 (3.8) |
| Pyuria | 0 | 0 | 0 | 2 (7.7) |
| Body as a whole - general disorders | 2 (11.1) | 3 (14.3) | 6 (25.0) | 1 (3.8) |
| Injury | 1 (5.6) | 1 (4.8) | 4 (16.7) | 0 |
| Central & periph nervous system disorders | 1 (5.6) | 5 (23.8) | 1 (4.2) | 3 (11.5) |
| Headache | 0 | 3 (14.3) | 0 | 1 (3.8) |
| Respiratory system disorders | 2 (11.1) | 1 (4.8) | 4 (16.7) | 3 (11.5) |
| Rhinitis | 0 | 1 (4.8) | 2 (8.3) | 1 (3.8) |
| Coughing | 1 (5.6) | 0 | 2 (8.3) | 1 (3.8) |
| Bronchitis | 0 | 0 | 2 (8.3) | 1 (3.8) |
| Metabolic and nutritional disorders | 1 (5.6) | 0 | 2 (8.3) | 5 (19.2) |
| Cachexia | 0 | 0 | 1 (4.2) | 2 (7.7) |
| Prealbumin decreased | 0 | 0 | 0 | 2 (7.7) |
| Skin and appendages disorders | 0 | 2 (9.5) | 4 (16.7) | 1 (3.8) |
| Skin ulceration | 0 | 2 (9.5) | 1 (4.2) | 0 |
| Psychiatric disorders | 2 (11.1) | 0 | 5 (20.8) | 1 (3.8) |
| Confusion | 0 | 0 | 2 (8.3) | 0 |
| HR and rhythm disorders | 0 | 1 (4.8) | 3 (12.5) | 1 (3.8) |
| Tachycardia | 0 | 0 | 2 (8.3) | 1 (3.8) |
| Platelet, bleeding & clotting disorders | 1 (5.6) | 3 (14.3) | 1 (4.2) | 1 (3.8) |
| Secondary terms | 1 (5.6) | 1 (4.8) | 3 (12.5) | 1 (3.8) |
| Fall | 1 (5.6) | 1 (4.8) | 3 (12.5) | 1 (3.8) |
| Red blood cell disorders | 0 | 0 | 0 | 4 (15.4) |
| Anaemia | 0 | 0 | 0 | 4 (15.4) |

N= number of patients with data; n= number of patients with event
[a] AEs reported at any time during treatment or within 5 days of end of treatment
[b] System organ class with frequency >10% in any prucalopride group
[c] Preferred term with frequency >5% in any prucalopride group

In Study INT-6, TEAEs were reported in 170 (71.4%) subjects in the prucalopride 2 mg, 178 (74.8%) subjects in the prucalopride 4 mg and 161 (67.1%) subjects in the placebo. There was a higher rate of headache, nausea, abdominal pain and diarrhoea in the prucalopride groups (Table 33).

**Table 33. Treatment-Emergent Adverse Events Reported by at Least 2.5% of Patients in any Prucalopride Treatment Group. All (Treated) Subjects Population**

| WHO system organ class<br>WHO preferred term | PLA<br>N=240 | PRU 2 mg<br>N=238 | PRU 4 mg<br>N=238 |
|---|---|---|---|
| Total no. of patients with AEs[a], n (%) | 161 (67.1) | 170 (71.4)[b] | 178 (74.8) |
| Gastro-intestinal system disorders | 95 (39.6) | 110 (46.2) | 120 (50.4) |
| Nausea | 34 (14.2) | 57 (23.9) | 56 (23.5) |
| Abdominal pain | 41 (17.1) | 55 (23.1) | 44 (18.5) |
| Diarrhoea | 13 (5.4) | 31 (13.0) | 30 (12.6) |
| Flatulence | 18 (7.5) | 21 (8.8) | 18 (7.6) |
| Vomiting | 11 (4.6) | 11 (4.6) | 17 (7.1) |
| Dyspepsia | 10 (4.2) | 11 (4.6) | 11 (4.6) |
| Haemorrhage rectum | 5 (2.1) | 5 (2.1) | 9 (3.8) |
| Gastroenteritis | 1 (0.4) | 2 (0.8) | 6 (2.5) |
| Centr & periph nervous system disorders | 49 (20.4) | 72 (30.3) | 89 (37.4) |
| Headache | 40 (16.7) | 62 (26.1) | 71 (29.8) |
| Dizziness | 4 (1.7) | 12 (5.0) | 11 (4.6) |
| Body as a whole - general disorders | 43 (17.9) | 40 (16.8) | 59 (24.8) |
| Fatigue | 6 (2.5) | 12 (5.0) | 14 (5.9) |
| Back pain | 6 (2.5) | 7 (2.9) | 11 (4.6) |
| Malaise | 5 (2.1) | 3 (1.3) | 11 (4.6) |
| Influenza-like symptoms | 5 (2.1) | 5 (2.1) | 8 (3.4) |
| Fever | 0 | 6 (2.5) | 5 (2.1) |
| Respiratory system disorders | 34 (14.2) | 26 (10.9) | 26 (10.9) |
| Sinusitis | 3 (1.3) | 4 (1.7) | 6 (2.5) |
| Pharyngitis | 8 (3.3) | 6 (2.5) | 4 (1.7) |
| Bronchitis | 4 (1.7) | 6 (2.5) | 2 (0.8) |
| Resistance mechanism disorders | 35 (14.6) | 28 (11.8) | 19 (8.0) |
| Infection viral | 28 (11.7) | 21 (8.8) | 14 (5.9) |
| Psychiatric disorders | 15 (6.3) | 15 (6.3) | 22 (9.2) |
| Anorexia | 3 (1.3) | 5 (2.1) | 6 (2.5) |
| Skin and appendages disorders | 10 (4.2) | 17 (7.1)[b] | 18 (7.6) |
| Rash | 2 (0.8) | 6 (2.5) | 5 (2.1) |
| Urinary system disorders | 10 (4.2) | 17 (7.1) | 16 (6.7) |
| Micturition frequency | 0 | 5 (2.1) | 7 (2.9) |
| Metabolic and nutritional disorders | 13 (5.4) | 13 (5.5) | 17 (7.1) |
| Hypercholesterolaemia | 0 | 1 (0.4) | 6 (2.5) |
| Musculo-skeletal system disorders | 10 (4.2) | 14 (5.9) | 10 (4.2) |
| Myalgia | 4 (1.7) | 7 (2.9) | 3 (1.3) |
| Heart rate and rhythm disorders | 7 (2.9) | 6 (2.5) | 17 (7.1) |
| Palpitation | 2 (0.8) | 1 (0.4) | 10 (4.2) |
| Reproductive disorders, female | 9 (3.8) | 10 (4.2) | 6 (2.5) |
| Cardiovascular disorders, general | 7 (2.9) | 4 (1.7) | 8 (3.4) |
| Vision disorders | 3 (1.3) | 4 (1.7) | 8 (3.4) |

In Study USA-11, TEAEs were reported in 166 (80.2%) subjects in the prucalopride 2 mg group, 160 (78.4%) subjects in the 4 mg group and 149 (71.3%) subjects in the placebo. Headache, nausea, diarrhoea, dizziness and vomiting occurred more frequently in the prucalopride groups and influenza like symptoms occurred more frequently in the prucalopride 4 mg group. Dysmennorrhoea was reported in three (1.4%) subjects in the prucalopride 2 mg group, two (1.0%) subjects in the 4 mg and none in the placebo.

In Study USA-13, TEAEs were reported in 173 (80.8%) subjects in the prucalopride 2 mg group, 163 (75.8%) subjects in the 4 mg and 140 (66.0%) subjects in the placebo. Compared to placebo,

there was a higher rate of headaches, nausea, abdominal pain, diarrhoea, flatulence and vomiting in the prucalopride groups.

In Study USA-25, TEAEs were reported in 64 (56.6%) subjects in the titrated prucalopride group, 59 (52.7%) subjects in the fixed 4 mg and 51 (43.6%) subjects in the placebo group. Abdominal pain, headache, nausea, diarrhoea and flatulence were more common in the prucalopride groups. There was also a higher rate of female reproductive disorders: four (3.5%) subjects in the titrated group, two (1.8%) subjects in the 4 mg compared to none in the placebo (Table 34).

**Table 34. Female reproductive AEs**

| | | | |
|---|---|---|---|
| REPRODUCTIVE DISORDERS, FEMALE | 0 ( 0.0) | 4 ( 3.5) | 2 ( 1.8) |
| AMENORRHOEA | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) |
| MENORRHAGIA | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.9) |
| DYSMENORRHOEA | 0 ( 0.0) | 1 ( 0.9) | 0 ( 0.0) |
| INTERMENSTRUAL BLEEDING | 0 ( 0.0) | 1 ( 0.9) | 0 ( 0.0) |
| MENOPAUSAL SYMPTOMS | 0 ( 0.0) | 1 ( 0.9) | 0 ( 0.0) |
| VAGINITIS | 0 ( 0.0) | 1 ( 0.9) | 0 ( 0.0) |

In Study USA-28, during treatment Phase I, TEAEs were reported in 170 (67.2%) subjects in the prucalopride 4 mg group and 129 (50.2%) subjects in the placebo group. During treatment Phase II, TEAEs were reported in 92 (44.9%) subjects in the prucalopride 4 mg group and 85 (38.1%) subjects in the placebo group. Headache, nausea, abdominal pain and diarrhoea were more common in the prucalopride group than the placebo group but the incidence of these events decreased in the second treatment phase

In Study INT-12 TEAEs were reported in 37 (48.7%) subjects in the prucalopride 1 mg, 29 (38.7%) subjects in the 2 mg, 38 (47.5%) subjects in the 4 mg and 32 (44.4%) subjects in the placebo group. Although abdominal pain, headache, diarrhoea and nausea were more common in the prucalopride groups, the incidence was less than that observed in the studies in the general population (Table 35).

**Table 35.Treatment-Emergent Adverse Events Reported by at Least 5.0% of Patients in any Prucalopride Treatment Group**

| WHO system organ class<br>WHO preferred term | PLA<br>N=72 | PRU 1 mg<br>N=76 | PRU 2 mg<br>N=75 | PRU 4 mg<br>N=80 |
|---|---|---|---|---|
| Total no. of patients with AEs, n (%)[a] | 32 (44.4) | 37 (48.7) | 29 (38.7) | 38 (47.5) |
| Gastro-intestinal system disorders | 6 (8.3) | 13 (17.1) | 6 (8.0) | 19 (23.8) |
| Abdominal pain | 4 (5.6) | 7 (9.2) | 3 (4.0) | 9 (11.3) |
| Diarrhoea | 0 | 5 (6.6) | 1 (1.3) | 5 (6.3) |
| Nausea | 2 (2.8) | 4 (5.3) | 1 (1.3) | 4 (5.0) |
| Body as a whole - general disorders | 8 (11.1) | 14 (18.4) | 7 (9.3) | 10 (12.5) |
| Back pain | 2 (2.8) | 2 (2.6) | 4 (5.3) | 3 (3.8) |
| Centr & periph nervous system disorders | 6 (8.3) | 6 (7.9) | 6 (8.0) | 10 (12.5) |
| Headache | 3 (4.2) | 5 (6.6) | 4 (5.3) | 7 (8.8) |
| Dizziness | 1 (1.4) | 0 | 0 | 4 (5.0) |
| Heart rate and rhythm disorders | 3 (4.2) | 2 (2.6) | 0 | 4 (5.0) |
| Musculo-skeletal system disorders | 4 (5.6) | 3 (3.9) | 2 (2.7) | 3 (3.8) |
| Urinary system disorders | 4 (5.6) | 3 (3.9) | 2 (2.7) | 3 (3.8) |
| Metabolic and nutritional disorders | 5 (6.9) | 1 (1.3) | 3 (4.0) | 2 (2.5) |
| Skin and appendages disorders | 3 (4.2) | 6 (7.9) | 1 (1.3) | 1 (1.3) |
| Psychiatric disorders | 2 (2.8) | 4 (5.3) | 1 (1.3) | 0 |

The aggregated data from the placebo controlled studies reinforced the increased incidence of headache, nausea and diarrhoea with prucalopride and that the incidence of these AEs increased in a dose dependent manner (Table 36).

