European Medicines Agency
*Evaluation of Medicines for Human Use*

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**CHMP ASSESSMENT REPORT**

**FOR**

**Resolor**

International Nonproprietary Name: Prucalopride

**Procedure No. EMEA/H/C/1012**

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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# 1 BACKGROUND INFORMATION ON THE PROCEDURE

## 1.1 Submission of the dossier

The applicant Movetis NV submitted on 8 May 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Resolor, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 17 July 2007.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

**Scientific Advice:**
The applicant received Scientific Advice from the CHMP on 18 June 1997, 17 December 1997, 26 March 1998 and 29 July 1999

The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

**Licensing status:**

The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:
Rapporteur: **Ian Hudson** Co-Rapporteur: **Tomas P Salmonson**

## 1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 8 May 2008.
- The procedure started on 28 May 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 August 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 August 2008.
- During the meeting on 25 September 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 September 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 March 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 8 May 2009.
- During the CHMP meeting on 29 May 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List Issues to all CHMP members on 6 July 2009 and 16 July 2009.
- During the meeting on 20-23 July 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion, by consensus, for granting a Marketing Authorisation to Resolor on 23 July 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 21 July 2009.

# 2 SCIENTIFIC DISCUSSION

## 2.1 Introduction

Chronic constipation is a common and often debilitating medical problem, with a demonstrated impact on quality of life (Wald, 2007; Dennison, 2005). Depending on the definition used, the prevalence of any kind of constipation varies between 5-15% of the general population in Europe, with some of the highest prevalence found in Spain and the lowest in the United Kingdom.

Besides problems of disordered defecation, chronic constipation is generally associated with a reduction in the giant migrating contractions that normally drive mass transits through the colon (Schiller, 2004). Evidence has emerged that morphological alterations of the enteric nervous system may underlie motility impairment in these patients (Bassotti, 1996).

Prucalopride was selected for development in chronic constipation because it has the potential to address the underlying motility problem and provide broad symptom relief beyond increase in stool frequency; particularly in patients that report a lack of adequate relief on currently available laxatives.

Prucalopride belongs to a chemical class of dihydrobenzofurancarboxamide-derivatives with potent enterokinetic activity. It is one of a new generation of selective, high-affinity 5-HT4 receptor agonists, likely explaining its enterokinetic effects (De Maeyer et al., 2008). Serotonin (5-HT) signalling in the GI tract is known to regulate a range of functions including motility and consequently interest has been directed toward developing selective 5-HT4 receptor agonists for treating disorders in which GI motility is impaired, such as constipation (Galligan and Vanner, 2005; Schiller, 2004)

This application is supported by 82 studies: 47 Phase I, 25 Phase II and 10 Phase III studies of which 3 were pivotal. In the Phase II/III double-blind placebo-controlled studies in chronic constipation, a total of 2717 patients were treated with doses of Prucalopride ranging from 0.5 to 4 mg. In the open long-term studies, 2595 patients with chronic constipation were treated with Prucalopride, 1490 of which received treatment for at least 6 months and 869 received at least 1 year of treatment.

The initially proposed therapeutic indication is as follows:

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

After review of the dossier, the indication has been revised and endorsed by the CHMP as follows:

"Resolor is indicated for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief."

The posology for adults is one tablet (2 mg) once daily. Based on pharmacokinetic considerations, the elderly (>65 years) should start with one 1 mg tablet once daily; if needed the dose can be increased to 2 mg once daily. At time of initial Marketing authorisation, the safety and efficacy of Prucalopride in children and adolescents younger than 18 years had not yet been established. Neither was sufficient data obtained in males to recommend the use of the medicinal product in this patient population. The applicant however committed to perform a post-marketing study in adult male patients, as part of agreed follow-up measures (FUMs).

## 2.2 Quality aspects

### Introduction

Resolor is presented as film-coated tablets containing 1 mg and 2 mg of Prucalopride succinate as active substance. The excipients used in the formulation of Resolor are lactose monohydrate, microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate.

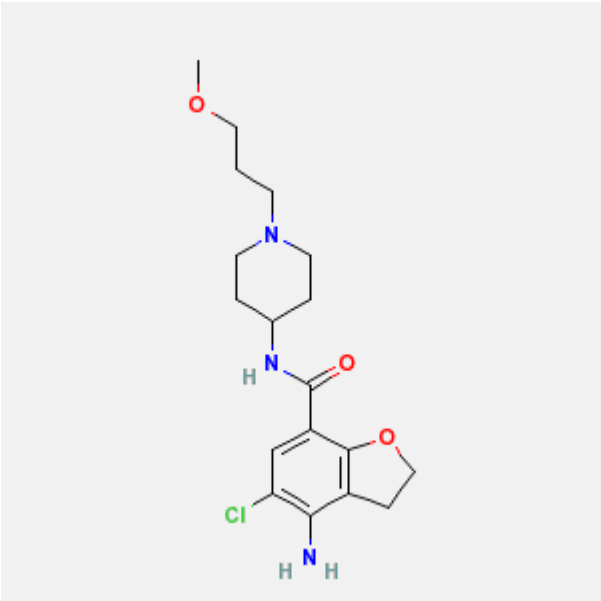
Resolor is administered via oral route and is packed in Alu/Alu blisters of 28 unit dose tablets.

### Active Substance

The active substance belongs to a chemical class of dihydrobenzofurancarboxamide-derivatives with potent enterokinetic activity.

Prucalopride succinate is chemically designated as 4-amino-5-chloro-2,3-dihydro-N-[1-(3-methoxypropyl)-4-piperidinyl]-7-benzofurancarboxamide butanedioate (1:1). The structure of Prucalopride is shown in Fig.1.

Figure 1: Chemical structure of Prucalopride




Prucalopride succinate is a white to almost white powder soluble in *N,N*-dimethylformamide, sulfinylbismethane and *N,N*-dimethylacetamide and sparingly soluble in methanol. In addition, Prucalopride succinate is freely soluble in acidic aqueous media and >90% of the active substance is absorbed with the $C_{max}$ being attained in 2-3 hours. The active substance is therefore in biopharmaceutics classification system (BCS) class I, i.e., high permeability, high solubility.

Prucalopride succinate is not hygroscopic and its melting point is ~198°C. The polymorph screening was investigated by infrared spectrometry and differential scanning calorimetry. No polymorphism was observed. Prucalopride succinate contains no chiral centres. The pKa for the piperidine moiety of Prucalopride succinate is 8.5, determined at 20°C. The pKa for the amino moiety of Prucalopride succinate is less than 3, determined at 20°C.

- Manufacture

Prucalopride succinate is synthesised in three steps from two starting materials. Step 1 does not affect the critical quality attributes (CQAs) of the final active substance and this step is identified as not critical. The last 2 process steps, step 2 and 3, impact the CQAs of the final active substance, and are therefore critical steps of the synthesis.

Confirmation of the chemical structure of Prucalopride succinate was provided by infrared spectroscopy,$^{1}$H Nuclear Magnetic Resonance (NMR) spectroscopy, $^{13}$C NMR spectroscopy, mass spectrometry and ultraviolet spectroscopy.

- Specification

The active substance specification includes tests for appearance (visual examination), identification (HPLC and IR), assay (HPLC), impurities (HPLC), loss on drying (Ph. Eur.), residue on ignition (Ph. Eur.), heavy metals and particle size (laser diffraction).
Three commercial scale batches of the active substance were manufactured using the proposed manufacturing process, at the proposed commercial manufacturing site. These batches were tested with validated analytical methods. The results demonstrate a consistent manufacturing process.

Acceptance criteria were set based on the analytical data, stability data, clinical and toxicological data and were in accordance with ICH Q6A.

- Stability

Stability studies were performed on three commercial scale batches at various storage conditions, i.e., long term conditions (25$^{o}$C/60% RH) for 24 months and accelerated conditions (30$^{o}$C/70% RH and 40$^{o}$C/75% RH) for 6 months according to the ICH guidelines on stability. No significant changes were observed in any of the parameters monitored under various storage conditions. In addition, photostability data was also provided as well as data on the forced degradation studies performed on one batch in solution. The effect of pH, oxidative agents and light was evaluated. The purpose of these studies was to identify potential degradation compounds of Prucalopride succinate. The results showed that Prucalopride succinate is sensitive to extreme light and metallic ions and is not stable in an oxidative medium.

The active substance is packaged in double low density polyethylene (LDPE) bags in a drum sealed with a metal band and cap.

Stability data provided indicates that the active substance is stable. The proposed retest period is considered to be acceptable.

**Medicinal Product**

- Pharmaceutical Development

Initial formulation work involved the development of oral solutions, intravenous injections and capsules. However, the pharmaceutical form of choice was an immediate release tablet. The tables were initially manufactured by wet granulation in 0.5mg, 1mg, 2mg, and 4mg strengths, and these were used in the clinical trials. The wet granulation process was later replaced by direct compression due to the formation of a lactose adduct induced by exposure to moisture. Bioequivalence between the wet granulation tablets (clinical formulation) and the direct compression tablets (commercial formulation) was demonstrated by bioequivalence trials. The studies demonstrate the wet-granulation batches are bioequivalent to the new direct compression tablets.

The shape of the commercial tablets was changed from oblong to circular during development and a new manufacturing site was proposed for the manufacture of the finished product. Dissolution studies

showed that for both oblong tablets and circular tablets the dissolution profiles were similar with more than 80% dissolved in 10 minutes, irrespective of process or site.

Moisture was shown to induce the formation of a lactose adduct in the finished product, which was confirmed in the stability studies. The lactose adduct was not observed in tablets packaged into moisture impermeable Alu/Alu blisters, even when stored for 12 months at condition 30°C/70% RH. Therefore, Alu/Alu blisters were chosen for the commercial packaging of Prucalopride succinate tablets.

The excipients used to manufacture the core tablets are all compendial. In addition, the solvent (purified water) used in the film-coating is compendial. The coating powders are commercially available mixtures. The two coating formulations are selected to provide taste-masking and colour differentiation between the tablet strengths.

Lactose monohydrate was used as diluent, microcrystalline cellulose was added to the formulation in the external phase as dry binder to increase tablet hardness during compression. In addition, microcrystalline cellulose functions as a disintegrant, due to swelling, when in contact with aqueous solutions. Colloidal silicon dioxide was used as a glidant to improve flowability and magnesium stearate was added to the formulation as a lubricant.

The effect of the Prucalopride succinate particle size on the blend flowability and subsequently on the blend uniformity and the tablet content uniformity was investigated. Particle size was demonstrated not to be critical within the specified range as tablets manufactured with different drug substance particle sizes all had equivalent tablet characteristics.

A dissolution method for Prucalopride succinate 1 mg and 2 mg tablets was developed. The test conditions were based upon the solubility of the drug substance. Prucalopride succinate is highly soluble in 0.1 N HCl and therefore the tests were carried out under sink conditions.

- Adventitious Agents

Satisfactory statements for lactose monohydrate and coating powders “white 1” and “pink” regarding the compliance of lactose monohydrate with the “Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products” and the European Council Directive 2001/83/EC concerning BSE/TSE were provided. None of the other excipients are derived from animal or human origin. Magnesium stearate is of vegetable origin.

- Manufacture of the Product

Prucalopride succinate tablets are prepared via a direct compression process, followed by film-coating and blistering. The critical parameters have been identified and the in-process controls applied during the manufacturing process for the film-coated tablets were considered acceptable.

Validation of the manufacturing process was performed on six validation batches. The results were consistent and satisfactory.

- Product Specification

The specification for Prucalopride succinate include tests for appearance (visual examination), identification (HPLC and IR), assay (HPLC), impurities (HPLC), content uniformity (Ph. Eur.), dissolution (HPLC) and microbial purity (Ph. Eur.).

The finished product specifications have been justified and all methods of analysis have been described and adequately validated.

Batch analysis data was provided for three primary batches (of each strength of the finished product) manufactured at the proposed commercial manufacturing site. The results were within the proposed specification for the drug product.

- Stability of the Product

Stability studies have been performed on three primary stability batches of each strength using a range of stability conditions (5°C, 25°C/60% RH, 30°C/65% RH, 30°C/70% RH, 40°C/75% RH and 50°C) from various manufacturing sites. Six months stability data at 25°C/60% RH and 30°C/65% RH (long term conditions) and at 40°C/75% RH (accelerated conditions) were provided for commercial batches manufactured at the proposed manufacturing site.

In summary, the stability results support the shelf-life and storage conditions as defined in the SPC.

## 2.3 Non-clinical aspects

### Introduction

The applicant stated that all safety pharmacology studies, pharmacokinetic studies and all toxicology studies were carried out either in accordance or in full compliance with GLP regulations.

### Pharmacology

- Primary pharmacodynamics

An adequate programme of pharmacology studies has been performed; of which only the pivotal studies are discussed in this assessment report. Prucalopride has a high affinity (Ki≤11 nM) for human 5-HT4 receptors expressed in human embryonic kidney (HEK) 293 cells. Prucalopride interaction with the 5-HT4 receptor leads to the elevation of cAMP-levels in the same cell line (EC50= 5 nM). Prucalopride interacted weakly with human sigma receptor binding sites (Ki-value 3.7 μM), with human dopamine-D2 receptors (Ki-values were 14.0 μM) and with 5HT3 receptors (Ki-value 3.8 μM). Affinity for other receptors, channels or transporters, was detected at concentrations exceeding its 5-HT4 receptor affinity by at least 150-fold (up to 10,000-fold). This adequately demonstrated that Prucalopride is a selective, high-affinity 5-HT4 receptor agonist.

In the guinea pig (isolated tissue preparation), Prucalopride facilitated both cholinergic as well as non-adrenergic non cholinergic (NANC) excitatory neurotransmission and enhanced colonic motility/colonic contractile motility patterns in dogs. It was also shown that Prucalopride stimulated antral, pyloric and duodenal contraction amplitude in the conscious dog, but does not affect antro-duodenal coordination in this species. The *in vivo* effects on the gastrointestinal tract were sensitive to complete blockade with a selective 5-HT4 receptor antagonist, illustrating that Prucalopride exerts its effects via a selective action on 5-HT4 receptors.