**Table 36. Chronic Constipation: Adverse Events Reported by ≥2% of Prucalopride-Treated Subjects in Phase II and 3 Double blind Placebo Controlled Studies Population: All Subjects.**

| System Organ Class<br>Preferred Term | Placebo<br>n (%) | PRU 0.5mg<br>n (%) | PRU 1mg<br>n (%) | PRU 2mg<br>n (%) | PRU 4mg<br>n (%) | All PRU<br>n (%) |
|---|---|---|---|---|---|---|
| **Total no. of subjects** | **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)** |

Key: AEs = adverse events; PRU = prucalopride

Note: AEs reported any time during treatment or within 5 days of end of treatment are included

In the open label follow up studies the rates of TEAEs did not appear to be dose related. The most commonly reported TEAEs were headache in 24.9% of subjects, diarrhoea in 17.1% of subjects, nausea in 13.4% of subjects and abdominal pain in 13.3% of subjects.

### Cardiovascular safety

In Study USA-3, there was an increase in mean pulse rate in the 2 mg group compared to the placebo group at Week 4 (0.50 bpm increase compared to a -2.42 bpm decrease; p=0.01) and at the double blind endpoint (mean change of 1.77 bpm compared to -2.58 bpm for placebo; p=0.001). There was also a relative increase in the 4 mg group of 1.05 bpm compared to -2.42 bpm for placebo (p=0.047) and a mean change of 1.46 compared to -2.58 bpm for placebo (p=0.02) at the double blind end point. In Study USA-3, there was a mean decrease in PR interval in the

prucalopride 0.5 mg group at the end of Week 2 (-7.20 msec) and at endpoint (-.12 msec) compared to placebo (p≤0.027). There were no apparent differences between the groups in ECG parameters.

In Study BEL-6, palpitations were reported by five (18.5%) prucalopride 4 mg group subjects compared with none in the placebo group. HR was higher in the prucalopride group relative to the placebo group at the end of the study (mean (SE) 78.6 (2.19) bpm compared with 72.7 (2.41) bpm, p = 0.049). The QRS interval also increased in the prucalopride group relative to placebo from baseline to end of study (mean (SE) change was 6.2 (1.93) ms for prucalopride and -1.3 (2.50) ms for placebo; p = 0.022).

In Study GBR-4, there were no significant changes from baseline in mean HR, SBP or diastolic blood pressure (DBP).

In Study USA-26, the median pulse rate increased by up to 6 bpm in the prucalopride 1 mg group. One subject in the prucalopride 0.5 mg discontinued the study medication due to non sustained ventricular tachycardia. There were no apparent trends in blood pressure. A greater proportion of subjects in the prucalopride groups had prolongation of QTc but this did not appear to increase with dose and was not clinically significant in any individual subject (Table 37). The results of the Holter monitor did not indicate an increase in the rate of arrhythmias in the prucalopride groups.

**Table 37. Number of Patients with Increases in QT Corrections <30 ms, 30-60 ms and >60 ms from Baseline during the Treatment Period.**

| Corrected QT interval | Treatment group | N | N' | <30ms n (%) | 30-60 ms n (%) | >60 ms n (%) |
|---|---|---|---|---|---|---|
| QTcB | PLA | 18 | 18 | 5 (27.8) | 13 (72.2) | 0 |
| | PRU 0.5 mg | 21 | 21 | 17 (81.0) | 3 (14.3) | 1 (4.8) |
| | PRU 1 mg | 24 | 22* | 10 (45.5) | 7 (31.8) | 5 (22.7) |
| | PRU 2 mg | 26 | 25* | 16 (64.0) | 7 (28.0) | 2 (8.0) |
| QTcF | Placebo | 18 | 18 | 11 (61.1) | 7 (38.9) | 0 |
| | PRU 0.5 mg | 21 | 21 | 17 (81.0) | 3 (14.3) | 1 (4.8) |
| | PRU 1 mg | 24 | 22* | 11 (50.0) | 8 (36.4) | 3 (13.6) |
| | PRU 2 mg | 26 | 25* | 19 (76.0) | 5 (20.0) | 1 (4.0) |

N' = number of patients with baseline data, n = number of patients with event during treatment period (Day 1, 3 hours to Day 28, 3 hours)

* For Patients #A36063 and #A36065 (1 mg group) and Patient #A36161 (2 mg group), no baseline ECG values were measured

In Study INT-6, palpitations were reported in 10 (4.2%) subjects in the prucalopride 4 mg group as compared to one (0.4%) subject in the 2 mg group and two (0.8%) subjects in the placebo group. Mean HR, SBP and DBP did not change from baseline and there were no significant differences between treatments. There were no significant differences between the treatments groups in subjects with QTc abnormalities.

In Study USA-11, heart rate and rhythm disorders were reported in seven (3.4%) subjects in the prucalopride 2 mg group, six (2.9%) subjects in the 4 mg group and one (0.5%) subject in the placebo group (Table 38). General cardiovascular disorders were reported in seven (3.4%) subjects in the prucalopride 2 mg group, four (2.0%) subjects in the 4 mg group and one (0.5%) subject in the placebo group (Table 38). There were no apparent differences between the groups in vital signs. There were higher proportions of subjects with prolongations of the QTc of 30 to 60 ms in the prucalopride groups at Week 12: eleven (6.5%) subjects in the 2 mg group, 14 (8.3%) subjects in the 4 mg group and five (2.8%) subjects in the placebo group (Table 39).

**Table 38. Cardiovascular AEs from Study USA-11.**

| WHO SYSTEM-ORGAN CLASS<br>WHO-PREFERRED TERM | PLACEBO<br>TOTAL<br>NO. (%) | PRU 2.0 MG<br>TOTAL<br>NO. (%) | PRU 4.0 MG<br>TOTAL<br>NO. (%) |
|---|---|---|---|
| HEART RATE AND RHYTHM DISORDERS | 1 ( 0.5) | 7 ( 3.4) | 6 ( 2.9) |
| TACHYCARDIA | 0 ( 0.0) | 1 ( 0.5) | 3 ( 1.5) |
| PALPITATION | 1 ( 0.5) | 2 ( 1.0) | 1 ( 0.5) |
| QT PROLONGED | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.5) |
| T WAVE INVERSION | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.5) |
| ARRHYTHMIA | 0 ( 0.0) | 1 ( 0.5) | 0 ( 0.0) |
| ARRHYTHMIA ATRIAL | 0 ( 0.0) | 2 ( 1.0) | 0 ( 0.0) |
| ARRHYTHMIA VENTRICULAR | 0 ( 0.0) | 1 ( 0.5) | 0 ( 0.0) |
| TACHYCARDIA SUPRAVENTRICULAR | 0 ( 0.0) | 1 ( 0.5) | 0 ( 0.0) |
| CARDIOVASCULAR DISORDERS, GENERAL | 1 ( 0.5) | 7 ( 3.4) | 4 ( 2.0) |
| HYPERTENSION | 1 ( 0.5) | 2 ( 1.0) | 2 ( 1.0) |
| ECG ABNORMAL | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.5) |
| OEDEMA DEPENDENT | 0 ( 0.0) | 1 ( 0.5) | 1 ( 0.5) |
| BLOOD PRESSURE FLUCTUATION | 0 ( 0.0) | 1 ( 0.5) | 0 ( 0.0) |
| HEART MURMUR | 0 ( 0.0) | 2 ( 1.0) | 0 ( 0.0) |
| HEART VALVE DISORDERS | 0 ( 0.0) | 1 ( 0.5) | 0 ( 0.0) |

**Table 39. Number and Percent of Patients With QTcB and QTcF Changes From Baseline – All-(Treated) Patients Population.**

| Timepoint Classification | PLA | | PRU 2 mg | | PRU 4 mg | |
|---|---|---|---|---|---|---|
| | N | n (%) | N | n (%) | N | n (%) |
| QTcF change | | | | | | |
| Week 4 | | | | | | |
| 30-60 ms | 186 | 7 (3.8) | 183 | 7 (3.8) | 181 | 10 (5.5) |
| >60 ms | 186 | 2 (1.1) | 183 | 2 (1.1) | 181 | 6 (3.3) |
| Week 12 | | | | | | |
| 30-60 ms | 176 | 5 (2.8) | 169 | 8 (4.7) | 168 | 9 (5.4) |
| >60 ms | 176 | 2 (1.1) | 169 | 4 (2.4) | 168 | 8 (4.8) |
| QTcB change | | | | | | |
| Week 4 | | | | | | |
| 30-60 ms | 186 | 9 (4.8) | 183 | 13 (7.1) | 181 | 11 (6.1) |
| >60 ms | 186 | 3 (1.6) | 183 | 3 (1.6) | 181 | 6 (3.3) |
| Week 12 | | | | | | |
| 30-60 ms | 176 | 5 (2.8) | 169 | 11 (6.5) | 168 | 14 (8.3) |
| >60 ms | 176 | 4 (2.3) | 169 | 4 (2.4) | 168 | 7 (2.4) |

In Study USA-13, there was no significant difference between the groups in the distribution of abnormal QTc. There was a slight increase in pulse rate in the prucalopride 2 mg group of up to 2.17 bpm.

In Study USA-25, there was a slightly higher rate of QTcB prolongation in the titrated group: twelve (11.7%) subjects in the titrated group, five (5.1%) subjects in the fixed 4 mg dose group and seven (6.4%) i subjects n the placebo group (Table 40). There was an increase in mean pulse rate of up to 3.71 bpm in the titrated prucalopride group.

In Study USA-28, a higher proportion of subjects in the prucalopride 4 mg group had increases in QTc of 30 to 60 ms during both treatment phases (Table 40). In the prucalopride group there were increases from baseline in mean pulse rate of up to 1.65 bpm and in SBP of up to 1.75 mmHg.

**Table 40. Number and Percent of Patients With QTcB and QTcF Changes From Baseline. All (Treated) Patients Population**

| ECG parameter Abnormality, n/N (%) | PLA | | PRU 4 mg | |
|---|---|---|---|---|
| | Treatment I N=257 | Treatment II N=223 | Treatment I N=253 | Treatment II N=205 |
| QTcF change | | | | |
| 30-60 ms | 8/239 (3.3) | 13/201 (6.5)[a]<br>12/207 (5.8)[b] | 10/229 (4.4) | 16/198 (8.1)[a]<br>14/202 (6.9)[b] |
| QTcB change | | | | |
| 30-60 ms | 16/239 (6.7) | 20/201 (10.0)[a]<br>23/207 (11.1)[b] | 24/229 (10.5) | 26/199 (13.1)[a]<br>29/202 (14.4)[b] |
| >60 ms | 1/239 (0.4) | 2/201 (1.0)[a]<br>0/207 (0)[b] | 0/229 (0) | 1/199 (0.5)[a]<br>1/202 (0.5)[b] |

In Study INT-12, QTcB was prolonged in one (1.8%) subject in the prucalopride 1 mg group, none in the 1 mg group, one (1.9%) subject in the 4 mg group and one (2.2%) subject in the placebo group. There was an increase in pulse rate of up to 1.96 bpm in the prucalopride 2 mg group that was not apparent in the other prucalopride groups or the placebo.

In The sponsor's Summary of the Aggregate data from the Phase II and 3 double blind placebo controlled studies population, as presented in The sponsor's Summary of Clinical Safety, there did not appear to be a consistent increase in mean pulse rate in the prucalopride groups. Blood pressure did not appear to change with treatment.

In the open label follow-up studies there did not appear to be a dose dependent effect of prucalopride upon pulse rate, blood pressure or QTc.

## Serious Adverse Events and Deaths

### Serious Adverse Events

In Study INT-1, SAEs were reported in one (2.2%) subject in the placebo group, one (2.2%) subject in the 0.5 mg group, three subjects in the 1.0 mg group (lung embolism\headache and injury). There were no SAEs reported in the 2.0 mg group.

In Study INT-2, SAEs were reported in two subjects in the placebo group, three (4.5%) subjects in the 0.5 mg bd group, six (9.7%) subjects in the 1.0 mg bd group and three (4.9%) subjects in the 2.0 mg bd group (Table 41).

**Table 41. Subjects with serious adverse events**

| | Adverse event | Drug related? | Outcome | Days in phase |
|---|---|---|---|---|
| **Placebo b.i.d.** | | | | |
| | bone disorder | no | resolved | -12 |
| | menstrual disorder | possible | resolved | 4* |
| **R093877 0.5 mg b.i.d.** | | | | |
| | injury | no | resolved | 14 |
| | pneumonia | no | resolved | 67 |
| | nerve root lesion | no | still present | 88* |
| **R093877 1 mg b.i.d.** | | | | |
| | injury | no | resolved | 59 |
| | anxiety | no | resolved | 29 |
| | abdominal pain | no | resolved | 29 |
| | melaena | no | resolved | 29 |
| | flatulence | no | resolved | 52 |
| | abdominal pain | no | resolved | 53 |
| | abdominal pain | possible | resolved | 1* |
| | condition aggravated | no | still present | 80 |
| | menstrual disorder | possible | resolved | 4* |
| | menstrual disorder | possible | resolved | 5* |
| | menstrual disorder | possible | resolved | 8* |
| | menstrual disorder | possible | resolved | 0* |
| | menstrual disorder | possible | resolved | 9* |
| **R093877 2 mg b.i.d.** | | | | |
| | condition aggravated | no | still present | 13 |
| | injury | no | resolved | 82 |
| | myalgia | no | still present | 13 |
| | back pain | no | still present | 13 |

In Study USA-3, SAEs were reported by one subject in the placebo group (Guillain-Barré syndrome) and one subject in the 1 mg group (diarrhoea, nausea and vomiting).

In Study USA-26 there were four subjects that reported SAEs: two deaths (reported below) and two subjects in the prucalopride 0.5 mg group (melaena/colitis/ diverticulitis and urinary tract infection/skin ulceration).

In Study INT-6, SAEs were reported in five (2.1%) subjects in the prucalopride 2 mg group (anxiety, bronchitis, infection viral, neoplasm not otherwise specified (NOS), pneumonia, (stridor, suicide attempt and uterine haemorrhage), six (2.5%) subjects in the 4 mg group (abrasion NOS, back pain, cardiac failure, dizziness, fibrillation atrial, headache, hypertension aggravated, MS aggravated, pulmonary oedema and upper respiratory infection) and five (2.1%) subjects in the placebo group (abdominal pain, anaemia, epistaxis, ileus, injury, migraine aggravated, unintended pregnancy and syncope).

In Study USA-11, SAEs were reported in three (1.4%) subjects in the prucalopride 2 mg group, seven (3.4%) in the 4 mg and eight (3.8%) in the placebo. A tabulation of SAEs was not provided in the Study report.

In Study USA-13, SAEs were reported by four (1.9%) subjects in the prucalopride 2mg group, five (2.3%) subjects in the 4 mg group and five (2.4%) subjects in the placebo group.

In Study USA-28, SAEs were reported in five (1.9%) subjects in the prucalopride 4 mg group and four (1.6%) subjects in the placebo group. There was no separate tabulation/listing of SAEs included with the sponsor's study reports for Studies USA-13 and USA-28.

In Study INT-12, SAEs were reported in one (1.3%) subject in the prucalopride 1 mg group, one (1.3%) subject in the 4 mg group and one (1.4%) subject in the placebo group.

There were no SAEs reported in Studies BEL-6, GBR-4 or USA-25.

The rate of SAEs in the open label studies was low (Table 42). There was no obvious pattern to the SAEs but the occurrence of vaginal haemorrhage in three subjects as a SAE might indicate an increased risk of menstrual disorders.

**Table 42. Chronic Constipation: Most Common (≥2 or more Prucalopride-Treated Subjects) Serious Adverse Events During or Post treatment for Phase II and 3 Double blind Placebo controlled Studies Population: All Subjects.**

| System Organ Class<br>Preferred term | Placebo<br>n (%) | PRU 0.5mg<br>n (%) | PRU 1mg<br>n (%) | PRU 2mg<br>n (%) | PRU 4mg<br>n (%) | All PRU<br>n (%) |
|---|---|---|---|---|---|---|
| **Total no. of subjects** | **1369** | **110** | **308** | **938** | **1361** | **2717** |
| **Infections and infestations** | **1 (0.1)** | **1 (0.9)** | **2 (0.6)** | **3 (0.3)** | **5 (0.4)** | **11 (0.4)** |
| Bronchitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 2 (0.1) |
| Pneumonia | 0 (0.0) | 0 (0.0) | 1 (0.3) | 0 (0.0) | 1 (0.1) | 2 (0.1) |
| **Surgical and medical procedures** | **8 (0.6)** | **0 (0.0)** | **1 (0.3)** | **2 (0.2)** | **8 (0.6)** | **11 (0.4)** |
| Abdominoplasty | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.1) | 2 (0.1) |
| Hysterectomy | 3 (0.2) | 0 (0.0) | 1 (0.3) | 0 (0.0) | 1 (0.1) | 2 (0.1) |
| Umbilical hernia repair | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.1) | 2 (0.1) |
| **Gastrointestinal disorders** | **6 (0.4)** | **1 (0.9)** | **1 (0.3)** | **4 (0.4)** | **4 (0.3)** | **10 (0.4)** |
| Abdominal pain | 3 (0.2) | 0 (0.0) | 0 (0.0) | 3 (0.3) | 1 (0.1) | 4 (0.1) |
| Constipation | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| **Nervous system disorders** | **5 (0.4)** | **0 (0.0)** | **3 (1.0)** | **0 (0.0)** | **2 (0.1)** | **5 (0.2)** |
| Headache | 0 (0.0) | 0 (0.0) | 1 (0.3) | 0 (0.0) | 1 (0.1) | 2 (0.1) |
| **Respiratory, thoracic and mediastinal disorders** | **1 (0.1)** | **0 (0.0)** | **2 (0.6)** | **2 (0.2)** | **1 (0.1)** | **5 (0.2)** |
| **Cardiac disorders** | **2 (0.1)** | **0 (0.0)** | **0 (0.0)** | **1 (0.1)** | **3 (0.2)** | **4 (0.1)** |
| Supraventricular tachycardia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| **Reproductive system and breast disorders** | **3 (0.2)** | **0 (0.0)** | **0 (0.0)** | **3 (0.3)** | **1 (0.1)** | **4 (0.1)** |
| Vaginal haemorrhage | 1 (0.1) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 1 (0.1) | 3 (0.1) |
| **General disorders and administration site conditions** | **2 (0.1)** | **0 (0.0)** | **0 (0.0)** | **1 (0.1)** | **2 (0.1)** | **3 (0.1)** |
| Chest pain | 2 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| **Injury, poisoning and procedural complications** | **0 (0.0)** | **0 (0.0)** | **1 (0.3)** | **1 (0.1)** | **1 (0.1)** | **3 (0.1)** |
| **Musculoskeletal and connective tissue disorders** | **3 (0.2)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **3 (0.2)** | **3 (0.1)** |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **2 (0.2)** | **1 (0.1)** | **3 (0.1)** |
| **Skin and subcutaneous tissue disorders** | **0 (0.0)** | **1 (0.9)** | **1 (0.3)** | **0 (0.0)** | **1 (0.1)** | **3 (0.1)** |
| **Psychiatric disorders** | **0 (0.0)** | **0 (0.0)** | **0 (0.0)** | **1 (0.1)** | **1 (0.1)** | **2 (0.1)** |
| Anxiety | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| **Vascular disorders** | **2 (0.1)** | **0 (0.0)** | **0 (0.0)** | **1 (0.1)** | **1 (0.1)** | **2 (0.1)** |

Key: PRU = prucalopride

### Deaths

In Study USA-26, two subjects died during the study: one in the prucalopride 1 mg group (lobar pneumonia) and one in the 2 mg group (bronchitis).

During Study INT-12, one patient in the placebo group died due to the arrhythmia and myocardial infarction.

There were four deaths reported during open label studies.

There were no deaths in Studies INT-1, INT-2, USA-3, BEL-6, GBR-4, INT-6, USA-11, USA-13, USA-25 or USA-28.

### Laboratory Findings

In Study USA-26 there were a higher number of laboratory test abnormalities in the prucalopride 2 mg group, with anaemia being reported in four (15.4%) subjects.

In Study INT-6 the pattern of abnormal laboratory tests was similar for prucalopride and placebo. However clinically significant elevation in plasma cholesterol was more common in the prucalopride 4 mg group: six (2.5%) subjects compared with 1 (0.4%) subject in the 2 mg group and no subjects in the placebo group (Table 43).