- Secondary pharmacodynamics

In receptor binding studies, apart from its affinity for 5-HT4 receptors, Prucalopride did not show any significant affinity for a large number of receptors, ion channels, and monoamine transporter at or below concentrations exceeding Prucalopride 5-HT4 receptor affinity by at least 150 and up to 10,000 fold. Effects on gastrointestinal motility and gastric/intestinal secretion were also investigated. Prucalopride had no effects mediated via 5-HT2A, 5-HT2B and 5-HT3 receptors nicotinic cholinoceptors, motilin receptors or cholecystokinin-A receptors and was devoid of M3-cholinoceptor antagonistic, anticholinesterase and non-specific inhibitory (‘spasmolytic’) activity. Prucalopride did not affect basal or pentagastrin-induced gastric acid secretion in isolated immature rat stomach. Prucalopride did not affect gastric pH under basal conditions or after histamine challenge (ED50: ≥ 40 mg/kg s.c. or p.o.) and did not affect histamine-induced gastric liquid secretion (ED50: > 40 mg/kg, s.c. or p.o.) in rats. In conscious dogs, up to a dose of 0.63 mg/kg Prucalopride administered intragastrically via a chronically implanted gastric cannula, did not affect basal or pentagastrin-

induced gastric acid secretion. Prucalopride, tested at 10 μM, did not affect basal or electrical field stimulation-induced secretion on isolated guinea pig colonic mucosa. In preparations of human terminal ileum, Prucalopride did induce a concentration-dependent electrogenic secretion in the terminal ileum (EC50 = 5 μM), but not in the ascending or sigmoid colon (up to 300 μM).
The *in vivo* pharmacological profile of Prucalopride was studied at doses of up to 40 mg/kg in rodents and 10 mg/kg in dogs. Apart from primarily effects on the gastrointestinal tract Prucalopride was devoid of any additional effects on overt or conditioned behaviour or of effects that would suggest interaction with various types of receptors (α1, α2 and β2 adrenoceptors; D1 and D2 dopamine receptors; H1 and H2 histamine receptors; M- and N-cholinoceptors; 5HT1A and 5HT2A serotonin receptors; μ- and κ-opioid receptors; tachykinin NK1 receptors; glucocorticoid receptors); neurotransmitter uptake (5HT, norepinephrine or dopamine); enzymes (monoamine oxidase, cyclooxygenase, methohexital metabolising enzymes); pain perception (pinna-, cornea- and tail withdrawal reflexes, hot plate response, acetic acid writhing and local anaesthesia); body functions (temperature, muscle tone, pupil diameter, respiration, lacrimation, salivation, gastric pH, emesis); convulsions (induced by pentylenetetrazole, electroshock or cerebral anoxia); cardioprotection (against ouabain or BaCl2); or hypoxia (after KCN, nitrogen or cerebral anoxia).

Binding to dopamine D2 receptors (Ki = 14 μM = 5150 ng/ml; 687x the therapeutic plasma level) or antagonism at these receptors (ED50 in the rat after p.o. administration at 49 mg/kg) was seen in rats and dogs. In a pharmacology study, 5 mg/kg p.o. Prucalopride increased serum prolactin levels in female rats. Increased serum prolactin levels were noted in a large number of other studies (general toxicology studies and specific investigative mechanistic studies).

- Safety pharmacology programme

The effect of Prucalopride on the major organ systems were investigated in a battery of safety pharmacology studies at doses up to 100 times the intended clinical dose in vivo and generally cardiovascular effects were only seen at very high doses and/or exposures.

Prucalopride had no effect on the IKr current at concentrations up to 1 μM (370 ng/ml; approximately 49-fold higher than the Cmax in man). The $EC_{50}$ for IKr inhibition in hERG-HEK cells in various *in vitro* studies was between 4.1 to 22 μM (i.e. between 200-fold and 1100-fold higher than the Cmax in man). The $EC_{50}$ for IKr inhibition in ventricular myocytes (guinea pig heart) was in the same range i.e. 10 μM (3700 ng/ml; approximately 490-fold higher than the Cmax at the therapeutic dosage in man).

An increase in mean arterial blood pressure was noted 20 and 30 minutes after infusion and increased duration of the QT- interval at 5 and 10 minutes were noted in anaesthetized guinea-pigs at 2.5 mg/kg i.v (approximately 95 times the clinical exposure). In anaesthetised rabbits at 0.16 mg/kg/min (mean plasma level 2654 ng/ml, approximately 350x clinically relevant exposure) increases in QT-, QTc-, JT- and JTc-interval were noted. At 0.04 or 0.08 mg/kg/min no significant change in heart rate (HR), mean arterial blood pressure (MAP) and ECG parameters including QT-, QTc-, JT- and JTc-interval or the dispersion of the QT- and QTc-interval was noted.

In anaesthetised dogs, the duration of the QT interval, APD70, APD90, APD70c and APD90c were slightly shortened at 5 mg/kg. MAP traces showed no occurrence of EADs or DADS and no rhythm abnormalities were noted in the ECG traces. No influence on blood pressures and other peripheral haemodynamic variables was noted. Prucalopride stimulated left ventricular contractility and relaxation at ≥0.63 mg/kg i.v. (median plasma level: 293 ng/ml), along with a modest increase in heart rate and cardiac output starting at ≥ 2.5 mg/kg i.v. (median plasma level: 1748 ng/ml). In conscious dogs increasing intravenous doses of 0.02, 0.04, 0.08, 0.16 and 0.31 mg/kg induced a dose dependent increase in systolic and diastolic blood pressure. This reached the level of statistical significance, starting at 0.04 mg/kg (systolic) and 0.08 mg/kg (diastolic). As a consequence of this, the pressure rate product, an index for myocardial oxygen consumption, increased significantly, starting at 0.08 mg/kg. Total systemic resistance increased significantly but transiently at 0.04 mg/kg only. A single high oral dose of 2.5 mg/kg of Prucalopride induced an increase in heart rate, diastolic and systolic blood pressure, pressure rate product, LV max, LV max, LV min, and cardiac output.

The effect of Prucalopride on cardiac 5-HT4 receptors (lusitropic, inotropic and chronotropic effects in porcine and human atrial tissues; increase in heart rate in anesthetized juvenile pigs) correlated with transient and limited increase in heart rate observed in volunteers at first exposure. These responses were observed non-clinically at concentrations or doses of 2-9 times the therapeutic plasma levels.

Given the findings with Prucalopride and the known cardiac toxicity associated with other 5-HT4 agonists, it is appropriate to include a summary of the preclinical cardiovascular findings in Section 5.3 of the SPC.

- Pharmacodynamic drug interactions

Both *in vitro* and *in vivo* studies have demonstrated that a 5-HT4 receptor antagonist can block the effects of Prucalopride (excluding simultaneous use of a 5-HT4 receptor agonist and an antagonist). Since the propulsion enhancing effects are linked to the effect of Prucalopride at receptors located on cholinergic neurons, resulting in the release of acetylcholine concomitant use of acetylcholinesterase inhibitors or anticholinergic compounds will respectively potentiate or reduce the response to Prucalopride.

**Pharmacokinetics**

***Absorption***
After single or repeated oral administration of Prucalopride to rats, rabbits and dogs, Prucalopride was rapidly absorbed. The oral bioavailability varied between species, presumably due to the extent of first-pass metabolism, and was very low in rabbits (≤ 5%), low to intermediate in rats (≤ 8-53%, depending on dose and gender), and high in dogs (77%) and humans (93%).

After repeated dosing in mice and rats, the $C_{max}$ and area under the curve (AUC) values increased either dose-proportionally or more than dose-proportionally depending on the study. Generally in rats, a more than dose proportional increase in $AUC_{0-24}$ was seen after repeated doses in the majority of toxicity studies. Both intravenous and subcutaneous administration in rats indicated a more than dose proportional increase in systemic exposure in terms of $AUC_{0-24}$, suggesting that the non linear kinetics seen in rats is partly due to a capacity limited elimination process of Prucalopride in rats. This was not as pronounced in mice, and in dogs dose linear kinetics were seen within the studied dose range. Repeated dose exposure parameters were generally similar to those after single dosing, indicating that Prucalopride does not induce liver enzyme activity and does not accumulate. Half-lives of elimination of Prucalopride from plasma were short (< 1hour) in rats (low doses) and rabbits, and much longer in dogs (7 h) and man (22.5 h). These results indicate that first-pass metabolism of Prucalopride is extensive in rats (at least at low doses) and rabbits, but much less extensive in dogs and humans.

No gender differences in kinetics were observed in mice and dogs, but plasma concentrations in female rats were about 2-fold higher than those in male rats, and necessitated a differential dose level scheme for the pivotal oral toxicity studies in rats. This difference seemed to level out after long term exposure (>6 month).

***Distribution***
The protein binding of Prucalopride in plasma of mice, rats, rabbits dogs and man was low from 27-37%. The blood-to-plasma concentration ratio in these species was 1.39-1.69. The tissue distribution in Prucalopride in male rats and pregnant female rats after single oral dosing was rapid and extensive. High concentrations of Prucalopride and/or its metabolites were found in oesophageal content, gastrointestinal content, bile and urine, and somewhat lower concentrations were found in intestinal tissues, liver, kidney, vagina, spleen, pancreas, bone marrow and most other glandular tissues. Limited exposure was seen in brain, bone and adipose tissues. Low levels of radioactivity were also seen in foetuses indicating placental transfer. No undue retention of radioactivity was seen in the rats. However, no distribution studies were conducted in pigmented rats which preclude assessment of potential distribution and retention of Prucalopride and/or its metabolites in melanin containing tissues. In dogs, the residual concentrations of unchanged Prucalopride after repeated oral dosing in a limited number of selected tissues were highest in colon tissue and lowest in brain and fat tissue.

***Metabolism***
In rats, Prucalopride was extensively metabolised, and some gender differences in the metabolic pattern were observed. Excretion of unchanged Prucalopride accounted for 6% of the dose in males and for 10% of the dose in females. The main metabolites in rat excreta were R106569 (resulting from hydroxylation; 30% in males; 58% in females), R129531 (resulting from hydroxylation, *O*-demethylation and oxidation; 17% in males, 3% in females), R112718 (resulting from hydroxylation and *O*-demethylation; 9% in males, 3% in females), and R107504 (resulting from *O*-demethylation and oxidation; 6% in males, 2% in females). *In vitro* studies of microsomes and hepatocytes indicated similar metabolic pattern of Prucalopride as in rat microsomes and hepatocytes.

In mice, Prucalopride was less extensively metabolised than in rats. The metabolic profiles for male and female mice were qualitatively and quantitatively similar. Unchanged Prucalopride and one major metabolite (R106569) was the major components in plasma, urine and faeces. The hydroxylated metabolite R106569 accounted for 36.0-41.8 % of the dose in male and female mice, respectively. All other metabolites accounted individually for less than 2.2% of the dose.

In rabbits, Prucalopride was less extensively metabolised than in rats, and the metabolic pathway was different. The main metabolite of Prucalopride in rabbits was the *N*-glucuronide, of which the urinary accounted for 47% of the dose. Unchanged Prucalopride in faeces (24% of the dose) might partially result from deconjugation of the *N*-glucuronide by the intestinal flora.

In dogs, Prucalopride was not extensively metabolised. The excretion of unchanged Prucalopride in urine accounted for 44% of the dose. The two major metabolites were R107504 (resulting from *O*-demethylation and oxidation; 18% of the dose) and R106569 (resulting from hydroxylation; 12% of the dose). In man, as in dog, Prucalopride was not extensively metabolised. Unchanged Prucalopride accounted for 59 to 84% of the total radioactivity in plasma. The major metabolite was R107504, resulting from *O*-demethylation and oxidation; 3% of the dose. All other human metabolites accounted for 0.3 to 1.9 % of dose. Three of these metabolites were not reported present in any other species *in vivo,* M18 is a conjugate, M19 and M20 are unidentified.

***Excretion***
In rats, Prucalopride undergoes extensive hepatic extraction and the absorbed product is excreted into faeces (63%) presumably via the biliary route or is excreted in urine (36%). In mice, excretion of Prucalopride and metabolites were through urine (49-57%) and faeces (37-41%) In rabbits and dogs, a larger proportion of Prucalopride is excreted in urine (53%, 72%, respectively) compared to faeces (44%, 21%, respectively). The routes of excretion in man, predominately through urine, are most similar to those in dogs.

***CYP450 enzyme induction***
Two *in vitro* enzyme induction studies were performed in rat hepatocytes in order to compare the enzyme induction potential of the products from the *O*-demethylation pathway with those of the hydroxylation pathway. The results showed that besides Prucalopride (1.6-2.7x), the following metabolites have some induction potential, R129531 (2.1-2.9x), R112718 (1.8-6.6x) and R107504 (1.8-3.7x). The following metabolites, R106569, R104068, R104065, R112716 and R084536, did not show any induction potential.

Induction studies *in vivo* revealed that Prucalopride is not inducing CYP enzyme activities of any considerably proportion. Repeated oral administration of Prucalopride at dose levels up to 20 mg/kg/day to male and female rats for six month had no significant effects on liver enzyme activities, microsomal protein and hepatic cytochrome P450 content. At the highest dose (160 mg/kg) to male rats the activity of CYP2B was 3-fold increased after six month exposure, which can be compared with the comparative control substance, phenobarbital, which showed a 47-fold increase in activity after one week exposure. Similar low induction potential by Prucalopride was seen for CYP1A activity, where no induction was seen after one month and a 3 to 9-fold increase was seen after 6 months at the highest doses (80 and 160 mg/kg/d).

In conclusion, dog is suggested to be the most appropriate species for toxicology studies since the major metabolic and excretory pathways of Prucalopride in dog are similar as in man. Mice, rats and rabbits are considered valuable since high systemic levels of unchanged Prucalopride are present.

**Toxicology**

Both the hydrochloride (R093877) and succinate (R108512) salts of Prucalopride have been used in the various toxicity studies including 1-month bridging studies in rat and dog. The chosen species for toxicology studies are considered relevant even if the dog is probably the most relevant species.

- Single dose toxicity

In single dose toxicity studies, Prucalopride showed low to medium acute toxicity with approximate lethal doses of 320-550 mg/kg and 600 mg/kg in female and male mice, respectively, and 600 mg/kg in rats after oral administration. At very high doses, Central Nervous System (CNS) and cardiovascular effects were seen.

- Repeat dose toxicity

Repeated-dose toxicity studies have been conducted in mice (up to 3 months), rats (up to 6 months) and dogs (up to 12 months). Target organs were liver, thyroid, mammary gland, pituitary gland, endocrine pancreas, female genital tract, male accessory sex organs, adrenal gland, kidney, heart, spleen and haematological system. In mechanistic studies, dose related increases in serum prolactin levels were demonstrated in male and female rats and mice and the NOAEL was 2.5 mg/kg in female rats. Using available pharmacokinetic and toxicokinetic data it can be calculated that prolactin was secreted *in vivo* in rats when Prucalopride reached plasma concentrations of 0.5-1 µM and above.

Liver: Prucalopride induced liver effects in rats and dogs. The liver findings observed in rats are described below in the carcinogenicity section. In dogs, increased liver weights were noted together with increased BIL, ALT and AST levels after 12 months at a dose of 30 mg/kg/day. The histological findings consisted of focal necrosis, swollen hepatocytes, pigmentation, and disturbed trabecular structure in two female dogs. *The NOAEL in dogs was 10 mg/kg/day which correspond to 244 times the therapeutic exposure*.