**Table 43. Treatment-Emergent Laboratory-Related Adverse Events Reported in >1 Patient in any Prucalopride Treatment Group. All (Treated) Subjects Population**

| Laboratory class<br>WHO preferred term | PLA<br>N=240 | PRU 2 mg<br>N=238 | PRU 4 mg<br>N=238 |
|---|---|---|---|
| Total no. of patients with laboratory-related AEs[a], n (%) | 11 (4.6) | 20 (8.4) | 26 (10.9) |
| Clinical chemistry | | | |
| Creatine phosphokinase increased | 4 (1.7) | 4 (1.7) | 5 (2.1) |
| Hypercholesterolemia | 0 | 1 (0.4) | 6 (2.5) |
| Hyperglycaemia | 2 (0.8) | 3 (1.3) | 4 (1.7) |
| Hypertriglyceridaemia | 0 | 1 (0.4) | 3 (1.3) |
| Hypokalaemia | 2 (0.8) | 0 | 2 (0.8) |
| Haematology | | | |
| Anaemia | 2 (0.8) | 3 (1.3) | 1 (0.4) |
| Eosinophilia | 0 | 2 (0.8) | 0 |
| Urinalysis | | | |
| Haematuria | 1 (0.4) | 4 (1.7) | 1 (0.4) |

In Studies USA-11 and USA-28, there were no apparent differences between the treatment groups in the pattern of clinically significant laboratory test abnormalities.

In Studies USA-13 and INT-12, there was no apparent pattern in clinically significant abnormalities of laboratory tests.

There were no apparent differences between treatment groups in laboratory parameters in Studies INT-1, INT-2, USA-3, BEL-6, GBR-4 and USA-25.

### Safety in Special Populations

Study USA-26, was conducted in an older population group and appeared to have a lower rate of headache but a higher rate of laboratory AEs, in particular anaemia.

In The sponsor's Summary of Clinical Safety, summary tables were provided for TEAEs and SAEs occurring in subjects ≥65 years age (Table 44). These data suggests that the overall reporting rates of TEAEs were reduced in the older age group. This might indicate greater tolerance to AEs in the older population. The pattern of SAEs was appropriate to the population and did not indicate any pattern associated with prucalopride.

**Table 44. Chronic Constipation: Most Common (≥2% in the ALL PRU Group) Adverse Events Reported by Subjects aged ≥65 Years in Phase II and 3 Double blind Placebo controlled Studies Population: All Subjects**

| System Organ Class<br>Preferred Term | Placebo<br>n (%) | PRU<br>0.5mg<br>n (%) | PRU 1mg<br>n (%) | PRU 2mg<br>n (%) | PRU 4mg<br>n (%) | All PRU<br>n (%) |
|---|---|---|---|---|---|---|
| **Total no. of subjects** | **214** | **25** | **113** | **203** | **223** | **564** |
| **Gastrointestinal disorders** | **45 (21.0)** | **7 (28.0)** | **26 (23.0)** | **51 (25.1)** | **76 (34.1)** | **160 (28.4)** |
| Nausea | 10 ( 4.7) | 2 ( 8.0) | 6 ( 5.3) | 18 ( 8.9) | 26 (11.7) | 52 ( 9.2) |
| Diarrhoea | 3 ( 1.4) | 1 ( 4.0) | 10 ( 8.8) | 11 ( 5.4) | 19 ( 8.5) | 41 ( 7.3) |
| Abdominal pain | 11 ( 5.1) | 0 ( 0.0) | 6 ( 5.3) | 5 ( 2.5) | 14 ( 6.3) | 25 ( 4.4) |
| Abdominal pain upper | 6 ( 2.8) | 0 ( 0.0) | 2 ( 1.8) | 4 ( 2.0) | 11 ( 4.9) | 17 ( 3.0) |
| Flatulence | 9 ( 4.2) | 0 ( 0.0) | 1 ( 0.9) | 7 ( 3.4) | 7 ( 3.1) | 15 ( 2.7) |
| Abdominal distension | 5 ( 2.3) | 0 ( 0.0) | 0 ( 0.0) | 7 ( 3.4) | 7 ( 3.1) | 14 ( 2.5) |
| Vomiting | 7 ( 3.3) | 1 ( 4.0) | 3 ( 2.7) | 4 ( 2.0) | 3 ( 1.3) | 11 ( 2.0) |
| **Nervous system disorders** | **18 ( 8.4)** | **5 (20.0)** | **7 ( 6.2)** | **26 (12.8)** | **38 (17.0)** | **76 (13.5)** |
| Headache | 11 ( 5.1) | 3 (12.0) | 5 ( 4.4) | 18 ( 8.9) | 30 (13.5) | 56 ( 9.9) |
| Dizziness | 3 ( 1.4) | 1 ( 4.0) | 0 ( 0.0) | 4 ( 2.0) | 12 ( 5.4) | 17 ( 3.0) |
| **Infections and infestations** | **21 ( 9.8)** | **8 (32.0)** | **12 (10.6)** | **22 (10.8)** | **26 (11.7)** | **68 (12.1)** |
| UTI | 7 ( 3.3) | 7 (28.0) | 2 ( 1.8) | 2 ( 1.0) | 6 ( 2.7) | 17 ( 3.0) |
| **General disorders and administration site disorders** | **13 ( 6.1)** | **1 ( 4.0)** | **10 ( 8.8)** | **15 ( 7.4)** | **25 (11.2)** | **51 ( 9.0)** |
| Fatigue | 1 ( 0.5) | 0 ( 0.0) | 3 ( 2.7) | 3 ( 1.5) | 8 ( 3.6) | 14 ( 2.5) |
| **Investigations** | **20 ( 9.3)** | **1 ( 4.0)** | **7 ( 6.2)** | **24 (11.8)** | **16 ( 7.2)** | **48 ( 8.5)** |
| **Musculoskeletal and connective tissue disorders** | **16 ( 7.5)** | **2 ( 8.0)** | **9 ( 8.0)** | **19 ( 9.4)** | **14 ( 6.3)** | **44 ( 7.8)** |
| Back pain | 5 ( 2.3) | 0 ( 0.0) | 2 ( 1.8) | 5 ( 2.5) | 4 ( 1.8) | 11 ( 2.0) |
| **Respiratory, thoracic and mediastinal disorders** | **9 ( 4.2)** | **1 ( 4.0)** | **6 ( 5.3)** | **7 ( 3.4)** | **9 ( 4.0)** | **23 ( 4.1)** |
| **Renal and urinary disorders** | **3 ( 1.4)** | **0 ( 0.0)** | **5 ( 4.4)** | **8 ( 3.9)** | **9 ( 4.0)** | **22 ( 3.9)** |
| **Cardiac disorders** | **6 ( 2.8)** | **1 ( 4.0)** | **6 ( 5.3)** | **3 ( 1.5)** | **11 ( 4.9)** | **21 ( 3.7)** |
| **Skin and subcutaneous tissue disorders** | **11 ( 5.1)** | **2 ( 8.0)** | **11 ( 9.7)** | **3 ( 1.5)** | **5 ( 2.2)** | **21 ( 3.7)** |
| **Injury, poisoning and procedural complications** | **5 ( 2.3)** | **3 (12.0)** | **8 ( 7.1)** | **4 ( 2.0)** | **4 ( 1.8)** | **19 ( 3.4)** |
| **Psychiatric disorders** | **5 ( 2.3)** | **0 ( 0.0)** | **5 ( 4.4)** | **6 ( 3.0)** | **4 ( 1.8)** | **15 ( 2.7)** |
| **Metabolism and nutrition disorders** | **2 ( 0.9)** | **1 ( 4.0)** | **2 ( 1.8)** | **7 ( 3.4)** | **4 ( 1.8)** | **14 ( 2.5)** |
| **Vascular disorders** | **3 ( 1.4)** | **2 ( 8.0)** | **1 ( 0.9)** | **6 ( 3.0)** | **5 ( 2.2)** | **14 ( 2.5)** |
| **Ear and labyrinth disorders** | **1 ( 0.5)** | **0 ( 0.0)** | **1 ( 0.9)** | **3 ( 1.5)** | **7 ( 3.1)** | **11 ( 2.0)** |

Key: PRU = prucalopride; UTI = urinary tract infection

### Immunological Events

There did not appear to be any association of prucalopride with immunologically mediated AEs.

### Safety Related to Drug Drug Interactions and Other Interactions

Erythromycin increased the frequency of diarrhoea with prucalopride (Study NED-14. In combination with paroxetine, headache and nausea appeared to be more frequent: headache: six (33.3%) subjects with prucalopride, six (33.3%) subjects with paroxetine and nine (50%) subjects with combined; nausea: four (22.2%) subjects with prucalopride, four (22.2%) subjects with paroxetine and seven (38.9%) subjects with combined (Study NED-12). There were no other increases in the frequency of AEs in the drug interaction studies.

Study BEL-27 indicated that co ingestion with food did not affect the rate of AEs.

### Discontinuation Due to Adverse Events (DAE)

In Study INT-1, DAE occurred in one (2.2%) subject in the placebo group, three (6.5%) subjects in the 0.5 mg group, three (7.0%) subjects in the 1.0 mg group and five (12.5%) subjects in the 2.0 mg group.

In Study INT-2, no DAEs were reported in the placebo group whilst three (4.5%) subjects in the 0.5 mg bd group, six (9.7%) subjects in the 1 mg bd group and seven (11.5%) subjects in the 2 mg bd group discontinued due to an AE. Headache and abdominal pain were common reasons for discontinuing.

In Study USA-3, three (6%) subjects in the prucalopride 1 mg group, two (4%) subjects in the 2 mg group and six (13%) subjects in the 4 mg group discontinued because of AEs. Nausea, abdominal pain and headache were the most common reasons for DAE.

In Study BEL-6, one subject in the prucalopride 4 mg group discontinued because of an AE.

In Study GBR-4, three subjects in the prucalopride 1 mg group discontinued because of an AE (severe back/groin pain, severe abdominal pain/diarrhoea and severe diarrhoea/vomiting). No subjects in the placebo group discontinued because of an AE.

In Study USA-26, three (14.3%) subjects in the prucalopride 0.5 mg group and one (4.2%) subjects in the 1 mg group discontinued because of an AE.

In Study INT-6, 14 (5.9%) subjects in the prucalopride 2 mg group, 36 (15.1%) subjects in the 4 mg group and 15 (6.3%) subjects in the placebo group discontinued because of an AE. Headache, abdominal pain and nausea were the most common AEs leading to discontinuation in the 4 mg group.

In Study USA-11, 17 (8.2%) subjects in the prucalopride 2 mg group, 16 (7.8%) subjects in the 4 mg group and four (1.9%) subjects in the placebo group discontinued because of an AE. Headache, nausea and diarrhoea were the most common reasons for DAE in the prucalopride groups.

In Study USA-13, eight (3.7%) subjects in the prucalopride 2 mg group, twelve (5.6%) subjects in the 4 mg group and five (2.4%) subjects in the placebo group discontinued because of an AE. The most common reasons for DAE in the prucalopride groups were abdominal pain, nausea, headache and diarrhoea.

In Study USA-25, four (3.5%) subjects in the titrated group, eight (7.1%) subjects in the fixed 4 mg dose group and one (0.9%) subject in the placebo group discontinued because of an AE. Nausea and headache were the most common reasons for DAE.

In Study USA-28 more subjects discontinued due to an AE during Treatment I (17 (6.7%) subjects in the prucalopride group and five (1.9%) subjects in the placebo group) compared to Treatment II (one (0.4%) subject in the prucalopride group and four (1.8%) subjects in the placebo group).