Thyroid: Thyroid effects were seen in rats and dogs. The thyroid findings in rats are described below in the carcinogenicity section. In dogs, thyroid weights were increased at a dose of 30 mg/kg/day *The dog NOAEL was 10 mg/kg/day which correspond to 244 times the therapeutic exposure*. Serum TSH, T3 and T4 levels have not been measured in the dog studies.

Mammary gland: Increased glandular development and secretion were demonstrated in both sexes in rats at ≥80 mg/kg/day. *The NOAEL was 20 mg/kg/day corresponding to 74-142 times the clinical exposure*.

Pituitary gland: In mice, hypertrophy of the pars intermedia of the pituitary gland was observed at doses of 80 mg/kg/day. *The NOAEL was 20 mg/kg/day corresponding to 19-27 times the clinical exposure*..

Endocrine pancreas: Increased pancreas weight was noted in rats at ≥ 20 mg/kg/day and 80 mg/kg/day in males and females, respectively. Thus*, NOAELs were 5 and 20 mg/kg/day corresponding to 5 and 142 times the clinical exposure, respectively.*

Female genital tract: In female rats at 20 mg/kg/day dosed for 6-months, reduced cyclic activity and pseudopregnancy status in the ovaries and vagina were seen. *The NOAEL was 5 mg/kg/day corresponding to 5 times the clinical exposure.* Decreased basophilic corpora lutea in ovary, increased atrophy and decreased glandular development and decreased height of epithelium in uterus were noticed at and above 40 and 80 mg/kg/day, in rats and mice, respectively. In addition, at 40 mg/kg/day decreased granulocytic infiltration in uterus and increased necrotic cells (epithelium) were observed in

the vagina in one study. Changes in the female genital tract, i.e. increased interstitial tissue in the ovaries and mammary gland development, were still apparent after a 1-month recovery period. See carcinogenicity section for further comments. In dogs, toxicity was induced in the female tract at 30 mg/kg since retardation of cyclic activity in female dogs, manifested as decreased glandular development in the uterus, was observed in the 12-month study. *The dog NOAEL was 10 mg/kg/day which correspond to 244 times the therapeutic exposure*.

Male accessory sex organs: In rats, ≥40 mg/kg resulted in changes in the prostate (from granulocytic infiltration to chronic inflammation. *NOAEL was 20 mg/kg/day at 74-142 times clinical exposure*. Changes in the prostate in males, i.e. increased granulocytes/cell debris, were still apparent after a 1-month recovery period. In addition at 80 mg/kg/day, a slight decrease in epithelial thickness was seen in seminal vesicles. See carcinogenicity section for further comments.

Adrenal gland: At 80 mg/kg/day, increased adrenal gland weight was observed in males after 6-months. *The NOAEL was 20 mg/kg/day corresponding to 74-142 times the clinical exposure*.

Kidney: In rats, consistent and reproducible findings on kidney weight, serum and urinary parameters were seen at doses above 5 mg/kg/day. *At NOAEL, 5 mg/kg/day, the exposure ratio is ≥ 6 times, based on AUC, the anticipated clinical exposure*. No adverse consistent kidney findings were observed in either mouse or dog. Taking into account the species differences with regard to excretion and metabolism, the observed kidney effects could be related to the extensive metabolism observed in rats. The rat is considered to be an animal species less relevant for humans. Further, no adverse kidney effects have been observed in the clinical data base. Thus, the kidney effects observed solely in rat are not considered relevant for humans.

Heart: Increased heart weight was noted in male rats administered ≥20 mg/kg/day resulting in exposures of 75 times above the therapeutic exposure levels. *The NOAEL was 5 mg/kg/day which correspond to 5 times the clinical exposure.* Slight increase in focal infiltration of chronic inflammatory cells was also noticed in the rat hearts.

Spleen and haematological system: Increased spleen weight was noticed. Haematological changes in male and female rats (decreased haematocrit, haemoglobin and red blood cells; increased MCV and MCH) were observed at and above 20 mg/kg/day. *The NOAEL was 5 mg/kg/day which correspond to 5-12 times the clinical exposure.*

Thymus: Slight individual cell necrosis was noticed in female rats dosed 80 mg/kg/day for 6-months. *The NOAEL was 20 mg/kg/day corresponding to 19-27 times the clinical exposure.*

- Genotoxicity

In the performed standard package of genetic toxicology studies, a positive *in vitro* finding was seen in the Ames test in strain TA100 of *Salmonella typhimurium* at concentration at and above 500 μg/plate in the absence and presence of rat liver activation system. An extensive series of follow-up *in vitro* and *in vivo* mutagenicity studies have been performed to define the genotoxic hazard.

The *in vitro* positive findings in TA100 together with the positive effect seen with the TA-mixed strain sample indicate mutations induction by base-pair substitution. Prucalopride did not induce *in vitro* mammalian mutation (mouse lymphoma) or chromosomal aberration (human lymphocyte) in the absence and presence of S9. Since Prucalopride has not been tested up to relevant toxicity levels in some tests, Prucalopride cannot be considered thoroughly tested in the presence of metabolic activation in the chromosomal aberration test and in the absence of metabolic action in the Mouse Lymphoma test. However, when taken together the results in the *in vitro* mammalian tests can be evaluated as a negative result.

In the first *in vitro* UDS-test in rat hepatocytes, at high cytotoxic concentrations of 100 μg/ml and above, increases in DNA-repair activity was observed and the results was classified as equivocal. In a repeat *in vitro* UDS-test, no DNA damage occurred at moderately cytotoxic concentrations up to 50

µg/ml. The tests were further followed up by an *in vivo* UDS test where the potential DNA-repair activity was measured in hepatocytes from male rats given up to 548 mg/kg Prucalopride in a single oral dose. In vivo in rat, no DNA-repair activity was observed at a calculated exposure margin of 2000 compared to the highest recommended dose in man.

No genotoxic activity was observed in the mouse micronucleus test up 640 mg/kg. In addition, the potential of Prucalopride to induce gene mutations and DNA adducts in the liver of Big Blue™ λ lac I transgenic rats was also assessed in a 28 day study at dose levels up to 80 mg/kg/day. The Prucalopride dosed animals were sacrificed 24 h after last administration. With respect to DNA adducts, using standard enrichment methods and solvents the results did not indicate that adducts were formed in the liver. In the second $^{32}P$ -postlabelling study (N185033), Prucalopride and its metabolites were assessed for their potential to form DNA adducts in rat and mouse tissues in which increased incidences of neoplastic findings were observed in carcinogenicity studies. In this DNA adduct study, Prucalopride was administered at 80 mg/kg to male rats, 40 mg/kg to female rats, and 80 mg/kg to male and female mice for 7 days. The organs examined were liver, thyroid, adrenals and mammary gland in rats and liver and mammary gland, in mice. Testes and uterus were also added in mice on specific request of FDA. Using specially developed solvents, modified bases were detected in the livers of male and female mice and rats but not in any other tissue.

In a newly performed DEREK analysis for Prucalopride and metabolites, no structural alerts were identified. In addition, the polarity of all hypothetical adducts of Prucalopride and its metabolites was calculated in a new in silico study and compared to the polarity of two reference MOCA adducts. The results indicate that the hypothetical adducts of Prucalopride and its metabolites have a lower polarity or a polarity in the same range as reference MOCA compounds.

In conclusion, although it was considered that there was no strong support for an epigenetic mechanism of carcinogenesis and without further support a genotoxic mechanism relevant for humans could not be ruled out, the applicant has adequately addressed the specified issues. Moreover, extensive in vivo genotoxicity testing has been performed (in vivo UDS, in vivo Micronucleus test, and DNA adducts in the liver of Big Blue™ λ lac I transgenic rats) with no indication of genotoxic potential. In addition, Prucalopride did not induce tumours in neonatal mice in a short term carcinogenicity study. The neonatal mouse model is considered relevant since it is expected to be sensitive to genotoxic carcinogens but not to nongenotoxic carcinogens (new metabolism data for mouse illustrates that the mouse is a relevant animal model for man). Further on, considering the extensive genotoxicity testing performed, the weight of evidence shows that Prucalopride raise no genotoxic concern.

- Carcinogenicity

In oral carcinogenicity studies, mice and rats were treated with Prucalopride succinate at the following dose levels 0, 10, 20 and 80 mg/kg/day (male and female mice), 0, 5, 20, 80 mg/kg/day (male rats) and 0, 5, 10, 40 mg/kg/day (female rats). A wide distribution of tumours to major organ systems was observed in the rat carcinogenicity study. Hepatocellular adenomas, thyroid follicular adenomas and benign mammary gland tumours were seen in males and female rats, whereas pituitary adenomas, pancreas islet cell adenomas and adrenal gland benign phaeochromocytomas were observed in male rats. In mice, mammary gland adenocarcinomas were observed in females.

Mechanistic studies were performed to possibly elucidate the mechanisms of the carcinogenicity findings. The focus was on the following changes: enhanced prolactin secretion and the liver changes and thyroid changes. The results of the additionally performed mechanistic studies are included in this section.

Prolactin secretion

In the rat carcinogenicity study with Prucalopride succinate, the adenomas in the pituitary gland, mammary gland, endocrine pancreas and the benign phaeochomocytomas in the adrenal medulla in rats dosed at 40 and 80 mg/kg are considered by the applicant to be related to an increase in prolactin secretion due to dopamine D2-receptor antagonistic effects. The mammary gland adenocarcinomas in mice at 80 mg/kg are also considered by the applicant to be related to prolactin release. *The NOAELs were 20 mg/kg/day in female mice, 20 mg/kg/day and 10 mg/kg/day, in male and female rats, respectively. The resulting exposure margins to the therapeutic levels are 20 times (female mice), 63 times (male rats) and 40 times (female rats).*

It is agreed that the mechanism causing hyperprolactinemia in rat and mouse at high dose levels of Prucalopride is considered to be the interaction of Prucalopride with pituitary DA2 receptors as demonstrated by the pituitary tissue levels that exceed the Ki value for binding of Prucalopride to the rat DA2 receptor at all doses where prolactin increases were measured. Prolactin increases were measured in male and female rat and mouse. Prolactin levels were assessed at oral doses from 0.63 mg/kg to 320 mg/kg. At and above the dose of 5 mg/kg p.o. a statistically significant increase in prolactin levels was observed. In conclusion, the applicant has well demonstrated, both *in vitro* and *in vivo,* that the observed tumours in mammary gland, pituitary gland, endocrine pancreas and adrenal gland most probably are due to hyperprolactinemia caused by an interaction between Prucalopride and DA2 receptors.

Liver and thyroid tumours

The incidence of liver hepatocellular adenomas was increased at all dose levels in male rats even at the lowest tested dose of 5 mg/kg/day, which is 6 times higher than the therapeutic plasma levels. In females, hepatocellular adenomas were noted at the mid and high doses, 10 and 40 mg/kg/day. *At NOAEL in female rats, the systemic exposure is 7 times higher than the clinical exposure.* The incidence of thyroid follicular adenomas was increased at the highest dose levels in male and female rats. *NOAEL is 20 and 10 mg/kg/day, in males and females, respectively resulting in exposure margins of 63 and 40.*

The adenomas emerged only late during the 24 month carcinogenicity studies. Hepatocellular and thyroid adenomas were observed in male and female rats from month 21 onwards (with only 2 exceptions in thyroid at lunar months 8 and 17).

**Table 1: Hepatocellular tumours in the rat carcinogenicity study**

| Description | Males –prucalopride doses (mg/kg body weight) | | | | | | | | | Females – prucalopride doses (mg/kg body weight)) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 5 | 10 | 20 | 40 | 80 | 160 | | Trend | 0 | 5 | 10 | 20 | 40 | | Trend |
| adenoma | 2 | 6 | | 8# | | 13## | | | Pos. | 0 | 0 | 2 | | 3 | | Pos. |
| adenocarcinoma | 0 | 0 | | 1 | | 2 | | | Neg. | 0 | 0 | 0 | | 0 | | Neg. |

# p<0.05, ## p<0.01, ### p<0.001: statistically significant changes with Fisher exact test (two-tailed)

The results of the additionally performed mechanistic studies including relevant results from the repeat dose toxicity and carcinogenicity studies are summarised below.

The new *in vivo* metabolism study in the mouse and the *in vitro* enzyme induction study in the rat, support the hypothesis of the rat-specific nature of the liver enzyme induction. This enzyme induction is considered to be a major event reflecting an enzyme adaptive liver reaction which is at the basis of the liver hyperplastic changes and adenoma formation. It also contributes indirectly to the hyperplastic changes and adenoma formation in the thyroid.

**<u>Figure 2:</u> Suggested mechanism for liver and thyroid findings in rats (taken from Applicants response)**

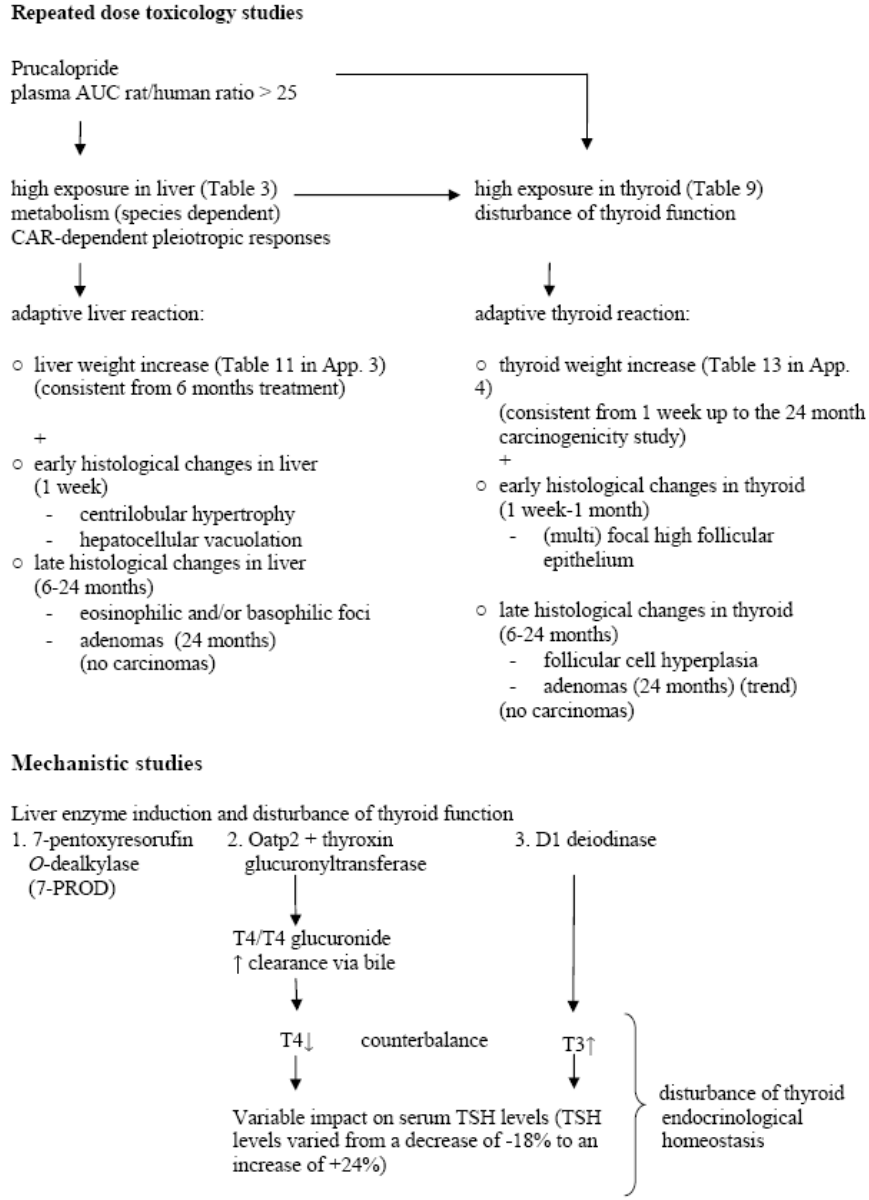



**Figure 2: Proposed epigenetic mechanisms for liver and thyroid adenoma findings in the rat**

Liver

In rats, slightly increased liver weights were observed after 1 week, 1 month (in one of two studies in females at 80 mg/kg/day) and after 6 months in males from 5 mg/kg/day and onwards in one study and at 160mg/kg/day in the other study. In females administered Prucalopride for 6 months, slight liver weight increases were seen at 20 mg/kg/day and at 80 mg/kg/day in the two studies, respectively. In some studies, females were more sensitive whilst in other studies males were most sensitive. In the two studies performed in rat with a recovery period, the effect on liver weights was mostly reversible. Slightly increased liver weights were increased in the rat carcinogenicity study at and above 20 mg/kg/day and 40 mg/kg/day in males and females, respectively.

Changes in bilirubin, ALP, AST and ALT levels were noted in most studies however not in the 6-month mechanistic study. Decreased ALP was the most consistent change seen in most rat studies. Decreased BIL was observed in two of the four mechanistic studies. In the two rat studies with a recovery period, the findings were reversible.

The early histological changes were limited (slightly increased incidences of centrilobular hypertrophy/vacuolation in the 1 week study; normal histology after 1 month of treatment), followed by a slight increase in incidence of basophilic and eosinophilic foci in a 6 months study, which was more pronounced and statistically significant after 24 month treatment. However, no clear histological changes in the liver were observed in the other rat repeat dose toxicity studies. Thus, an increased incidence of centrilobular hypertrophy frequently associated with liver weight increases and adaptive enzyme induction was not observed in the repeat dose toxicity or carcinogenicity studies.

Nevertheless, further data indicates that down-stream metabolites of Prucalopride, R112718 and/or R129531, might be responsible for the "enzyme induction" and thus, causing the liver tumours in rats.

- New metabolism data for the mouse show that Prucalopride was less extensively metabolised than in rats. Unchanged Prucalopride and one major metabolite (R106569) was the major components in plasma, urine and faeces. The hydroxylated metabolite R106569 accounted for 36.0 and 41.8 % of the dose in male and female mice, respectively. All other metabolites accounted individually for less than 2.2% of the dose. In addition, the new metabolism data for mouse illustrates that the mouse is a more relevant animal model for man than the rat.
- New *in vitro* induction data in rat hepatocytes are available. A new *in vitro* enzyme induction study was performed in rat hepatocytes in order to compare the enzyme induction potential of the products from the *O*-demethylation pathway with those of the hydroxylation pathway. The results showed that besides Prucalopride (1.6-2.7x), the following metabolites have some induction potential, R129531 (2.1-2.9x), R112718 (1.8-6.6x) and R107504 (1.8-3.7x).

Taking into account the differences in metabolism observed between male rats, female rats and mice and the available in vitro induction data on individual metabolites together with the observed liver tumour incidences in the carcinogenicity studies in rats and mice, the following two pathways are of special interest. Prucalopride →R106569 →R112718→R129531 (Pathway A) and Prucalopride →R104065 →R107504 (Pathway B). From the data it can be concluded that it is plausible that either or both of the two down-stream metabolites R112718 and R129531 are responsible for the suggested enzyme induction mechanism causing the observed liver tumours in rats. It also gives an explanation to why it is difficult to show a clear correlation between the observed liver tumours and the classical "enzyme induction mediated manifestations" which have been rather elusive and difficult to ascertain in the performed toxicity studies. It could probably have been easier to prove a connection if tissues samples from the carcinogenicity study had been available and used.

In addition, it is agreed that the rat is considered to be an animal species less relevant for humans. The new metabolism data for mouse illustrates that the mouse is a more relevant animal model for man and, further, no liver and thyroid tumours were observed in the mouse carcinogenicity study. Furthermore, in man involvement of the liver in metabolism of Prucalopride and thus in exposure of the liver and thyroid to the metabolites of Prucalopride, is very limited. Calculated human tissue exposure to Prucalopride in the liver is far below the concentration needed to induce liver enzyme activity in rat hepatocytes. Thus, the observed liver and thyroid tumours are not considered relevant for humans.

Thyroid

In rats, thyroid weights were slightly increased in males after doses of ≥160 mg/kg/day but not in females. In the carcinogenicity study, increased thyroid weights were also only observed in males at 80 mg/kg/day. In the only study (1-month mechanistic toxicity) where recovery (6 weeks) was included, the effect on thyroid weight was reversible. Changes in T3, T4 and TSH levels were noted in some rat studies. However, the most consistent change was an increased T3 level, observed in all of the four performed mechanistic studies. In mechanistic studies when rats were treated orally for 6 months with a dose of Prucalopride (80 mg/kg/day) only minor increases in bile excretion, excretion of T4G and unchanged T4 were observed. No relevant effect on thyroxin UDP-glucuronyltransferase activity was seen and 5'-monodeiodinase and thyroid peroxidase activities were not either affected. In the 6-month mechanistic study in rats, the hepatic expression level of the transport protein Oatp2 was measured semiquantitatively and resulted in a significant ($P<0.05$) but small increase of about 2.5-fold, in the average Oatp2 expression levels was observed.

- Reproduction Toxicity

Oral reproduction toxicology studies in rats did not elicit adverse effects up to 20 mg/kg in fertility and peri- postnatal studies, whereas secondary effects due to maternal prolactin-mediated toxicity were seen at 80 mg/kg. In the oral embryofoetal developmental studies in rats and rabbits, no teratogenicity and embryotoxicity were seen up to the highest doses of 80 mg/kg, corresponding with exposure ratios versus humans of 931 in rats (based upon Cmax) and 39 in rabbits (based upon AUC0-24h). Significant excretion of Prucalopride into breast milk was showed in a human study.

- Other toxicity studies

Phototoxicity

Prucalopride absorbs UV light between 290 and 700 nm. Based upon an evaluation of the UV absorbance and the documented presence of Prucalopride in eyes and skin, photosafety studies were deemed necessary and a tiered approach was selected starting with an *in vivo* phototoxicity test.

A single oral administration of Prucalopride (2.5, 5 and 10 mg/kg) was given to Crl:LE (Long-Evans) pigmented rats (Study BOV000030). After 1 hour the rats were exposed for 30 minutes to a standard UV radiation from a xenon lamp. Mean plasma levels 1 h after dosing, were 102, 390 and 1016 ng/ml for the 2.5, 5 and 10 mg/kg dose levels, respectively. It is agreed that the results of the UV exposure and subsequent scoring of the skin responses show that Prucalopride does not induce phototoxicity related skin or eye reactions at any of the doses tested during the 4 day observation period. Thus, Prucalopride is not considered to be phototoxic.

**Ecotoxicity/environmental risk assessment**

An environmental risk assessment was conducted in compliance with the EU guideline (CHMP/SWP/4447/00). A Phase I environmental risk assessment based on a refined $F_{pen}$ was provided. In addition, one ready biodegradation study and one short-term toxicity study in *Daphnia magna* was presented. No conclusion on the environmental risk can be drawn at the moment and a full Phase II assessment is still required. This will be carried out as a post-authorisation follow-up measure.

## 2.4 Clinical aspects

**Introduction**

**GCP**

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

**Pharmacokinetics**

The pharmacokinetic profile of Prucalopride was investigated in numerous studies following intravenous and oral administration (thirty-five studies in 718 subjects). A wide dose range has been studied: single doses ranged from 0.125 mg to 6 mg, while steady-state pharmacokinetic parameters were determined after o.d. dosing of 1 mg up to 20 mg.

- Absorption

The absolute oral bioavailability of Prucalopride was assessed in a trial in 14 subjects comprising three periods (Study PRU-BEL-32). A 2 mg Prucalopride tablet was administered in randomized cross-over order under fasting conditions as a 10-min i.v. infusion. The pharmacokinetic parameters after the i.v. treatment and the tablet fasting and the time course of the mean plasma concentrations after the i.v. infusion and after the tablet in fasting conditions is shown in the Table 2 and Figure 3 below.

**Table 2: Summary of Prucalopride PK parameters, obtained by non-compartmental analysis, after single oral administration of 2mg Prucalopride as a 10-min i.v. infusion and p.o. as a tablet in fasting conditions to 14 healthy subjects (PRU-BEL-32).**

| Parameter | | 10-min i.v. infusion | | | Tablet fasting | | |
|---|---|---|---|---|---|---|---|
| | | Mean | ± | SD | Mean | ± | SD |
| $t_{max}$ | h | | - | | 2.1 | ± | 0.9 |
| $C_{end\ infusion}/C_{max}$ | ng/ml | 9.21 | ± | 5.96 | 4.34 | ± | 0.82 |
| $AUC_{\infty}$ | ng.h/ml | 108 | ± | 21 | 99.2 | ± | 17.2 |
| $t_{1/2term}$ | h | 22.5 | ± | 3.8 | 21.2 | ± | 3.7 |
| $F_{abs}$ | % | | - | | 93.2 | ± | 11.6 |

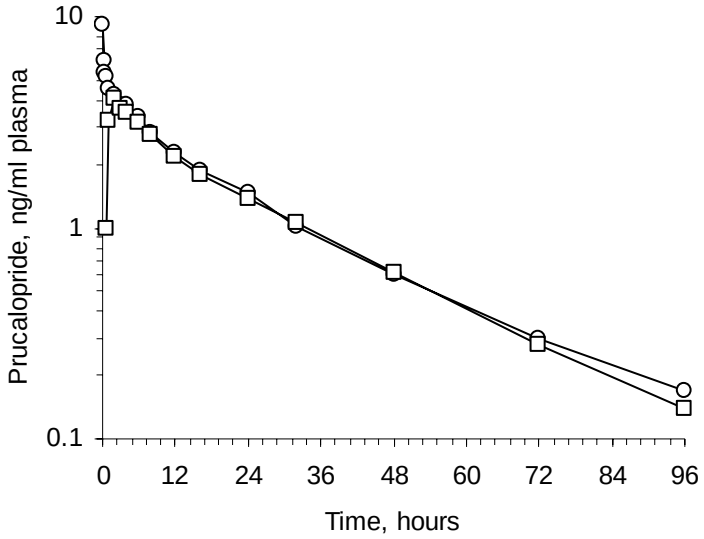



**Figure 3: Semilogarithmic plot of the mean Prucalopride plasma concentrations in function of time after single oral administration of 2mg Prucalopride as a 10-min i.v. infusion (○) and p.o. as a tablet in fasting conditions (□) to 14 healthy subjects (PRU-BEL-32).**

The peak plasma concentration after oral administration was about half the concentration observed at the end of the 10-min i.v. infusion. The absolute oral bioavailability was > 90%.

After a single oral intake of 2 mg Prucalopride, $C_{max}$ was attained in 2-3 hours. Concomitant intake of food did not influence the oral bioavailability of Prucalopride.

In PRU-BEL-2, a randomized, placebo-controlled dose-escalation study, Prucalopride was administered twice daily. Each dose regimen of Prucalopride, 0.5, 1 and 2 mg b.i.d. (every 12 hours), was administered to 8 subjects for 6 consecutive days, with a last dose taken in the morning of day 7. Further repeated-dose kinetics of Prucalopride after once daily dosing were established in several trials in healthy subjects investigating the effect of Prucalopride on pharmacodynamic and/or safety parameters. In all studies, steady-state was attained within 2-3 days of dosing at the target dose-level. On once daily treatment with 2 mg Prucalopride, steady state plasma concentrations fluctuated between 2.5 and 7 ng/ml. An *in vitro* study in Caco-2 cells and in MDCK cells was performed to

evaluate if Prucalopride is a P-gp substrate/inhibitor and to provide further information in future studies on the possible involvement of active renal secretion transporters. It was concluded that Prucalopride is a weak P-gp substrate.

- Distribution

The plasma protein binding of Prucalopride is low, at 28-33% (Study FK 1913). In whole blood, 66% of the drug is distributed to blood cells. After i.v. dosing, Prucalopride is rapidly and extensively distributed and has a large volume of distribution (Vdss of 567 L). No concentration dependency was evident and only a small pH –dependent binding was observed. The fraction unbound was similar in healthy subjects and in subjects with severe renal impairment (0.68 to 0.72).

- Elimination

*In-vitro*, liver metabolism in human hepatocytes is very slow; *in-vivo*, metabolism is not the major route of elimination (approximately 35% is non-renal elimination). In the AME study (PRU-BEL-16) with radiolabelled Prucalopride, a large fraction of the dose was excreted unchanged (about 60% of the administered dose in the urine and at least 6% in the faeces). The active secretion stands for 43% of the total clearance. The most important metabolite, R107504 accounted for only 2.6-3.5% of the dose, whereas 7 other metabolites each represented between 0.3% and 1.9% of the dose. In plasma, R107504 was the only, and a very minor, metabolite.

The accumulation ratio after o.d. dosing ranged from 1.9 to 2.3. Prucalopride has a low plasma clearance (317 mL/min), and a terminal half-life of about 1 day, determined after intravenous administration. The pharmacokinetics of Prucalopride appears to be dose-proportional and time-independent between doses of 1-4 mg.

Regarding the activity of the metabolites, this was tested in an in vitro model (isolated oesophagus tunica muscularis mucosae of the rat. Based on the results and the knowledge about the mass balance, the metabolites likely play a limited role compared to the effect of Prucalopride, given the low exposure to the metabolites, the low protein binding of Prucalopride and the comparable or lower potency of the metabolites to the 5-HT4-receptor.

- Pharmacokinetics in target population

A population analysis using NONMEM was performed. Data from healthy volunteers and patients with chronic constipation was used. The pharmacokinetics was found to be best described by a two-compartment model with lag-time, followed by first-order absorption process. Out of the tested covariates on CL/F (age, body mass index, body weight, creatinine clearance, daily dose of Prucalopride, healthy volunteers versus patients, race, sex and single versus multiple dose administrations), creatinine clearance was the only parameter that affected the apparent oral clearance of Prucalopride.