In Study INT-12, two (2.6%) subjects in the prucalopride 1 mg group, 4 (5.3%) subjects in the 2 mg group, seven (8.8%) subjects in the 4 mg group and three (4.2%) subjects in the placebo group discontinued because of an AE. The higher rate in the prucalopride 4 mg group appeared to be due to an increased rate of abdominal pain, diarrhoea, dizziness and headache.

### Evaluator's Overall Conclusions on Clinical Safety

The incidence of treatment emergent AEs increased with prucalopride dose. Dose related AEs, occurring with increased frequency with prucalopride were: headache, abdominal pain, nausea, diarrhoea, vomiting and dizziness. Menstrual disorders, including dysmenorrhoea might occur to a greater extent with prucalopride but require further study.

Some studies indicated an increase in the pulse rate with prucalopride. The increase was small but this might be clinically significant over a long period of time. The findings with regard to QT prolongation were inconsistent but raise the possibility that QT prolongation might be a safety issue with prucalopride.

The rate of SAEs was low and there did not appear to be any patterns of SAEs related to prucalopride.

There were few deaths and those that did occur were in the studies conducted in the older population.

There was no apparent pattern of laboratory test abnormalities associated with prucalopride.

There appeared to be a greater tolerance for prucalopride in the older age group.

Erythromycin increased the frequency of diarrhoea with prucalopride. In combination with paroxetine, headache and nausea appeared to be more frequent.

The rate of DAE was higher in the prucalopride groups and appeared to be due to headache, abdominal pain, nausea, diarrhoea and vomiting.

## List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

### Pharmacokinetics

**Question 1**

What further studies does the Sponsor propose conducting to establish the transmembrane solute transporters involved in the renal secretion of prucalopride?

**Question 2**

What further studies does the Sponsor propose conducting to establish the enzyme pathways involved in the biotransformation of prucalopride?

**Question 3**

Is there any evidence available to establish whether any genetic influences exist upon renal secretion or biotransformation?

### Pharmacodynamics

**Question 4**

Has the Sponsor performed a Thorough QT Study?

### Efficacy

**Question 5**

How effective is prucalopride in comparison with commonly used treatments for constipation?

**Question 6**

Does the Sponsor have any data with regard to prucalopride used in combination with other medical treatments for constipation?

**Question 7**

Does the Sponsor have data indicating where in the sequence of treatment regimens for constipation prucalopride should be used?

**Question 8**

Does the Sponsor have any long term efficacy data from randomized controlled trials?

### Safety

**Question 9**

Does the Sponsor have any additional analyses or data regarding menstrual disturbance, in particular dysmenorrhoea, in subjects treated with prucalopride?

**Question 10**

Dose the Sponsor have any additional data regarding menstrual disturbance, in particular dysmenorrhoea, in subjects treated with prucalopride and not co-medicated with the OCP?

**Question 11**

Does the Sponsor have any information regarding effective treatments for the headache experienced as a result of prucalopride?

**Question 12**

Does the Sponsor have any additional data or analyses with regard to the risk of bowel perforation?

The sponsor addressed these questions in a letter dated 16 June 2011

## Clinical Summary and Conclusions

Prucalopride has a $T_{max}$ of around 3 hours and a $t_{1/2}$ of around 24 hours. Food does not affect bioavailability. SC administration of 1 mg was bioequivalent with IV administration. The solution formulation was bioequivalent with a tablet formulation. The formulations used in development and those intended for marketing were bioequivalent. Prucalopride had protein binding of 29% in human plasma and 66% of prucalopride in blood was distributed to blood cells.

A total of 70% of a prucalopride dose was excreted unchanged, 60 to 64% in urine and 6% in faeces. The PK of prucalopride appear to be dose proportional in the IV dose range 0.063 mg to 5 mg and the oral dose range 0.125 to 6 mg for single dose and oral dose range 1 mg to 6 mg for multiple dosing. Steady state plasma concentrations were attained within 3 to 4 days.

Elimination of prucalopride is primarily renal. Renal clearance involves tubular secretion as well as filtration. At steady state, which is attained within 4 days, $C_{max}$ and AUC were 26% and 28% higher, respectively, in elderly subjects. The $t_{1/2}$ was shorter in children (aged 4 to 12 years) than in adults (mean (SD) 19 (3) hours) and apparent clearance was higher (13.6 (4.5) L/h). All degrees of renal impairment resulted in decreased clearance with 50% of the normal clearance in severe renal impairment. Prucalopride clearance correlated CrCL estimated by the Cockroft-Gault formula. The Cockroft-Gault formula uses age, weight, sex and creatinine to estimate creatinine clearance and all of these individual characteristics can be taken to influence prucalopride clearance.

Exposure of a breast fed infant to maternal prucalopride was estimated to be, adjusted for body weight, about 6% of the maternal dose, indicating that prucalopride exposure is about 16 times lower in the infant than in the mother. However, neonates have deceased renal function compared with older children and adults which might result in decreased clearance of prucalopride in neonates relative to older children and adults.

Prucalopride decreased digoxin AUC, average and trough plasma concentrations by 10%, indicating the potential for interactions involving p-glycoprotein. Ketoconazole increased the bioavailability of prucalopride by 40% indicating the metabolic clearance of prucalopride has the potential for inhibition.

There has been insufficient investigation of which transporters are responsible for active secretion of prucalopride and the effect of inhibition of drug transporters in the kidney upon the PK of prucalopride. There has been insufficient investigation of the metabolic pathways of prucalopride and which enzymes are involved in biotransformation of prucalopride.

In healthy volunteers, co ingestion with food did not influence effect. Headache, flatulence, diarrhoea and dizziness appeared to be dose related. Oro-caecal transit time was reduced with prucalopride. However, colonic transit time was not decreased. Stools were looser with prucalopride than placebo. Prucalopride did not affect rectal distention thresholds, anorectal electrosensory thresholds or anorectal manometry.

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 effect on colonic transit time.

Two studies have been performed of the effect of prucalopride on QTc with single doses up to 10 mg and in prucalopride steady state and did not find a consistent effect upon QTc. However, the doses examined were only five times the sponsor's recommended dose. The Sponsor does not appear to have performed a Thorough QT Study.

## Benefit Risk Assessment

### Benefits

The Pivotal Studies (Study INT-6, Study USA-11 and USA-13) demonstrated that both the 2 mg and 4 mg dose levels were superior to placebo but there was no apparent difference in efficacy between the dose levels. The studies were identical in design. These studies support the 2 mg dose level in the general adult population.

Study USA-25 indicated that titration of a treatment dose from 1 mg to 4 mg had no greater efficacy than commencing at 4 mg.

Study USA-28 demonstrated that prucalopride at the 4 mg dose level retained efficacy with retreatment (after a period of time without treatment).

Study INT-12 demonstrated that for subjects ≥65 years age prucalopride was superior to placebo and there was no additional benefit of increasing the dose to 2 mg or 4 mg from the 1 mg dose level. This supports the 1 mg dose level in subjects ≥65 years age.

The dose finding studies did not clearly indicate the optimal dose to be taken into the Phase III studies but in general support the findings of the Phase III studies. In Study INT-1 and Study INT-2, prucalopride, given at either 1 mg or 2 mg once daily, was superior to placebo with no difference between doses and no difference between once and twice daily dosing. These studies excluded the 0.5 mg dose level from further development. In Study USA-3 there was an increase in treatment effect up to the 4 mg dose level and statistically significant effect for the 2 mg and 4 mg dose levels but no significant difference between the 0.5 mg and 1 mg dose levels. Study BEL-6 investigated the 4 mg dose level and found statistically and clinically significant benefit compared to placebo.

Study GBR-4 found that mean oro-caecal transit time was significantly shorter in the prucalopride 1 mg group compared with the placebo group and concluded a statistically and clinically significant benefit of the 1 mg dose compared with placebo. Study USA-26 found no significant difference between prucalopride at doses up to 2 mg daily with placebo in subjects aged over 65 years. This study does however appear to have been underpowered.

Tolerance to prucalopride did not appear to occur and there did not appear to be any withdrawal effects.

The efficacy outcome measures were appropriate. The inclusion criteria used an appropriate definition for chronic idiopathic constipation.

The current Australian submission did not contain convincing efficacy data for any indication other that chronic idiopathic constipation. The inclusion and exclusion criteria for the pivotal studies excluded subjects with constipation secondary to drugs or to any other medical condition.

The current Australian submission did not contain any data comparing prucalopride with any other active treatment measure. Hence it is not known how effective prucalopride is in comparison with commonly used treatments for constipation. In addition, the current Australian submission did not contain any data with regard to prucalopride use in combination with other medical treatments for constipation.

The placebo controlled trials were up to 12 weeks in duration. Hence, long term efficacy of prucalopride has not been demonstrated in an appropriately designed study.

### Risks

The incidence of treatment emergent AEs increased with prucalopride dose. Dose related AEs which occurring with increased frequency with prucalopride treatment included: headache, abdominal pain, nausea, diarrhoea, vomiting and dizziness. Menstrual disorders, including dysmenorrhoea might occur to a greater extent with prucalopride but this requires further study.

Some studies indicated an increase in the pulse rate with prucalopride. The increase was small but this might be clinically significant over a long period of time. The findings with regard to QT prolongation were inconsistent but raise the possibility that QT prolongation might be a safety issue with prucalopride.

The rate of SAEs was low and there did not appear to be any patterns of SAEs related to prucalopride.

There were few deaths and those that did occur were in the studies conducted in the older population.

There was no apparent pattern of laboratory test abnormalities associated with prucalopride.

There appeared to be a greater tolerance for prucalopride in the older age group.

Erythromycin increased the frequency of diarrhoea with prucalopride. When prucalopride was given in combination with paroxetine, headache and nausea appeared to be more frequently reported.

The rate of DAE was higher in the prucalopride groups and appeared to be due to headache, abdominal pain, nausea, diarrhoea and vomiting.

### Safety Specification

The safety specification currently includes the following safety concerns with inadequate/unknown information:

- Genotoxicity
- Reproductive toxicity
- Cardiovascular safety

The important identified risks of:

- Palpitations
- Headache

The important potential risks of:

- Cardiovascular ischaemic events
- Ischaemic colitis
- QT prolongation and related arrhythmias
- Syncope

The following issues should also be included as important potential risks:

- Menstrual disturbance
- Bowel perforation

### Balance

Although the efficacy of prucalopride at the 1 mg and 2 mg dose levels has been demonstrated in comparison with placebo there remain some unresolved, potentially serious safety issues. These relate to the cardiovascular safety of prucalopride. The sponsor has not demonstrated any advantage for prucalopride over currently available treatments for constipation. Therefore, there is no compelling reason to approve prucalopride prior to the resolution of the cardiovascular safety issues.

## Conclusions

The clinical evaluator proposed that prucalopride should not be approved for the following indication:

*For the treatment of chronic constipation in adults in whom laxatives fail to provide adequate relief.*

The reason for rejecting this indication is that the indication is too broad. Evidence of efficacy has only been provided to support the indication of chronic idiopathic constipation.