- Variability

The inter-individual variability is low as seen from the pharmacokinetic studies. A coefficient of variance (CV%) up to approximately 30 % in phase I studies is observed for Prucalopride. The intra-individual variability is likely also low.

- Special populations

*Elderly*
The effect of age on the pharmacokinetics of Prucalopride was studied in an open, parallel-group trial in 12 healthy elderly and 12 young subjects (Study PRU-NED-5). Elderly subjects ranged in age from 65 to 81 years. Five of them were 75 years or older. A single dose of 1 mg Prucalopride was administered on day 1, followed by a 7-day treatment with 1 mg o.d. on days 5-11. On both study days (1 and 11) Prucalopride was administered in fasting conditions.

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 elderly. The dose in elderly is initially 1 mg, with a possibility to increase to 2 mg, if the 1 mg dose is well tolerated.

*Impaired renal function*
The pharmacokinetics of a single oral dose of 2 mg Prucalopride were studied in subjects with various degrees of renal impairment and compared to those in subjects with normal renal function (Study PRU-USA-6). 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 (ClCR 50-79 ml/min) and moderate (ClCR 25-49 ml/min) renal impairment. In subjects with severe renal impairment (ClCR ≤ 24 ml/min), plasma concentrations were 2.3 times the levels in normal subjects. It is recommended to reduce the dose to 1 mg in subjects with severe renal impairment. It is acceptable to have no dose adjustments in patients with mild and moderate renal impairment.

*Impaired hepatic function*
A study in patients with liver impairment will be performed, expected results to be available as final report Q3 2011. The applicant recommends a reduced dose in patients with severe hepatic impairment as a precautionary measure given the lack of data in this group. The study will clarify in what groups of hepatic impairment dose adjustments will be necessary. Based on the currently available data, a relevant statement is included in the SPC until such time as the new data become available.

- Pharmacokinetic interaction studies

*In vitro* interaction data does not indicate any significant CYP-inhibition potential by Prucalopride.

*In vivo* drug-drug interaction studies did not reveal important drug-drug interactions including with drugs such as warfarin or digoxin which have narrow safety margins. However, limited interactions were observed in 2 occasions: 1) Prucalopride enhanced the systemic exposure of erythromycin by about 30%, and 2) on co-administration with ketoconazole, Prucalopride plasma levels were increased by 40%. Although neither of these findings are likely to have major clinical implications, they were unexpected. The effect on erythromycin is likely explained by the large variability in erythromycin absorption. The interaction with ketoconazole is likely explained by an effect on p-gp involving the active renal secretion of Prucalopride. Since the active renal secretion stands for approximately 43 % of the total elimination, there is another active renal secretion transporter involved in the elimination of Prucalopride, since upon total inhibition of this pathway (of p-gp and other unknown transporter(s)), the exposure may theoretically increase up to 75 %.

**Pharmacodynamics**

- Mechanism of action

Prucalopride is a dihydrobenzofurancarboxamide with enterokinetic activities. It is a selective, high affinity serotonin (5-HT4) receptor agonist, which is likely to explain its enterokinetic effects. Only at concentrations exceeding its 5-HT4 receptor affinity by at least 150-fold, affinity for other receptors was detected in the *in-vitro* studies.

- Primary and Secondary pharmacology

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

Most pharmacodynamic studies using various techniques show that Prucalopride accelerates colonic transit, both in healthy subjects and in patients. Prucalopride at a dose of 2 mg accelerates colonic

transit in healthy volunteers but did not alter gastric emptying or small bowel transit in healthy humans (Study PRU-USA-7). In patients with chronic constipation, Prucalopride 4 mg was significantly more effective than placebo in decreasing GI and colonic transit time. The dose of 4 mg also significantly increased gastric emptying and small bowel transit. Daily treatment with Prucalopride 2 mg resulted in improvements of most pharmacodynamic efficacy measures when compared to placebo though these effects did not consistently reach the level of significance, most likely due to the small sample size (Study PRU-USA-21).

The data on colonic transit in the pharmacodynamic studies in healthy volunteers and patients were confirmed by data on total gut and colonic transit measurements performed in the dose-finding Phase II studies.

**Clinical efficacy**

The evaluation of efficacy of Prucalopride in the treatment of chronic constipation included 25 phase II and 10 phase III studies.

A tabular overview of key studies is provided in Table 3.

**Table 3. Overview of key studies in the Phase II and III programme for Prucalopride**

| | | |
|---|---|---|
| **Chronic Constipation** | | |
| Dose response in adults | 3 Double-blind placebo-controlled studies: PRU-INT-1 (4 weeks), PRU-INT-2 (12 weeks) and PRU-USA-3 (4 weeks) | ($n_{ITT}$=651) |
| Pivotal efficacy studies in adults | 3 Double-blind, placebo-controlled studies: PRU-INT-6, PRU-USA-11 and PRU-USA-13 (each 12 weeks)<br>Dose-titration study: PRU-USA-25 (4 weeks)<br>Retreatment study: PRU-USA-28 (4 weeks) | ($n_{ITT}$=1924)<br>($n_{ITT}$=342)<br>($n_{ITT}$=462) |
| Dose response & efficacy in elderly | 1 Phase II dose-finding study: PRU-USA-26 (4 weeks)<br>1 Phase III efficacy and dose-response study: PRU-INT-12 (4 weeks) | ($n_{ITT}$=89)<br>($n_{ITT}$=300) |
| Long-term efficacy | 7 Open long-term follow-up studies: PRU-USA-22 (36 months), PRU-BEL-8, PRU-INT-4 (each 30 months), PRU-INT-10, PRU-INT-3, PRU-NED-4 (each 24 months) and PRU-FRA-1 (Part 2; 24 weeks) | ($n_{ITT}$=2595) |
| **Studies in Special Constipation Populations** | | |
| Opioid-induced constipation | 1 Double-blind, placebo-controlled study in non-cancer patients: PRU-INT-8 (4 weeks)<br>Open long-term study: PRU-INT-17 (12 months) | ($n_{ITT}$=190)<br>($n_{ITT}$=109) |
| Patients with MS or SCI | 2 Double-blind placebo-controlled studies (1 in each patient group, PRU-BEL-18 & PRU-DEN-2; each 4 weeks)<br>1 Long-term follow-up study: PRU-INT-9 (12 months) | ($n_{ITT}$=22)<br>($n_{ITT}$=44) |

ITT: intent-to-treat

The Phase II programme for Prucalopride included 6 double-blind placebo-controlled studies to evaluate the efficacy and safety of different doses (0.5 mg to 4 mg o.d. and 0.5 mg to 2 mg twice daily [b.i.d.]) of Prucalopride in patients with chronic constipation. Three of these studies (PRU-INT-1, PRU-INT-2 and PRU-USA-3) provided the data to support the selection of dose for Phase III. In addition, one of the studies was performed in frail elderly patients living in a nursing facility (PRU-USA-26).

The Phase III programme included 6 double-blind placebo-controlled trials to evaluate the efficacy and safety of oral doses of 2 mg and 4 mg o.d. Prucalopride in adult patients with chronic constipation. Three trials (PRU-INT-6, PRU-USA-11 and PRU-USA-13) were the pivotal 12-week trials to support the efficacy of Prucalopride.

In addition, one Phase III trial was done to further validate the efficacy and safety of oral doses of Prucalopride 1 mg, 2 mg and 4 mg o.d. in elderly patients with chronic constipation (PRU-INT-12). In

this trial, a 1 mg arm was included because of pharmacokinetic data indicating that a dose reduction in the elderly might be warranted and literature data that a number of specific factors may be typical to this population and as such may represent a specific subpopulation.

Further, one trial looked at the effect of retreatment (PRU-USA-28) and one trial looked at the benefit of up-titrating (PRU-USA-25).

- Dose response studies

*Adults*

The dose selection for Phase III was based on the data from 3 double-blind, placebo-controlled Phase II dose-finding studies in patients with chronic constipation. The studies evaluated doses in the range from 0.5 to 4 mg per day given for 4 to 12 weeks. These studies are summarised below.

**Study PRU-INT-1**

Study PRU-INT-1 was a multicentre, randomised, double-blind, placebo-controlled, parallel-group, Phase II, dose-finding trial to evaluate the efficacy and safety of 0.5 mg, 1 mg, or 2 mg Prucalopride in patients with chronic constipation. The study consisted of 2 phases: a 4-week drug-free run-in phase followed by a 4-week randomised, double-blind, placebo-controlled treatment phase. Prucalopride was given orally as a capsule o.d. before breakfast.

The study population included 174 patients (mean age: 44.4 [18-73] years) with a long-standing chronic constipation with a median duration of 15 years (1−60 years). Between 68% and 85% of patients in each treatment group reported a lack of adequate effect from diet changes or laxative treatment. Efficacy was evaluated by means of visual analogue scale (VAS) scores and diary data (self-assessment) and also through symptom evaluation and colonic transit time (investigator assessment). The main efficacy variable 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. (If a patient passed no stools for 3 or more consecutive days, he/she was allowed bisacodyl as rescue medication.)

**Study PRU-INT-2**

Study PRU-INT-2 was a multicentre, randomised, double-blind, placebo-controlled, parallel-group, Phase II, dose-finding trial to evaluate the efficacy and safety of 0.5 mg, 1 mg, or 2 mg Prucalopride in patients with chronic constipation. The study consisted of 2 phases: a 4-week drug-free run-in phase, followed by a 12-week randomised, double-blind, placebo-controlled treatment phase. Prucalopride was given orally as a capsule b.i.d.

The study population, which included 253 patients (mean age: 40.5 [18−70] years) had long-standing chronic constipation with a median duration of 15.5 years (0−60 years) and more than 84% of patients in each treatment group had not shown an adequate response to either diet changes or laxative treatment. Efficacy was evaluated similarly to study PRU-INT-1.

**Study PRU-USA-3**

Study PRU-USA-3 was a multicentre, randomised, double-blind, placebo-controlled, parallel-group, Phase II, dose-comparison trial to assess optimal dose, efficacy and safety of 0.5 mg, 1 mg, 2 mg, or 4 mg Prucalopride in patients with chronic constipation. The trial consisted of 3 phases: a 4-week drug-free run-in phase, followed by a 4-week randomised, double-blind, placebo-controlled treatment phase, followed by a 4-week drug-free run-out phase. Prucalopride was given orally as a capsule o.d. before breakfast or in the morning. The study population included 231 patients (mean age: 42.1 [21−70] years). Mean duration of constipation was around 20 years and approximately 80% reported inadequate relief with laxatives. The primary efficacy parameter was the proportion of the subjects

who had had at least three or more SCBM (spontaneous complete bowel movement) /week at the end of double-blind treatment (i.e., endpoint: last 7 days in double-blind phase).

Across all 3 studies, daily doses of 2 mg and 4 mg of Prucalopride consistently resulted in a statistically significant improvement of bowel habit, i.e. increased stool frequency, decreased stool consistency and straining, and reduction of severity of constipation at 4 weeks of treatment. After completion of PRU-INT-1 and PRU-INT-2, a new primary endpoint was used for the third study, PRU-USA-3: ≥3 SCBM per week (i.e. the endpoint later used in Phase III studies). Therefore, the results of PRU-USA-3 provided the primary basis for Phase III dose selection. The results for the primary efficacy parameter are shown in Table 4 below and show a dose response with 2 and 4 mg o.d. reaching statistical significance. These results were supported by the secondary endpoints including frequency of SCBM and bowel movement as well as assessment of stool hardness, straining and the patient's assessment of efficacy and disease severity.

**Table 4: Primary endpoint data from PRU-USA-3**

| Parameter | Placebo N=45 | PRU 0.5 mg N=41 | PRU 1 mg N=47 | PRU 2 mg N=46 | PRU 4 mg N=45 |
|---|---|---|---|---|---|
| % of patients with ≥3 SCBM/week | | | | | |
| 4-week run-in | 0 | 0 | 0 | 0 | 2.2 |
| 4-week treatment | 13.3 | 24.4 | 23.4 | 32.6§ | 55.6*** |

***p<0.001, §p<0.05 vs.placebo (2-sided p-value)

Based on the results of PRU-USA-3, 2 mg o.d. was considered the lowest effective dose in the adult population. This was confirmed by a post-hoc analysis including PRU-INT-1, PRU-INT-2 and PRU-USA-3 using the endpoint of ≥3 SCBM per week.

*Elderly*

**Study PRU-INT-12**

A Phase III study in an elderly population (PRU-INT-12) evaluated the effects of 3 doses of Prucalopride (1, 2 and 4 mg o.d.). Because of the pharmacokinetic profile in elderly, the 1 mg dose was included in addition to the 2 and the 4 mg o.d. doses. The trial consisted of 2 phases: a 2-week drug-free run-in phase followed by a randomised, 4-week, double-blind, placebo-controlled treatment phase. Prucalopride was given orally as tablets o.d. The study included 303 elderly patients (mean age: 76.4 [64–95] years) with long-standing chronic constipation (mean duration: 21.6 years (1–80 years). Between 80.0% and 96.1% of patients had used laxatives prior to the trial in the different treatment groups and 79.5% claimed that these agents did not provide adequate relief. At run-in, patients had a mean of 0.8 SCBM per week.

The results for the key efficacy parameters are shown in Table 5 below. Data demonstrate that all doses, including the 1 mg o.d., were efficacious in the elderly population with chronic constipation.

**Table 5 : Efficacy results by dose from study in elderly patients (PRU-INT-12)**

| Parameter | Placebo N=70 | PRU 1 mg N=76 | PRU 2 mg N=75 | PRU 4 mg N=79 |
|---|---|---|---|---|
| % of patients with ≥3 SCBM/week | 20.0 | 39.5* | 32.0 | 31.6 |
| % of patients with increase of ≥1 SCBM/week | 33.8 | 61.1** | 56.9* | 50.7§ |
| % of patients with improvement of ≥1 on PAC-QOL satisfaction subscale | 25.8 | 48.5* | 29.0 | 40.9 |

**p<0.01; *p<0.025 , §<0.05 vs. placebo (pairwise comparison)

In summary, based on the results of PRU-USA-3 and taking into account the data generated in PRU-INT-1 and PRU-INT-2, the doses selected for the pivotal Phase III trials of 2 mg and 4 mg o.d appear reasonable. For elderly patients, the efficacy data indicated that a lower dose of 1 mg o.d. is appropriate and this was supported by the pharmacokinetic data showing an increase in exposure in this population.

- Main studies

The evidence of efficacy was shown in 3 identically designed double-blind placebo-controlled studies in patients with chronic constipation **(PRU-INT-6, PRU-USA-11, PRU-USA-13)**. One was performed in Europe and two in the USA using 2 and 4 mg o.d. oral doses of Prucalopride.

Trial **PRU-INT-6** was a multicentre, randomised, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy, safety, and effect on quality of life of Prucalopride 2 and 4 mg including 716 male and female patients (mean age 43.9 [17–89] years) with chronic constipation.

Trial **PRU-USA-11** was a multicentre, randomised, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy, safety, and effect on quality of life of 2 and 4 mg Prucalopride including 620 male and female patients (mean age 48.3 [18–85] years) with chronic constipation.

Trial **PRU-USA-13** was a multicentre, randomised, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy, safety, and effect on quality of life of 2 and 4 mg Prucalopride including 641 male and female patients (mean age 47.9 [18–95] years) with chronic constipation.

These trials are described together. However, the results of the different studies are presented both individually, for the primary and most important secondary endpoints, and in pooled data analyses.

METHODS

*Study Participants*

An overview on patient demographics for the Phase III pivotal trials is given in Table 6.

**Table 6**

**Table 2.7.3-10: Patient demographics for Phase III pivotal trials (PRU-USA-11, PRU-USA-13, PRU-INT-6) in patients with chronic constipation - ITT population**

| Total no. of patients | Placebo 645 | PRU 2 mg 640 | PRU 4 mg 639 | All PRU 1279 |
|---|---|---|---|---|
| Gender, n (%) | | | | |
| Female | 580 ( 89.9) | 566 ( 88.4) | 558 ( 87.3) | 1124 ( 87.9) |
| Male | 65 ( 10.1) | 74 ( 11.6) | 81 ( 12.7) | 155 ( 12.1) |
| Age, years | | | | |
| <18 years, n (%) | 0 ( 0.0) | 1 ( 0.2) | 0 ( 0.0) | 1 ( 0.1) |
| 18-40 years, n (%) | 227 ( 35.2) | 232 ( 36.3) | 213 ( 33.3) | 445 ( 34.8) |
| 41-64 years, n (%) | 343 ( 53.2) | 321 ( 50.2) | 337 ( 52.7) | 658 ( 51.4) |
| 65-75 years, n (%) | 60 ( 9.3) | 61 ( 9.5) | 65 ( 10.2) | 126 ( 9.9) |
| >75 years, n (%) | 15 ( 2.3) | 25 ( 3.9) | 24 ( 3.8) | 49 ( 3.8) |
| Mean (SE) | 46.2 (0.55) | 46.4 (0.58) | 47.5 (0.57) | 46.9 (0.41) |
| Median (min;max) | 45 (18 ; 82) | 45 (17 ; 95) | 46 (18 ; 89) | 46 (17 ; 95) |
| Race, n (%) | | | | |
| Black | 29 ( 4.5) | 40 ( 6.3) | 33 ( 5.2) | 73 ( 5.7) |
| Caucasian | 589 ( 91.3) | 575 ( 89.8) | 574 ( 89.8) | 1149 ( 89.8) |
| Hispanic | 11 ( 1.7) | 8 ( 1.3) | 16 ( 2.5) | 24 ( 1.9) |
| Oriental | 4 ( 0.6) | 9 ( 1.4) | 2 ( 0.3) | 11 ( 0.9) |
| Other | 12 ( 1.9) | 8 ( 1.3) | 14 ( 2.2) | 22 ( 1.7) |
| Weight, kg | | | | |
| Mean (SE) | 68.7 (0.56) | 69.8 (0.57) | 68.7 (0.57) | 69.2 (0.41) |
| Median (min;max) | 65 (42 ; 131) | 67.4 (40 ; 141) | 65.5 (37 ; 141) | 66.8 (37 ; 141) |
| Height, cm | | | | |
| Mean (SE) | 165.1 (0.32) | 165.2 (0.34) | 165.5 (0.34) | 165.3 (0.24) |
| Median (min;max) | 165 (107 ; 196) | 165 (132 ; 193) | 165 (134 ; 191) | 165 (132 ; 193) |

Source: Module 5.3.5.3/Display SUB.2.2.1.A

Patients were included based on the following criteria: 2 or fewer SBMs per week in the previous 6 months and, in addition, very hard (little balls) or hard stools and/or a sensation of incomplete evacuation and/or straining during defecation, at least a quarter of the stools. The inclusion criteria are based on the accepted definition of chronic constipation. Exclusion of patients with irritable bowel syndrome (IBS) was based on the Rome Working Group definition of IBS.

During a 2-week drug-free run-in phase (Weeks -2 through 0), the patients recorded their bowel habits and any use of rescue medication (bisacodyl) in daily diaries to confirm the existence of constipation. Organic disorders as a cause of constipation were ruled out using the results of either a barium enema or a colonoscopy. The run-in phase included physical examination, medical history, recording of concomitant therapies, safety laboratory tests, vital signs and electrocardiogram (ECG) and pharmacokinetic evaluation. The patients were eligible for the 12-week double-blind treatment phase (Weeks 0 through 12) if their diary data during run-in confirmed that they met the entry criteria for chronic constipation. Patients who did not meet the criteria were considered ineligible and were discontinued from the study.

Table 7 below provides a summary of the constipation history prior to enrolment into the pivotal studies.

**Table 7: History of constipation for Phase III pivotal studies (PRU-INT-6, PRU-USA-11, PRU- USA-13) in patients with chronic constipation - ITT population**

| Parameter | Placebo N=645 | PRU 2 mg N=640 | PRU 4 mg N=639 | All PRU N=1279 |
|---|---|---|---|---|
| Duration of constipation, years | | | | |
| Mean (SE)<br>Median (min;max) | 20.44 (0.616)<br>20 (0.5 ; 77) | 19.84 (0.622)<br>16 (0.5 ; 70) | 20.18 (0.643)<br>17 (0.3 ; 82) | 20.01 (0.447)<br>16 (0.3 ; 82) |
| Average freq./week spontaneous bowel movement over previous 6 months, n (%) | | | | |
| No spontaneous BM<br>>0 and ≤1<br>>1 and ≤3<br>>3 | 259 (40.2)<br>224 (34.7)<br>153 (23.7)<br>9 (1.4) | 251 (39.2)<br>224 (35.0)<br>153 (23.9)<br>12 (1.9) | 262 (41.0)<br>206 (32.2)<br>155 (24.3)<br>16 (2.5) | 513 (40.1)<br>430 (33.6)<br>308 (24.1)<br>28 (2.2) |
| Subject main complaint, n (%) | | | | |
| Infrequent defecation<br>Abdominal bloating<br>Abdominal pain<br>Feeling not completely empty<br>Straining<br>Hard stools | 185 (28.7)<br>163 (25.3)<br>98 (15.2)<br>95 (14.7)<br>68 (10.5)<br>36 (5.6) | 202 (31.6)<br>152 (23.8)<br>102 (15.9)<br>83 (13.0)<br>65 (10.2)<br>36 (5.6) | 184 (28.8)<br>159 (24.9)<br>85 (13.3)<br>97 (15.2)<br>80 (12.5)<br>34 (5.3) | 386 (30.2)<br>311 (24.3)<br>187 (14.6)<br>180 (14.1)<br>145 (11.3)<br>70 (5.5) |
| Laxative taken, n (%) | | | | |
| No<br>Yes | 89 (13.8)<br>556 (86.2) | 92 (14.4)<br>548 (85.6) | 98 (15.3)<br>541 (84.7) | 190 (14.9)<br>1089 (85.1) |
| Overall therapeutic effect, n (%) | | | | |
| Adequate<br>Inadequate | 106 (17.0)<br>516 (83.0) | 115 (18.5)<br>507 (81.5) | 100 (16.2)<br>517 (83.8) | 215 (17.4)<br>1024 (82.6) |

*Treatments & assessments*

Eligible patients admitted to the double-blind phase were randomly allocated to one of 3 treatment arms: Prucalopride (2 or 4 mg), or matching placebo given once daily before breakfast or in the morning if they didn't eat breakfast, starting on the day after the randomisation visit.

Patients continued to maintain their daily diaries throughout the 12-week double-blind treatment phase. Visits were scheduled for the end of Weeks 2, 4, 8, and 12. At each visit, the patients provided global assessments of their constipation severity and the therapeutic effect of study medication on 5-point Likert scales [absent (0), mild (1), moderate (2), severe (3) and very severe (4)] and completed a Patient Assessment of Constipation-Symptoms questionnaire (PAC-SYM) regarding specific symptoms of constipation. The patients also completed 2 health-related QOL questionnaires, the Patient Assessment of Constipation-Quality of Life questionnaire (PAC-QOL) and the 36-item Short Form Health Survey (SF-36™) at the randomisation visit (Visit 2) and after 4 and 12 weeks of double-blind treatment without assistance in interpretation of the questionnaire.

Blood samples were taken for determination of Prucalopride plasma concentrations at predefined time points.

Safety and tolerability, including recording of AEs, clinical laboratory tests, vital signs, physical examination including body weight, and ECG, were assessed at scheduled visits during the treatment period.

*Objectives*

To evaluate the efficacy, safety and effect on the quality of life of 2 & 4 mg Prucalopride in patients with chronic constipation.

*Outcomes/endpoints*

The primary parameter was the proportion (%) of patients with an average of 3 or more spontaneous, complete bowel movements per week (responders, ≥3 SCBM/week). The key time-points included the entire double-blind phase (Weeks 1 through 12), and the double-blind phase of Weeks 1 through 4 (first 4 weeks). A bowel movement was defined as spontaneous if no laxatives were taken in the 24 hours preceding that bowel movement. If a time of laxative use was recorded on a diary, but the number of tablets was not recorded, it was assumed that laxative use occurred then. If the number of laxative tablets was recorded, but no time, the time of laxative use was imputed.

A bowel movement was considered complete only if the patient responded 'yes' to the diary question 'Did the stool make you feel like you completely emptied your bowels?'. On some diaries, patients ticked the box for this question instead of filling in 0 (for 'no') or 1 (for 'yes'). In this case, it was assumed that the patient was answering the question in the affirmative. Bowel movements with missing values for this parameter were considered as not complete.

If, based on the primary imputation method, at least 5% of randomised patients had missing values for average SCBM/week, they were considered non-responders for the primary parameter.

The main secondary endpoint was the proportion of patients with an average increase of ≥1 SCBM per week from run-in.

Other secondary endpoints included:

- ✓ Time to first spontaneous bowel movement (SBM) and the average SBM per week.
- ✓ Stools consistency and severity of constipation
- ✓ Use of laxatives
- ✓ Evaluation of the patient assessment of constipation symptoms using validated Patient Assessment of Constipation – Symptoms (PAC-SYM) and quality of life Patient Assessment of Constipation – Quality of Life (PAC-QOL) questionnaires.

*Sample size*

There were 720 patients randomised into trial PRU-INT-6, 628 into trial PRU-USA-11 and 651 into trial PRU-USA-13.

*Randomisation*

Patients were randomly allocated to the treatments groups using a randomisation code stratified by centre.

*Blinding (masking)*

All study medication was supplied in identically appearing containers that were labelled with the protocol number, medication number, week number, and number of tablets (18 tablets at Visits 2 and 3; 36 tablets at Visits 4 and 5). Tablets were identical in appearance, taste, and smell.

*Statistical methods*

All randomised patients who took at least one dose of double-blind study medication were included in the analysis of safety, demographic, and baseline characteristic data (all-[treated] subjects population). Analyses of efficacy and QOL data were based on the intent-to-treat (ITT) population, defined as all randomised patients who took at least one dose of double-blind study medication and who provided any follow-up data for one or more key efficacy variables; in turn, ITT patients were allocated to treatments actually received.

Because there were a substantial number of protocol violators, an additional per-protocol analysis was performed for a selection of the efficacy parameters to determine whether they influenced the conclusions.

The per-protocol population is the ITT population with the following exclusions:

- Patients with, on average, >2 SCBM per week during the run-in.
- Patients with, on average, ≤2 SCBM per week during run-in but without the straining, consistency, or completeness inclusion criteria fulfilled.
- Patients with average number of days per week with laxative use >3.0 over the entire treatment period.
- Patients with treatment duration less than 63 days (i.e. 75% out of 84 days) or more than 96 days.
- Patients with less than an average of 0.75 tablets of study medication taken per day over the entire treatment period (i.e. less than 75% compliant).

All statistical tests were interpreted at the 5% significance level (2-sided) unless specified otherwise.

Primary endpoint

The difference between each active treatment group and placebo was analysed using the Cochran-Mantel-Haenszel test controlling for investigator/country.

Secondary endpoints

Endpoints based upon proportions were analysed in the same way as the primary endpoint.

Continuous endpoints were analysed using analysis of covariance (ANCOVA) with treatment, run-in value and investigator/country as factors. Ordinal categorical parameters with more than 10 categories were considered as continuous parameters and thus change from baseline scores on a 5-point scale or higher were considered as continuous data.

The Van Elteren test controlling for investigator/country was used for the between-treatment group comparison of ordinal categorical variables with less than 10 categories.

Time to event data were analysed by the methods for survival data analysis. The Kaplan-Meier curve was used to describe the distribution and the log-rank test was used for the between-treatment group comparison.

Adjustments for multiplicity

No adjustment was made for the 2 primary time-periods (weeks 1-4 and weeks 1-12) which were considered for the primary endpoint. This means that both time-periods are required to produce statistically significant results for the trial to be considered positive.

To adjust for comparing the two doses against placebo, Holm's step-down procedure was used. If both p-values are greater than 0.025 then neither dose is considered superior to placebo. If both p-values are less then 0.05 and the smallest is also less than 0.025 then both doses are considered superior to placebo. If one p-value is less than 0.025 but the other is greater than 0.05, then only the dose associated with the smaller p-value is considered superior to placebo.

RESULTS

*Participant flow*

The majority of patients completed the trials as planned. The most common reason for premature discontinuation was adverse events, with the frequency of withdrawal being highest in the 4mg group.