If there is resolution of the cardiovascular safety issues (QT prolongation, increased resting heart rate and tachyarrhythmias) then the following indication might be considered for approval:

*For the treatment of chronic idiopathic constipation in adults in whom laxatives fail to provide adequate relief.*

### Recommended Conditions for Registration

The sponsor should provide data from a Thorough QT Study.

The sponsor should further investigate the potential for menstrual irregularities, particularly in those patients not taking the OCP.

# V. Pharmacovigilance Findings

## Risk Management Plan

Table 57 summarises the Ongoing Safety Concerns submitted by the sponsor and evaluated by TGA's Office of Product Review.

**Table 57. Summary of Ongoing Safety Concerns**

| | |
|---|---|
| Important identified risks | Palpitations<br>Headache – removed as of RMP v6.0 |
| Important potential risks | Cardiovascular and cerebrovascular ischaemic events<br>Ischaemic colitis<br>QT prolongation and related ventricular events<br>Syncope<br>Overdose/abuse/misuse as laxative<br>Off-label paediatric use<br>Off -label use by men |
| Important missing information | Efficacy of long term use<br>Safety in pregnant women<br>Safety in paediatrics<br>Safety in patients with hepatic impairment<br>Safety in patients with severe and unstable cardiovascular disease<br>Drug interaction with oral contraceptives – study completed post-approval Q3 2010 (removed as of RMP v5.0)<br>Efficacy and safety in males |

Routine pharmacovigilance[11] is proposed by the sponsor to monitor all Ongoing Safety Concerns associated with prucalopride.

[11] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

### Summary of OPR Recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted EU RMP is applicable without modification in Australia unless so qualified:

It is recommended to the Delegate that the sponsor:

- Clarify the inclusion of the safety concern 'Off-label use by men' and pharmacovigilance Study M0001-C302 (FUM004) in light of the proposed indication.
- Update the RMPs language to provide consistency in the Australian context (for example, Replace SmPC with PI, replace tradename Resolor with Resotrans and update the indication to that proposed in Australia), or provide an Australian specific annex which identifies this issue and any Australian relevant changes or issues.
- Include, as identified in the Clinical Evaluation Report, 'Menstrual disturbance' and 'Bowel perforation' as potential risks. In addition, these potential risks should be addressed with adequate pharmacovigilance and risk minimisation activities.
- Provide justification about the selection of the trial 'M0001-C401 (FUM005)' to further elucidate the safety concern 'Efficacy of long term use', given the study is only 24 weeks in duration.
- Provide start dates listed for the three planned studies (M0001-EPI-1-FUM006, M0001-C401 (FUM005) and M0001-C303).
- Provide protocols M0001-EPI-1-FUM006, M0001-C401 (FUM005) and M0001-C303 and "Special Questionnaires for follow-up" for evaluation.

# VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

### Quality

There are no quality objections to registration. Prucalopride was considered at the 138th meeting of the Pharmaceutical Subcommittee of the ACPM.

It was noted that the population PK model was not able to be tested. It was requested that future pharmacometric analyses have data and model key files ("control streams") provided electronically in the standard .csv and text formats, respectively to allow for independent review. For this analysis it was noted that a large number of samples below the lower limit of quantitation (LLOQ) were removed from the dataset. There are a variety of well established ways to handle this other than excluding them. The impact on the analysis of this exclusion could not be tested with the data provided.

### Nonclinical

There were no nonclinical objections to registration. The nonclinical evaluator noted that *in vivo* and *in vitro* studies showed a high binding affinity of prucalopride for 5-$HT_4$ receptors. Secondary and safety pharmacology studies concentrated on the potential effects of prucalopride on cardiac 5-$HT_4$ receptors. There was no inhibition of the hHERG channel activity *in vitro* nor was there any evidence of arrhythmia in isolated heart muscle. In a number of *in vivo* studies there was little change in cardiovascular parameters, other than reversible increases in HR and BP at exposures 10 fold that expected in the clinic. A potential pharmacodynamic drug interaction with acetylcholinesterase inhibitors or anticholinergic compounds was identified.

Acute oral toxicity was low with symptoms in dogs indicative of CNS toxicity at dose levels 33 fold higher than the expected clinical exposure. In rats repeated exposure was associated with persistent changes related to increased prolactin levels as a result of hypertrophy in the pituitary at approximately 100 times the clinical exposure. In dogs the NOAEL was 250 times higher than the expected clinical exposure.

Prucalopride, its degradation products and its production intermediates do not have genotoxic potential. In a mouse carcinogenicity study there was a positive trend in mammary gland adenocarcinomas, considered to be related to the increased levels of prolactin following pituitary hyperplasia. The NOAEL was 27 times the clinical exposure. In rats there was an increase in tumour incidence in the liver and thyroid (related to reversible liver hypertrophy and increased T3 levels) as well as in the mammary gland, pituitary gland, pancreas and adrenal gland. The NOAEL was 7 times the clinical exposure for liver tumours and 45 times the clinical exposure for endocrine tumours. Mechanistic studies were conducted to examine the potential mechanism for tumour formation in rodents. The nonclinical evaluator considered that the carcinogenic potential of prucalopride had been adequately studied and the mechanism of formation of the observed tumours appropriately investigated. A threshold for tumour formation had been demonstrated with an adequate margin between the threshold exposure level and the clinical exposure level.

There was no effect on fertility or embryofetal development in rats and rabbits. Reduced nursing behaviour and slightly reduced pup survival due to maternal toxicity were observed.

## Clinical

The clinical evaluator did not recommend approval of the proposed indication and recommended an alternative indication of treatment of chronic idiopathic constipation in adults in whom laxatives fail to provide adequate relief. This indication more accurately reflects the study population. The evaluator raised questions concerning the pharmacology, efficacy and safety of prucalopride that were addressed in a response to the clinical evaluation report. Information from The sponsor's response has been taken into consideration in the current assessment.

*Pharmacology*

Oral bioavailability of prucalopride is approximately 93%. Food does not affect the rate or extent of absorption. The 1 mg and 2 mg tablets are bioequivalent at equal dose. $T_{max}$ is 2.5 to 3 hours and $t_{½}$ is approximately 24 hours at steady state. Protein binding of prucalopride is approximately 29% in human plasma. In blood approximately 66% of prucalopride is distributed to blood cells. Prucalopride undergoes oxidative N-dealkylation resulting in the metabolite M2. However 70% of an oral dose is excreted unchanged, 64% in urine and 6% in faeces. PK are linear within the dosage range of 0.125 to 6 mg daily PO.

Renal clearance involves active secretion. All degrees of renal impairment result in increased exposure to prucalopride, with halving of the drug clearance in severe renal impairment. In children aged 4 to12 years the $t_{½}$ is reduced compared to adults, with a mean (SD) of 19 (3) hours. Prucalopride is excreted in human breast milk with breast fed infants estimated to receive about 6% of the maternal dose.

Ketoconazole, a potent inhibitor of cytochrome P450 3A4 (CYP 3A) and also an inhibitor of p-glycoprotein, increased the plasma exposure to prucalopride by 40%. Erythromycin, an inhibitor of CYP 3A did not affect the PK of prucalopride. However, prucalopride increased exposure to erythromycin by 25%. Prucalopride decreased digoxin AUC by ~10%, indicating some potential for interactions involving p-glycoprotein. Neither probenecid nor cimetidine affected the PK of prucalopride. The clinical evaluator considered that the metabolism of prucalopride had not been sufficiently elucidated and that there had been insufficient investigation into which renal transporters are responsible of its active secretion and of the effect of inhibition of active secretion.

Prucalopride at doses up to 10 mg daily at steady state did not prolong the mean QT interval by > 5 msec at any timepoint during the 48 hours from dosing in healthy adult subjects. Prucalopride was associated with dose related headache, flatulence, diarrhoea and dizziness. Oro-caecal transit time but not colonic transit time was reduced. Prucalopride did not affect rectal distension thresholds, anorectal electrosensory thresholds or anorectal manometry. 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 effect on colonic transit time.

*Efficacy*

Six Phase II/ dose finding studies and six Phase III studies in subjects were submitted. Total daily doses from 0.5 to 4 mg daily and twice daily versus once daily dosing were assessed.

The pivotal studies (INT-6, USA-11 and USA-13) had an identical design. They were double blind, placebo controlled studies comparing 2 mg and 4 mg once daily oral doses of prucalopride with placebo in subjects with chronic constipation. After a two week drug free run in period subjects received prucalopride 2 or 4 mg daily or placebo for 12 weeks. Chronic constipation was defined as an average of 2 or fewer spontaneous complete bowel movements (SCBMs) per week (without use of a laxative within 24 hours of the movement) and the presence of one or more of the following symptoms for at least 6 months before the selection visit:

- very hard (little balls) and/or hard stools at least a quarter of the stools;
- or sensation of incomplete evacuation following at least a quarter of the stools;
- or straining at defecation at least a quarter of the time.

Rescue treatment with bisacodyl was allowed if the subject did not have a bowel movement for three or more consecutive days. Rescue enemas were also permitted.

The primary endpoint was the proportion of subjects who achieved a mean of ≥3 SCBMs per week over the 12 weeks of double blind study treatment. Secondary endpoints included the proportion of subjects with an average increase over baseline of at least one SCBM per week, average score for stool consistency and straining during defecation, time to first SCBM after first dose of study drug, average number of bisacodyl tablets or enemas used per week, symptom related data from the validated PAC-SYM questionnaire and the validated PAC-QoL questionnaire (satisfaction subscale score).

The majority of subjects in these pivotal studies were women (90.8% in INT-6, 87.9% in USA-11 and 86.6% in USA-13). Subjects reported a history of chronic constipation for a median of close to 20 years. Around 40% reported no spontaneous bowel movements most weeks prior to study enrolment (and laxatives were required). Some 17-18% considered their pre study treatment for constipation adequate and around 14% were not taking laxatives in the period prior to study enrolment. Around 40% of subjects were not taking bulk forming agents or a diet to manage constipation. Some 20.9% of patients given placebo and 18.9% of patients given prucalopride received bisacodyl. Some 7.4% of patients given placebo and 5.9% of patients given prucalopride received fleet enema at least once during the study.

In each of these studies, by Week 12 of double blind treatment there was a statistically significant difference between placebo and each dose of prucalopride as shown in Table 58 below:

**Table 58. Number of subjects with an average of ≥ 3 SCBM per week (Weeks 1 – 12)**

| Study | Placebo | 2 mg prucalopride | 4 mg prucalopride |
|---|---|---|---|
| **INT-6** | 23/240 (9.6%) | 46/236 (19.5%)* | 56/237 (23.6%)* |
| **USA-11** | 25/193 (13.0%) | 55/190 (28.9%)* | 54/187 (28.9%)* |
| **USA-13** | 25/207 (12.1%) | 50/209 (23.9%)* | 48/204 (23.5%)* |

*statistically significant versus placebo

From the above results it was concluded that no prucalopride dose response was apparent, with the 2 mg daily dose of prucalopride having similar efficacy to the 4 mg daily dose. Prucalopride resulted in 10 to 16% more individuals than placebo having at least 3 bowel movements per week without the aid of bisacodyl. Pooled results from these studies showed that 22.5% of subjects given placebo, 42.3% of subjects given 2 mg prucalopride and 47.3% of subjects given 4 mg prucalopride had an average increase over baseline of ≥1 SCBM per week. Mean use of rescue treatment with bisacodyl was less than one day a week for all groups in all pivotal studies is summarised in Table 59.

**Table 59. Mean days / week rescue treatment with bisacodyl was taken**

| Study | Placebo | 2 mg prucalopride | 4 mg prucalopride |
|---|---|---|---|
| **INT-6** | 0.8 | 0.4 | 0.5 |
| **USA-11** | 0.9 | 0.5 | 0.5 |
| **USA-13** | 0.7 | 0.6 | 0.5 |

A subgroup analysis of efficacy in men compared with women from the pooled pivotal studies is shown in Table 60 below.

**Table 60. Efficacy in female versus male subjects (Weeks 1to 12) in pivotal studies**

| Efficacy endpoint | Placebo | 2 mg prucalopride | 4 mg prucalopride |
|---|---|---|---|
| **Average of ≥ 3 SCBM per week** | F 10.7%<br>M 16.9% | F 24.4%*<br>M 17.6% | F 24.4%*<br>M 27.2% |
| **Average increase of ≥ 1 SCBM per week** | F 24.2%<br>M 28.1% | F 45.0%*<br>M 27.9% | F 46.3%*<br>M 52.0%* |

*$p < 0.05$

Noting the relatively poor response of males to the 2 mg dose of prucalopride and having considered that there was no pharmacological reason why men should respond differently from women, the sponsor performed post hoc analyses. In the group of men given 2 mg prucalopride there were proportionally more subjects with severe constipation (demonstrated by no complete bowel motions during the run in period) than in the male placebo or 4 mg prucalopride groups. From information provided in The sponsor's response to the clinical evaluation, the Delegate calculated that 31/68 (45.6%) of men given 2 mg prucalopride in the pivotal studies had no complete bowel movement (CBM) in the run in period compared with 17/64 (26.5%) given placebo and 19/75 (25.3%) given 4 mg prucalopride.

Males and females who had less severe constipation (demonstrated by having >0 complete bowel motions during the run in period) had similar efficacy responses. The proportion of these men with an average ≥ 3 SCBM per week (Weeks 1 to 12) was similar to that of women for both dose groups; 17.0% (8/47) of men given placebo, 32.4% (12/37) of men given 2 mg prucalopride and 37.5% (21/56) of men given 4 mg prucalopride. The sponsor concluded that the skewed distribution of male subjects with no complete bowel motions during the run in period in combination with the relatively small number of males in the pivotal studies prevented the response for the 2 mg dose in men reaching statistical significance on the primary endpoint.

Time to onset of efficacy was examined in the pivotal studies. The response to prucalopride was generally apparent from the first week of the 12 week double blind treatment period (sponsor's Clinical Summary). In each pivotal study, results for the Week 1-4 efficacy analysis were similar to those of the primary analysis of the Week 1-12 treatment period. It is reasonable to conclude from this that responses should be apparent within the first 4 weeks of treatment.

Study USA-28 examined the effect of retreatment. No loss of efficacy with retreatment was apparent after a two week treatment break and no rebound effect was seen during the treatment break.

A study in subjects aged at least 65 years examined the proposed dose for this age group of 1 mg daily for 4 weeks. USA-26 enrolled 100 nursing home residents. A greater proportion of men were included compared with other Phase II/III studies and inclusion of subjects who had any treatment for constipation in the preceding 4 weeks was permitted. The primary efficacy endpoint was the subject's Global Assessment of severity of constipation and efficacy of treatment. No statistically significant differences between the treatment groups were demonstrated.

*Safety*

No clear safety concerns have arisen from review of the data submitted. A total of 2717 subjects meeting study definitions of chronic constipation were exposed to prucalopride in double blind, placebo controlled Phase II and III studies with median exposure of 57 days. Some 2,595 subjects with chronic constipation were treated with prucalopride in open studies with a median treatment duration of 284.4 days (40.6 weeks). Some 1,490 subjects were treated for 6 months or longer and 869 subjects were treated for more than 1 year (>365 days).

In the double blind, placebo controlled studies in chronic constipation, adverse events were reported in 68.6% of subjects given any dose of prucalopride and in 60.3% of subjects given placebo. The most frequently reported adverse drug reactions (ADRs) in subjects given prucalopride were headache (21.6% versus 11.8% placebo), nausea (17.0% versus 7.7% placebo), diarrhoea (12.1% versus 3.3% placebo) and abdominal pain (10.3% versus 9.3% placebo). The frequency of each of these ADRs increased with increasing dose of prucalopride. In the open studies similar ADRs were reported. Overall few subjects in any groups withdrew due to ADRs.

The overall incidence of serious adverse events (SAEs) with prucalopride was low (2.1%) and similar to placebo (1.9%). There was no apparent dose relationship noted. Individual SAEs were isolated incidents, reported by at most 0.1% of the prucalopride treated subjects. There were three deaths in the double blind placebo controlled studies in chronic constipation: two subjects given prucalopride and one given placebo. All were elderly subjects and these deaths were not considered treatment related.

There were two reports of supraventricular tachycardia (SVT) in subjects given prucalopride (no such reports in the placebo group). Small increases from baseline in mean heart rate were seen in some Phase I studies but these were not consistently reported across studies.

The clinical evaluator was concerned about the risk of bowel perforation associated with use of prucalopride and requested any additional data or analyses of bowel perforation The Delegate considered that this was a potential risk that had not been fully considered in the RMP. Any prokinetic treatment given to patients with chronic constipation could potentially cause bowel perforation. Some assurance that this would be a rare event is provided by the clinical trial data. However, this was in a limited population of patients with chronic constipation. In The sponsor's response to the clinical evaluation results of Study PRU-USA-5 were discussed. In this study prucalopride was given via SC injection to patients undergoing elective partial colectomies. Three cases of bowel perforation/ fistula were reported. However, none of these were considered by the study investigators to be related to study medication.

The clinical evaluator also noted the absence of information on the effect of prucalopride on menstrual disorders, in particular dysmenorrhoea. There was concern that the prokinetic effect of prucalopride would exacerbate dysmenorrhoea. This was explored in the additional analyses provided in sponsor's response to the clinical evaluation. Dysmenorrhoea was not strongly associated with prucalopride in patients not taking oral contraceptives. Prolactin levels were measured in the Phase II/III clinical studies and pooled results showed a decrease in mean prolactin levels from baseline to Week 4 in the prucalopride dose groups but not in the placebo group.

## Risk Management Plan

The RMP submitted appeared to be the EU RMP and specified the EU indication that excludes use in men. However, the sponsor has proposed that prucalopride be indicated in both men and women in Australia. The sponsor has proposed routine pharmacovigilance for all identified safety concerns.

The RMP reviewer has supported the clinical evaluator's concerns regarding the possibility of bowel perforation as an adverse effect of prucalopride and the absence of exploration of the effect of prucalopride on patients with dysmenorrhoea. Dysmenorrhoea as an adverse event has now been satisfactorily explored and no strong association noted.

The sponsor identified palpitations as a risk and stated that at the therapeutic dose palpitations occurred at a frequency not significantly higher than in the placebo group, although increased in

frequency at 4 mg daily (twice the therapeutic dose). Ischemic colitis and syncope were identified as additional risks by Swiss Medic and the Committee for Medicinal Products for Human Use (CHMP), respectively.

The sponsor has advised that the following studies are planned:

- M001-EPI-1-FUM006 to examine the following cardiovascular and cerebrovascular ischaemic events; QT prolongation and related ventricular arrhythmias; potential for off-label paediatric use; and safety in pregnant women.
- M001-C401-FUM005 to examine efficacy of longer term use (to 24 weeks).
- M0001-C303 to examine efficacy and safety in paediatric patients.

A safety and efficacy study in males, a potential for off label use in males and a single dose PK study in patients with moderate and severe hepatic impairment are also either planned or underway.

Overall the RMP evaluator accepted The sponsor's proposal for routine pharmacovigilance with the additional studies as proposed and underway. The RMP evaluator requested that the RMP refer to the indication proposed for Australia, include menstrual disturbance and bowel perforation as potential risks and address questions concerning the protocols and start dates for the proposed postmarket clinical studies.

## Risk-Benefit Analysis

### Delegate Considerations

*Pharmacology:* The clinical evaluator had 5 questions concerning pharmacology aspects of the submission. The Delegate regarded these as having been satisfactorily addressed by the sponsor and there are no current pharmacology concerns.

*Diagnostic criteria in pivotal clinical trials:* There are no TGA adopted guidelines for medicinal products for use in the management of chronic constipation. In The sponsor's Clinical Expert's Report it was noted that the most widely used criteria for diagnosis of chronic constipation are the Rome II criteria for functional constipation. These require the presence of 2 or more of the following symptoms for at least 3 months:

1. ≤ 2 bowel movements per week

2. Hard stools at least 25% of the time

3. Incomplete evacuation at least 25% of the time

4. Straining at least 25% of the time

Abdominal pain is not required, loose stools are not present and there are insufficient criteria for irritable bowel syndrome.

In contrast, the criteria to determine chronic constipation in clinical trials were an average of two or fewer spontaneous complete bowel movements (SCBMs) per week (without use of a laxative within 24 hours of the movement) and the presence of one or more of the following symptoms for at least 6 months before the selection visit:

- Very hard (little balls) and/or hard stools at least a quarter of the stools;
- or sensation of incomplete evacuation following at least a quarter of the stools;
- or straining at defecation at least a quarter of the time.

Neither of these definitions requires a maximum number of bowel movements in any time period. However the Rome II criteria include a maximum of two motions per week as one of 4 criteria with at least 2 of the 4 criteria required to meet the definition. The remaining criteria have an element of subjectivity (for example, how much straining qualifies as straining and how hard are stools required to be). The clinical trial definition allowed for the inclusion of subjects who had >3 stools per week with the aid of laxatives used intermittently.

*Selection criteria in pivotal clinical trials:* The severity of chronic constipation in the study population prior to enrolment appears to have been variable with 14% not taking laxatives and 40% not on a diet or taking bulk forming agents to manage constipation prior to study enrolment. Some 17% of patients considered their prior treatment to be adequate. During the pivotal studies mean laxative use was less than 1 day a week in all treatment groups, including placebo. Use of bisacodyl was permitted only if no spontaneous bowel motion had occurred in the preceding 3 days. Mean use during double blind treatment was <1 /week in all groups. Severity of chronic constipation was not a baseline demographic factor and no attempt was made to define severity or to identify a subgroup of subjects by severity of their chronic constipation prior to commencement of the pivotal studies. It therefore appears that the pivotal studies examined efficacy of prucalopride in a population that is unlikely to be representative of the population in which prucalopride would be used in clinical practice, that is, those with moderate to severe chronic constipation that has not responded to adequate alternate measures such as diet, bulk forming agents, fluids, exercise and intermittent laxatives. This is of particular concern given the absence of an active comparator.