**Table 8a: PRU-INT-6**

| | Placebo | 2 mg | 4 mg |
|---|---|---|---|
| Screened (n=865) | | | |
| Randomised | 240 | 238 | 242 |
| Not treated | 0 | 0 | 4 |
| Completed | 207 (86%) | 207 (87%) | 183 (76%) |
| Withdrawn | 33 (14%) | 31 (13%) | 55 (23%) |
| Adverse event | 16 (7%) | 15 (6%) | 35 (14%) |
| Insufficient response | 7 | 3 | 5 |
| Ineligible | 1 | 1 | 1 |
| Lost to follow-up | 1 | 3 | 2 |
| Withdrew consent | 5 | 5 | 8 |
| Non-compliant | 1 | 0 | 2 |
| Other | 2 | 4 | 2 |

**Table 8b: PRU-USA-11**

| | Placebo | 2 mg | 4 mg |
|---|---|---|---|
| Screened (n=832) | | | |
| Randomised | 213 | 210 | 205 |
| Not treated | 4 | 3 | 1 |
| Completed | 182 (85%) | 172 (82%) | 173 (84%) |
| Withdrawn | 27 (13%) | 35 (17%) | 31 (15%) |
| Adverse event | 4 (2%) | 18 (9%) | 16 (8%) |
| Insufficient response | 5 | 2 | 1 |
| Ineligible | 0 | 3 | 0 |
| Lost to follow-up | 3 | 3 | 2 |
| Withdrew consent | 7 | 3 | 5 |
| Non-compliant | 4 | 4 | 4 |
| Other | 4 | 2 | 3 |

**Table 8c: PRU-USA-13**

| | Placebo | 2 mg | 4 mg |
|---|---|---|---|
| Screened (n=880) | | | |
| Randomised | 214 | 216 | 221 |
| Not treated | 2 | 2 | 6 |
| Completed | 188 (88%) | 194 (90%) | 185 (84%) |
| Withdrawn | 24 (11%) | 20 (9%) | 30 (14%) |
| Adverse event | 5 (2%) | 8 (4%) | 13 (6%) |
| Insufficient response | 3 | 1 | 0 |
| Ineligible | 3 | 0 | 0 |
| Lost to follow-up | 2 | 3 | 2 |
| Withdrew consent | 5 | 4 | 7 |
| Non-compliant | 1 | 4 | 3 |
| Other | 5 | 0 | 5 |

*Recruitment*

For PRU-INT-6 the first subject visit was 13 March 1998 and the last subject visit was 19 July 1999.
For PRU-USA-11 the first subject visit was 2 April 1998 and the last subject visit was 24 May 1999.
For PRU-USA-13 the first subject visit was 18 March 1998 and the last subject visit was 4 May 1999.

*Conduct of the study*

In trial PRU-USA-13 there were 50 patients from 2 sites who were excluded from the ITT population because of poor trial conduct

*Baseline data*

The treatment groups were comparable at baseline for SCMB per week, the basis of the primary efficacy analysis.

**Table 9: Average frequency of SCBM during the 2-week run-in (SCBM/week) – ITT population**

| | Placebo | | 2mg | | 4mg | |
|---|---|---|---|---|---|---|
| | n | Mean (se) | n | Mean | n | Mean |
| PRU-INT-6 | 239 | 0.4 (0.05) | 236 | 0.4 (0.05) | 237 | 0.5 (0.05) |
| PRU-USA-11 | 192 | 0.4 (0.05) | 189 | 0.5 (0.05) | 187 | 0.5 (0.05) |
| PRU-USA-13 | 212 | 0.4 (0.05) | 213 | 0.4 (0.04) | 215 | 0.5 (0.07) |

*Numbers analysed*

Two sites were excluded from analyses of efficacy data in study PRU- USA-11, due to ignoring good clinical practice rules, giving an ITT analyses set of 570 patients for this trial.

**Table 10a: PRU-INT-6**

| | Placebo | 2 mg | 4 mg |
|---|---|---|---|
| Randomised | 240 | 238 | 242 |
| Treated | 240 (100%) | 238 (100%) | 238 (98%) |
| ITT population | 240 (100%) | 236 (99%) | 237 (98%) |
| Per-protocol | 183 (76%) | 203 (85%) | 173 (71%) |

**Table 10b: PRU-USA-11**

| | Placebo | 2 mg | 4 mg |
|---|---|---|---|
| Randomised | 213 | 210 | 205 |
| Treated | 209 (98%) | 207 (99%) | 204 (>99%) |
| ITT population | 193 (91%) | 190 (90%) | 187 (91%) |
| Per-protocol | 157 (74%) | 152 (72%) | 155 (76%) |

**Table 10c: PRU-USA-13**

| | Placebo | 2 mg | 4 mg |
|---|---|---|---|
| Randomised | 214 | 216 | 221 |
| Treated | 212 (99%) | 214 (99%) | 215 (97%) |
| ITT population | 212 (99%) | 214 (99%) | 215 (97%) |
| Per-protocol | 186 (87%) | 185 (86%) | 171 (77%) |

*Outcomes and estimation*

**Study PRU-INT-6**

Over the 12-week treatment period, 19.5% and 23.6% of patients in the Prucalopride 2 and 4 mg groups, respectively, had ≥3 SCBM per week, as compared with 9.6% of placebo-treated patients (2 mg p≤0.01; 4 mg p≤0.001). Over Weeks 1 through 4, 23.7% and 26.6% of patients in the Prucalopride 2 and 4 mg groups, respectively, had ≥3 SCBM per week compared with 10.4% of placebo-treated patients (p≤0.001, in both cases).

**Table 11: Proportion of patients with ≥3 SCBM/week – ITT population**

| | Placebo | 2mg | 4mg |
|---|---|---|---|
| Weeks 1-12 | 23/240 (9.6%) | 46/236 (19.5%) | 56/237 (23.6%) |
| 95% CI, p-value | | (4, 16), p=0.002 | (7, 21) p<0.001 |
| Weeks 1-4 | 25/240 (10.4%) | 56/236 (23.7%) | 63/237 (26.6%) |
| 95% CI, p-value | | (7, 20), p<0.001 | (9, 23) p<0.001 |

For the main secondary parameter (the proportion of patients with an average increase of ≥1 SCBM per week from run-in), significant improvements were seen for both Prucalopride 2 and 4 mg treatment groups compared with placebo. Over the 12-week treatment period, the proportion of patients with an average increase of ≥1 SCBM per week was 38.1% and 44.1% in the 2 and 4 mg

groups, respectively, compared with 20.9% of placebo patients (p≤0.001, in both cases). Over Weeks 1 through 4, 41% and 46% of patients in the Prucalopride 2 and 4 mg groups, respectively, had an increase of ≥1 SCBM per week, compared with 20.9% of placebo patients (p≤0.001, in both cases).
Prucalopride significantly improved the time to first bowel movement when compared with placebo. The median time required to have the first SCBM in the Prucalopride 2 and 4 mg groups was 113 and 49.5 hours after the first dose, respectively, compared with 493 hours in the placebo group (p≤0.001, in both cases). Prucalopride significantly reduced laxative use when compared to placebo. The average number of bisacodyl tablets taken per week was approximately 2 in all treatment groups during the baseline period. The mean decrease during the 12-week treatment period was 0.8 in the Prucalopride 2 mg group, 0.6 in the Prucalopride 4 mg group, and 0.2 tablets taken per week in the placebo group. The average weekly bisacodyl use over the 12-week treatment period was significantly lower in each of the Prucalopride groups compared to placebo (p≤0.003). Enema use was rare in all treatment groups. The average number of days with laxative use per week during the baseline period (approximately 1 day per week) was comparable in all treatment groups. Despite this low number, the mean decrease observed during both the 12-week and 4-week treatment period in the Prucalopride groups (ranging from -0.3 to -0.4) was significantly greater than the change on placebo (range -0.1 to -0.2; p<0.001).

Statistically significant decreases in severity from run-in were seen for the overall score, stool symptoms and abdominal symptoms on the validated PAC-SYM questionnaire in both Prucalopride groups compared with placebo.

The patients completed a disease-specific and validated quality of life questionnaire (PAC-QOL). On a scale of 0 to 4, with 4 representing the lowest satisfaction with overall bowel habits, the mean run-in scores for satisfaction ranged from 3.08 to 3.17 across treatment groups. During the course of the trial, the mean scores improved to 2.22 to 2.34 in the Prucalopride groups and to 2.85 to 2.89 in the placebo group. The magnitude of improvement from baseline was 2 to 3 times greater in the Prucalopride groups (i.e. -0.76 to -0.87) when compared with placebo (i.e. -0.26 to -0.30; p<0.001). At Weeks 4 and 12, the proportion of patients with an improvement from run-in of at least 1 point in the PAC-QOL satisfaction score was 42.8% and 45.6%, respectively, in the Prucalopride 2 mg group and 44.6% and 45.8%, respectively, in the Prucalopride 4 mg group, compared with 22.8% and 21.8%, respectively, with placebo (p≤0.001, in all cases).

**Study PRU-USA-11**

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

**Table 12: Proportion of patients with ≥3 SCBM/week – ITT population**

| | Placebo | 2mg | 4mg |
|---|---|---|---|
| Weeks 1-12 | 25/193 (13.0%) | 55/190 (28.9%) | 54/187 (28.9%) |
| 95% CI, p-value | | (8, 24), p<0.001 | (8, 24) p<0.001 |
| Weeks 1-4 | 19/193 (9.9%) | 61/190 (32.1%) | 70/187 (37.4%) |
| 95% CI, p-value | | (14, 30), p<0.001 | (19, 36) p<0.001 |

For the main secondary parameter (the proportion of patients with an average increase of ≥1 SCBM per week from run-in), significant improvements were seen for both the Prucalopride 2 and 4 mg treatment groups compared with placebo. Over the 12-week treatment period, the proportion of patients with an average increase of ≥1 SCBM per week was 50.3% and 51.1% in the 2 and 4 mg groups, respectively, compared with 25.9% of placebo patients (p≤0.001, in both cases). Over Weeks 1 through 4, 56.5% and 58.8% of patients in the Prucalopride 2 and 4 mg groups, respectively, had an increase of ≥1 SCBM per week, compared with 24.3% of placebo patients (p≤0.001, in both cases).
Prucalopride significantly improved the time to first bowel movement when compared with placebo. The median time required to have the first SCBM in the Prucalopride 2 and 4 mg groups was 32.5 and 25 hours after the first dose, respectively, compared with 297 hours in the placebo group (p≤0.001, in

both cases). Prucalopride significantly reduced laxative use when compared with placebo. The mean number of bisacodyl tablets taken per week was approximately 2 in all treatment groups during the run-in period. The mean decrease per week during the 12-week treatment period was 1.1 in the Prucalopride 2 mg group, 0.7 in the Prucalopride 4 mg group, and 0 tablets in the placebo group. The average weekly bisacodyl use over the 12-week treatment period was significantly lower in each of the Prucalopride groups compared with placebo ($p \leq 0.001$, in both cases). Enema use was rare in all treatment groups. The average number of days with laxative use or enema per week during the run-in period (approximately 1 day per week) was comparable in all treatment groups. Despite this low number, the mean decrease observed during both the 12-week and 4-week treatment periods in the Prucalopride groups (ranging from 0.3 to 0.5) was significantly greater than the decrease in the placebo group (range 0 to 0.1; $p \leq 0.001$, in all cases).

Statistically significant decreases in severity from run-in were seen for the overall score, stool symptoms and abdominal symptoms on the validated PAC-SYM questionnaire for both Prucalopride groups compared with placebo (for stool symptoms: at Week 12 only significant for the 4 mg dose vs. placebo).

The patients completed a disease-specific and validated quality of life questionnaire (PAC-QOL). On a scale of 0 to 4, with 4 representing the lowest satisfaction with overall bowel habits, the mean run-in scores ranged from 3.33 to 3.38 across treatment groups. During the course of the trial, the mean scores improved to 2.22 - 2.43 in the Prucalopride groups and to 2.95 - 3.10 in the placebo group ($p \leq 0.001$). The magnitude of improvement from baseline was 4 to 5 times greater in the Prucalopride groups (i.e. -0.97 to -1.16) when compared with the placebo group (i.e. -0.20 to -0.32; $p < 0.001$)). At Weeks 4 and 12, the proportion of patients with an improvement from run-in of at least 1 point in the PAC-QOL satisfaction score was 53.5% and 47.1%, respectively, in the Prucalopride 2 mg group and 51.2% and 47.8%, respectively, in the Prucalopride 4 mg group, compared with 18.5% and 25.2%, respectively, with placebo ($p \leq 0.001$, in all cases).

**Study PRU-USA-13**

Over the 12-week treatment period, 23.9% and 23.5% of patients in the Prucalopride 2 and 4 mg groups, respectively, had ≥3 SCBM per week as compared with 12.1% of placebo-treated patients ($p \leq 0.01$, in both cases). Over Weeks 1 through 4, 29.2% and 28.9% of patients in the Prucalopride 2 and 4 mg groups, respectively, had ≥3 SCBM per week compared with 11.5% of placebo-treated patients ($p \leq 0.001$, in both cases).

**Table 13: Proportion of patients with ≥3 SCBM/week – ITT population**

| | Placebo | 2mg | 4mg |
|---|---|---|---|
| Weeks 1-12 | 25/207 (12.1%) | 50/209 (23.9%) | 48/204 (23.5%) |
| 95% CI, p-value | | (5, 19), p=0.002 | (4, 19) p=0.003 |
| Weeks 1-4 | 24/208 (11.5%) | 61/209 (29.2%) | 59/204 (28.9%) |
| 95% CI, p-value | | (10, 25), p<0.001 | (10, 25) p<0.001 |
| Missing=failure* | | | |
| Weeks 1-12 | 25/212 (11.8%) | 50/214 (23.4%) | 48/215 (22.3%) |
| Weeks 1-4 | 24/212 (11.3%) | 61/214 (28.5%) | 59/215 (27.4%) |

95% CI and p-values for difference from placebo in response rates (%).
*INT-6 and USA-11 use missing=failure as the primary analysis, so these figures are the best ones to compare to the other trials.

For the main secondary parameter (the proportion of patients with an average increase of ≥1 SCBM per week from run-in), significant improvements were seen for both the Prucalopride 2 and the 4 mg treatment groups compared with placebo. Over the 12-week treatment period, the proportion of patients with an average increase of ≥1 SCBM per week was 42.6 % and 46.6 % in the 2 and 4 mg groups, respectively, compared with 27.5% of placebo patients ($p \leq 0.001$, in both cases). Over Weeks 1 through 4, 48.8% and 51.5% of patients in the Prucalopride 2 and 4 mg groups, respectively, had an increase of ≥1 SCBM per week, compared with 25.5% of placebo patients ($p \leq 0.001$, in both cases).

Prucalopride significantly improved the time to first bowel movement when compared with placebo. The median time required to have the first SCBM in the Prucalopride 2 and 4 mg groups was 55 and 46 hours after the first dose, respectively, compared with 311 hours in the placebo group ($p \leq 0.001$, in both cases). Prucalopride significantly reduced laxative use when compared with placebo. The mean number of bisacodyl tablets taken per week was approximately 2 in all treatment groups during the run-in period. The mean decrease during the 12-week treatment period was 0.7 in the Prucalopride 2 mg group, 1 in the Prucalopride 4 mg group, and 0.1 tablets in the placebo group. The average weekly bisacodyl use over the 12-week treatment period was significantly lower in each of the Prucalopride groups compared with placebo (2 mg $p \leq 0.01$; $p \leq 0.001$). Enema use was rare in all treatment groups. The average number of days with laxative use per week during the run-in period (approximately 1 day per week) was comparable in all treatment groups. Despite this low number, the mean decrease observed during both the 12-week and 4-week treatment periods in the Prucalopride groups (ranging from -0.3 to -0.5) was significantly greater than the change with placebo (-0.1; $p \leq 0.001$, except for 2 mg at Weeks 1 through 4: $p \leq 0.05$).