The small number of men in the clinical trial program had potential to limit the generalisability of study results. Men constituted ~10% of the study population. However, given that functional constipation is much more common in women than men it is not surprising that women composed most of the study population. The post hoc analyses of efficacy results in men enrolled in the pivotal studies is adequate to demonstrate that there is no major difference in expected response to prucalopride between men and women once baseline severity of constipation has been taken into account. The Delegate did not propose to limit use of prucalopride to women only.

The selection criteria in the efficacy studies excluded patients with secondary causes for their constipation such as those taking medications associated with constipation as well as patients with endocrine, metabolic or neurological conditions associated with constipation. This would constitute a large group of patients in whom efficacy has not been assessed and also limits the generalisability of the efficacy results.

Use of prucalopride as an adjunct to other treatments has not been proposed by the sponsor nor adequately assessed in clinical trials.

Results from one study (INT-8, discussed under *Clinical findings* above) suggest prucalopride is not effective in constipation due to opioids. The sponsor has responded to this concern by proposing that the indication be amended to refer only to chronic functional constipation rather than chronic constipation as was initially proposed. The sponsor has stated that the term chronic function constipation is consistent with the constipation experienced by patients in the clinical trials, whereby the cause of their constipation could not be explained by the presence of structural or tissue abnormalities and all secondary constipation has been excluded. This was accepted.

*Extent and duration of demonstrated efficacy:* A strong dose response relationship was not apparent. The dose finding studies did not convincingly show a dose response relationship. However, it is clear that the 2 mg daily dose has similar efficacy to the 4 mg daily dose.

Efficacy in the pivotal studies was modest and relative efficacy against a laxative or "treatment as usual" was not examined. There may be a subgroup in those studies that responded to prucalopride extremely well however this was not apparent from the analyses presented.

Comparative efficacy with placebo was examined for a maximum of 12 weeks, yet long term use has been proposed. In the response to the clinical evaluation the sponsor has noted that an open, uncontrolled study that includes an assessment of efficacy over a longer period is underway. From the limited information on this study provided in the sponsor's response to the clinical evaluation, this study assessed efficacy using a quality of life questionnaire. No quantitative assessment of ongoing efficacy appears to be planned. Given the above, the Delegate did not consider that continuous use of prucalopride could be supported for longer than 12 weeks.

Time to onset of response was determined in the pivotal studies and those individuals likely to benefit from treatment appear to be readily identified within 4 weeks of treatment commencement.

*Lack of active comparator in pivotal studies:* In The sponsor's response to the clinical evaluation the sponsor has noted some clinical trials of laxatives for the treatment of constipation performed in recent years did not include active comparators. The Delegate did not regard this as sufficient justification for not including standard treatment, or treatment as usual, or an active comparator in the pivotal trials for prucalopride. Such use would have greatly enhanced the ability of these studies to determine the clinical utility of prucalopride. The Delegate considered that the lack of an active comparator was a major weakness in the pivotal studies design.

It would also have been useful to examine how prucalopride performed as an "add on" to adequate standard therapies for constipation in patients with moderate to severe chronic constipation. The sponsor has previously contended that laxatives would not be the comparator of first choice because prucalopride is intended for use in subjects in whom laxatives fail to provide adequate relief. In addition prucalopride is intended for long term use, whereas laxatives should be used only if required and on an intermittent basis. Given this argument, the extent of failure to respond to an adequate trial of laxatives should be included in the indications for use of prucalopride.

*Safety issues*: Although no clear safety issues are apparent from the data submitted it is not known how prucalopride would perform when given to those patients who most need an additional treatment for chronic constipation, that is, those with severe constipation taking intermittent laxatives with insufficient relief or who were not responsive to a variety of laxatives/ diet/ bulking agents. While these subjects would have been included in the clinical trial population no subgroup analysis of this group was performed.

It is not clear whether prucalopride would be associated with bowel perforation if used in a population with bowel obstruction or pseudo obstruction. Prucalopride should not be used in patients with these conditions. Prucalopride should also not be used in patients who have recently undergone abdominal surgery.

**Conclusion and recommendation**

The Delegate proposed to approve Resotrans (prucalopride) for registration with the amended indication of:

*Treatment of chronic functional constipation for up to 12 weeks 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.

The advice of the ACPM is requested, particularly on the following issues:

- Whether the limitations of the development program with regard to the demonstration of efficacy preclude its registration.
- Whether it is appropriate to permit use of prucalopride in men given the small number of men studied and the post hoc analyses performed to assess efficacy in this group.
- Whether longer term use could be permitted in the absence of robust long term efficacy data.
- Whether it is appropriate to limit the indications as proposed or whether that information would be more appropriately included in the *Precautions* section of the PI.
- Whether use should be contraindicated in patients with severe hepatic impairment in the absence of PK data for this group.
- Whether the proposed post market studies in addition to routine pharmacovigilance are sufficient or whether some additional pharmacovigilance activity is warranted.
- Should the conditions of registration include that the initial prescription for Resotrans be from a gastroenterologist?

### Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

In expressing its view that this submission for prucalopride succinate (Resotrans) tablets 1mg and 2mg was suitable to be considered for approval, the ACPM considered the following matters:

**Efficacy**

The ACPM agreed with the Delegate that evidence of efficacy, albeit modest, was provided in the pivotal studies. The sponsor has not demonstrated any advantage for prucalopride over currently available treatments for constipation nor as an 'add on' to adequate standard therapies. The Committee agreed with the Delegate that lack of an active comparator is a major weakness in the design of the pivotal studies. There are very limited data in men but this is considered reasonable as the condition is far more commonly reported in women. There is no known physiological reason for a difference in efficacy between men and women.

**Safety**

There remain some unresolved, potentially serious safety issues. These relate to the cardiovascular safety of prucalopride (QT prolongation, increased resting heart rate and tachyarrhythmias). Generally the incidence of treatment emergent adverse events increased with dose. However, there was no correlation between plasma concentration and change in QTc steady state interval. The increase in pulse rate reported was small but may be clinically significant in the longer term, while findings with regard to QT prolongation were inconsistent. The Committee considered that the routine pharmacovigilance plan along with proposed studies should provide more substantial evidence relating to the potential safety issues raised.

The ACPM was also concerned that the safety and efficacy data submitted refer only to relatively short term use, whereas patients may well use the product for a considerable period.

The ACPM agreed with the restrictions included by the Delegate in the statement of the indications but did not consider there should be a restriction of prescription to gastroenterologists. The ACPM was also of the view that the sponsor should be encouraged to submit a further study on the pharmacokinetics of prucalopride in patients with renal impairment such that the pharmacokinetics are assessed at steady state.

### Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Resotrans prucalopride (as succinate) 1 mg tablet blister pack and Resotrans prucalopride (as succinate) 2 mg tablet blister pack for oral administration, one tablet per day, 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"*

# Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

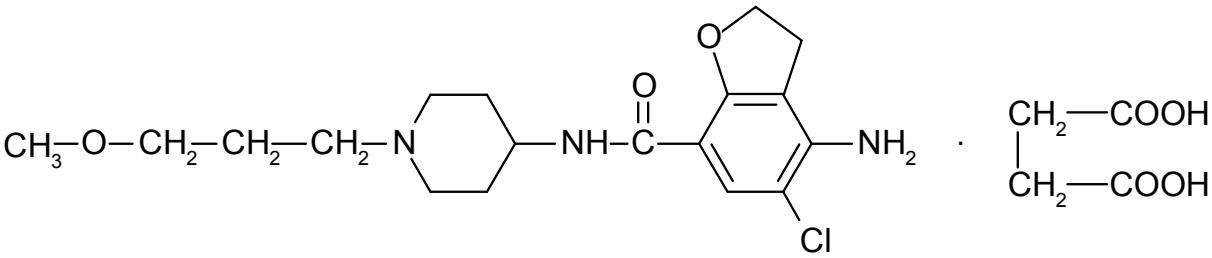
# RESOTRANS™
# Tablets

## PRODUCT INFORMATION

### 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:



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

CAS Registry No: 179474-85-2

### DESCRIPTION

Prucalopride succinate is a white to almost white powder.

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

RESOTRANS tablets contain the following inactive ingredients:

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

Coating: hypromellose, titanium dioxide, lactose, macrogol 3000 and glycerol triacetate. Additionally, in the coating, the 2 mg tablet contains iron oxide red, iron oxide yellow and indigo carmine C173015.

**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 1**.

**Table 1**: **Partition coefficient P**

| Aqueous buffered solution | Partition coefficient P | Log P | pH of solution |
|---|---|---|---|
| Phosphate-NaOH solution | $1.78 \times 10^2$ | 2.25 | 12.0 |

# PHARMACOLOGY

## Pharmacodynamics
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.

## Pharmacokinetics
### 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 ($Vd_{ss}$) 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.

### Elimination
A large fraction of the active substance is excreted unchanged (about 60% of the administered dose in urine and at least 6% in faeces). 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 **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS**).

***Hepatic Impairment***
Non-renal elimination contributes to about 35% of total elimination, and hepatic impairment is unlikely to affect the pharmacokinetics of prucalopride to a clinically relevant extent (see **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS**).

***Paediatric Population***
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 **DOSAGE AND ADMINISTRATION**). RESOTRANS is not recommended in children or adolescents (see **PRECAUTIONS** under **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 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.

## 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.

## 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

## PRECAUTIONS

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.

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.

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 subjects with severe renal impairment (see **DOSAGE AND ADMINISTRATION**).

## Use in Patients with Hepatic Impairment

It is unlikely that hepatic impairment will affect RESOTRANS metabolism and exposure in man to a clinically relevant extent. No data are available in patients with mild, moderate or severe hepatic impairment, and therefore a lower dose is recommended for patients with severe hepatic impairment (see **DOSAGE AND ADMINISTRATION**).

## 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, 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.

## 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

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 phaeochromocytomas, 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 $D_2$ 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.

## 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.

## Interactions with Other Medicines

*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. Although prucalopride 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 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%.

Studies in healthy subjects showed that there were no clinically relevant effects of RESOTRANS on the pharmacokinetics of warfarin, digoxin, alcohol and paroxetine. 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.

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.

### 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 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 4**.

**Table 4: Chronic constipation: adverse events reported by ≥ 2% of RESOTRANS-treated subjects in Phase II and III double-blind placebo-controlled studies. Population: All patients**

| System Organ Class<br>Preferred Term | Placebo<br>n (%) | RESOTRANS 0.5 mg<br>n (%) | RESOTRANS 1 mg<br>n (%) | RESOTRANS 2 mg<br>n (%) | RESOTRANS 4 mg<br>n (%) | All RESOTRANS<br>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 (≥ 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.

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 supratherapeutic 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.

# 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 not requiring dialysis (GFR < 30 mL/min/1.73m$^2$) is 1 mg once daily (see **CONTRAINDICATIONS** and **Pharmacokinetics**). No dose adjustment is required for patients with mild to moderate renal impairment.

*Patients with hepatic impairment*: 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 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.

## Method of administration

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

# OVERDOSAGE

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.

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 in order to protect from moisture.

# POISON SCHEDULE OF THE MEDICINE

S4 - Prescription Only Medicine

# SPONSOR

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Date of TGA approval: 4 October 2011

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

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Reference/Publication #