Statistically significant decreases in severity from run-in were seen for the overall score, stool symptoms and abdominal symptoms on the validated PAC-SYM questionnaire for both Prucalopride groups compared with placebo (for stool symptoms: at Week 12 only 2 mg was statistically significant from placebo).

The patients completed a disease-specific and validated quality of life questionnaire (PAC-QOL). On a scale of 0 to 4, with 4 representing the lowest satisfaction with overall bowel habits, the mean baseline ranged from 3.37 to 3.43 across treatment groups. During the course of the trial, the mean scores improved to 2.42 to 2.51 in the Prucalopride groups and to 3.01 to 3.06 in the placebo group. The magnitude of improvement from baseline was 2 to 3 times greater in the Prucalopride groups (i.e. -0.86 to -0.97) when compared with placebo (i.e. -0.39 to -0.44; $p<0.001$). At Weeks 4 and 12, the proportion of patients with an improvement from run-in of at least 1 point in the PAC-QOL satisfaction score was 42.6% and 43.5%, respectively, in the Prucalopride 2 mg group, and 44.8% and 44.4%, respectively, in the Prucalopride 4 mg group, compared with 22.3% and 26%, respectively, with placebo ($p \leq 0.001$, in all cases).

- Analysis performed across trials (pooled analyses and meta-analysis)

*Pooled data from the three pivotal trials*

- **Primary Efficacy Endpoint**

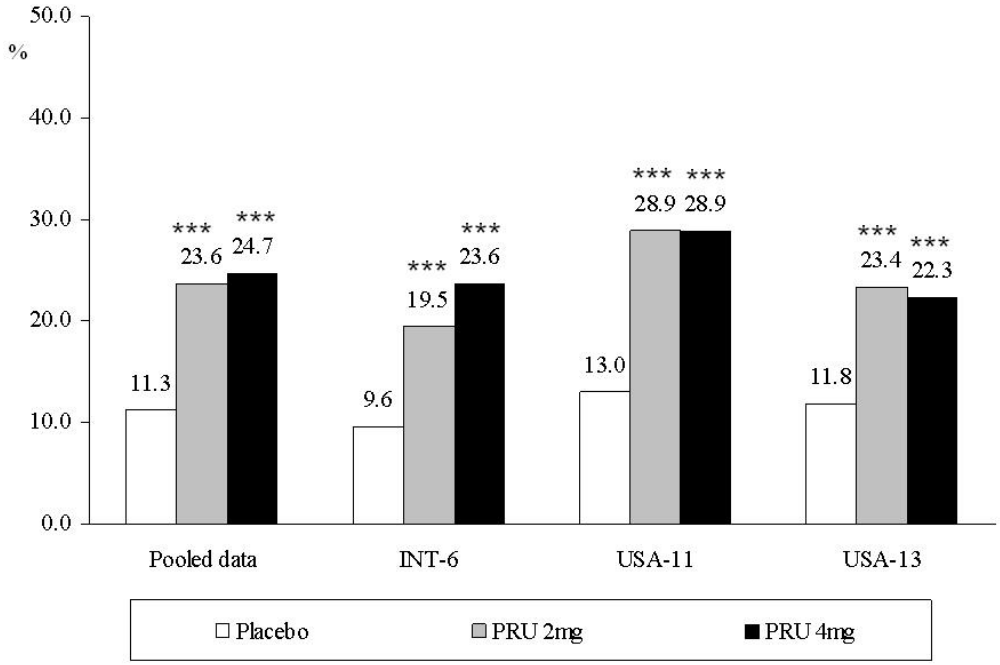
The results of the primary endpoint for the pooled data from the 3 pivotal studies are presented in Table 14 and Figure 4 shows the results by study. Results of the 3 studies are consistent in showing a statistically significantly higher proportion of patients with ≥3 SCBM per week in Prucalopride 2 mg and 4 mg treatment groups when compared to placebo. Over the 12-week treatment period, 23.6% of patients receiving Prucalopride 2 mg achieved ≥3 SCBMs per week, compared to 11.3% of placebo patients. The positive effect of treatment was evident over the first 4 weeks and was maintained over the 12 weeks of the study. The 4 mg results did not provide a significant incremental benefit over the 2 mg.

**Table 14: Number (%) of patients with ≥3 SCBM per week – pooled data from PRU-INT-6, PRUUSA-11, PRU-USA-13 – ITT population**

| | Placebo N=645 | | PRU 2 mg N=640 | | PRU 4 mg N=639 | |
|---|---|---|---|---|---|---|
| Time-point | N | n (%) | N | n (%) | N | n (%) |
| Run-in | 643 | 4 (0.6) | 638 | 5 (0.8) | 639 | 8 (1.3) |
| Weeks 1-12 | 645 | 73 (11.3) | 640 | 151 (23.6)*** | 639 | 158 (24.7)*** |
| Weeks 1-4<br>Weeks 5-8<br>Weeks 9-12 | 645<br>628<br>630 | 68 (10.5) 83<br>(13.2) 89 (14.1) | 640<br>612<br>612 | 178 (27.8)***<br>147 (24.0)***<br>154 (25.2)*** | 639<br>592<br>593 | 192 (30.0)***<br>152 (25.7)***<br>152 (25.6)*** |

***p<0.001 vs. placebo (pairwise comparison)

**Figure 4: Number (%) of patients with ≥3 SCBM per week in each of the 3 pivotal studies**




***p<0.001 vs. placebo

- **Increase of ≥1 SCBM per week**

Table 15 shows the proportion of patients with an average increase of 1 SCBM per week for the pooled population. These data indicate that 43.1% of the patients that received 2 mg Prucalopride compared to 24.6% of placebo-treated patients had an increase of at least 1 SCBM per week. The 4 mg results did not provide a significant incremental benefit over the 2 mg.

**Table 15: Number (%) of patients with an average increase of ≥1 SCBM per week – pooled data from PRU-INT-6, PRU-USA-11, PRU-USA-13 –ITT population**

| | Placebo N=645 | | PRU 2 mg N=640 | | PRU 4 mg N=639 | |
|---|---|---|---|---|---|---|
| Time-point | N | n (%) | N | n (%) | N | n (%) |
| ≥1 SCBM/week increase | | | | | | |
| Weeks 1-12 | 630 | 155 (24.6) | 612 | 264 (43.1)*** | 593 | 279 (47.0)*** |
| Weeks 1-4 | 632 | 148 (23.4) | 613 | 295 (48.1)*** | 596 | 308 (51.7)*** |
| Weeks 5-8 | 628 | 165 (26.3) | 612 | 254 (41.5)*** | 592 | 265 (44.8)*** |
| Weeks 9-12 | 630 | 157 (24.9) | 612 | 245 (40.0)*** | 593 | 248 (41.8)*** |

***p<0.001 vs. placebo (pairwise comparison)

- **Quality of Life Assessment**

A consistent significant improvement in patient satisfaction with treatment and their bowel habits (subscale of PAC-QOL) was observed with Prucalopride across the pivotal Phase III studies. Table 16 shows the proportion of patients who had a ≥1-point improvement in the satisfaction subscale score (on a 5-point scale): 45.3% of patients on Prucalopride 2 mg compared to 21.3% on placebo. This improvement in satisfaction score is important given the high level of dissatisfaction expressed at baseline in these studies (mean score >3 on a 0 to 4 scale, with 4 representing the lowest satisfaction).

The improvement with Prucalopride was also statistically significant when compared to placebo for the overall PAC-QOL and each of the remaining subscales (physical discomfort, psychosocial discomfort, worries and concerns) at every time-point (p<0.001).

**Table 16: Proportion of patients with improvement of ≥1 in PAC-QOL satisfaction score – pooled data from PRU-INT-6, PRU-USA-11, PRU-USA-13 – ITT population**

| | Placebo N=645 | | PRU 2 mg N=640 | | PRU 4 mg N=639 | |
|---|---|---|---|---|---|---|
| Time-point | N | n (%) | N | n (%) | N | n (%) |
| Week 4**a** | 605 | 129 (21.3) | 598 | 271 (45.3)*** | 588 | 270 (45.9)*** |
| Week 12**a** | 618 | 137 (22.2) | 621 | 273 (44.0)*** | 603 | 261 (43.3)*** |

**a** Data at endpoint
***p<0.001 vs. placebo (pairwise comparison)

The clinical relevance of these results has been assessed by looking at the correlation between improvements in the quality of life and other efficacy assessments. This analysis showed that subjects with a 1-point improvement on the satisfaction subscale also have improvements on other efficacy parameters such as change in percentage of patients with at least 3 SCBM per week (primary endpoint), patients' global evaluation of the severity of constipation-related symptoms, and patients' global evaluation of the efficacy treatment. More patients on Prucalopride than on placebo had a higher improvement in the PAC-QOL satisfaction score, as can be observed from the cumulative distribution curves.

- Ancillary analysis

*Gender effect*

Most studies were conducted in (Caucasian) women with chronic constipation. The majority of patients in the pivotal trials were female: 89.9% of the patients in the placebo group and 87.9% of all Prucalopride-treated patients. Female patients in the Prucalopride 2 mg group were more sensitive to the beneficial effect of treatment than males, but at the 4 mg dose, there were no clear differences between the sexes. The analysis of the proportion of patients with an average increase of ≥1 SCBM by sex yielded similar findings.

**Table 17: Number (%) of patients with ≥3 SCBM per week by sex – pooled data from PRU-USA-11, PRU-USA-13, PRU-INT-6 – ITT population**

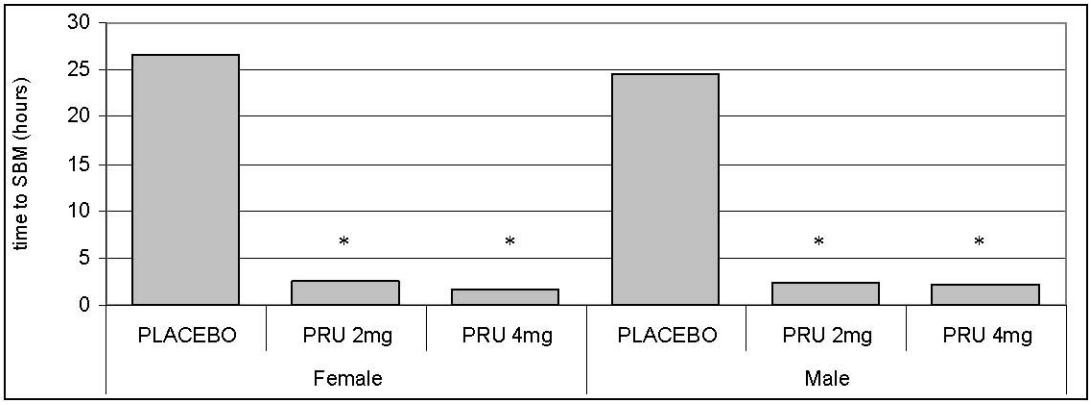
| | **Placebo** | | **PRU 2 mg** | | **PRU 4 mg** | |
|---|---|---|---|---|---|---|
| **Time-point** | **N** | **n (%)** | **N** | **n (%)** | **N** | **n (%)** |
| Female n (%) | | | | | | |
| Run-in | 578 | 4 (0.7) | 565 | 5 (0.9) | 558 | 7 (1.3) |
| Weeks 1-12 | 580 | 62 (10.7) | 566 | 138 (24.4)*** | 558 | 136 (24.4)*** |
| Weeks-1-4 | 580 | 58 (10.0) | 566 | 166 (29.3)*** | 558 | 169 (30.3)*** |
| Male n (%) | | | | | | |
| Run-in | 65 | 0 (0.0) | 73 | 0 (0.0) | 81 | 1 (1.2) |
| Weeks 1-12 | 65 | 11 (16.9) | 74 | 13 (17.6) | 81 | 22 (27.2) |
| Weeks 1-4 | 65 | 10 (15.4) | 74 | 12 (16.2) | 81 | 23 (28.4) |

***p<0.001 vs. placebo (pairwise comparison)

The number of males in the studies was low, about 10%. Furthermore, the results for the men are not statistically significant but there appears to be a trend that male patients require a higher dose. In addition, the placebo response was higher in the male population, which further makes the assessment more difficult. Hence, the pivotal studies were conducted almost exclusively in women. This raises concerns that the medicinal product has not been sufficiently evaluated in men. Also, the limited data available indicates the possibility of better efficacy with the 4-mg dose in males.

However, from a PK/PD or mechanism of action perspective, there is no difference in response between males and females (as shown by colonic transit time). Similar reductions in time to first stools are obtained in both males and females as illustrated in the figure below:

**Figure 5: Prucalopride, 2 and 4 mg, reduces time to first stool in male patients in the pivotal trials; this effect was statistically significant (p<0.001), with similar values at the 2 and 4 mg dose and similar values for the response in males and females.**




* p<0.001 vs placebo

The pharmacodynamic effect is clearly similar in males and females compared to placebo. The small number of male subjects in double blind studies seems to explain the lack of statistical significance of the 2mg dose which is further compounded by the higher proportion of male patients with severe constipation at baseline in this subgroup.

This limitation of data in men will need to be further addressed by the provision of new relevant efficacy data. The applicant commits to a post-authorization efficacy study in males (FUM). The results of this study should be awaited before men are included for treatment with Prucalopride.

*Long term efficacy*

A total of 2595 patients with chronic constipation received treatment with Prucalopride in an open-label setting in 5 Phase II studies (PRU-BEL-8, PRU-INT-3, PRU-INT-4, PRU-NED-4, PRU-FRA-1 [Part 2]) and 2 Phase III studies (PRU-INT-10, PRU-USA-22). The primary objective of all of these studies was the collection of long-term safety data, but long-term efficacy was also assessed using either the PAC-QOL satisfaction subscale (PRU-USA-22 and PRU-INT-10) or the visual analogue scales (VAS) to assess the patient's perception of treatment effectiveness and severity of constipation (Phase II studies).

From the 3 pivotal trials 1455 patients (494 were treated with placebo and 961 with Prucalopride) continued in long term open-label (OL) phase for treatment with Prucalopride up to 24 months. In the OL phase, efficacy was measured by means of the PAC-QOL satisfaction scale at each 3 month visit. Mean scores for the PAC-QOL satisfaction scale during both the DB and OL phase are shown in Table 18. Values of the PAC-QOL satisfaction scale range from 0 to 4 and lower values indicate improvement - more satisfaction

**Table 18: Evolution of mean PAC-QOL satisfaction score during the double blind and open label phase for patients from the pivotal trials**

| | Randomisation group in pivotal trial | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | PLACEBO | | | PRU 2MG | | | PRU 4MG | | |
| | N | Mean | S.E. | N | Mean[#] | S.E. | N | Mean[#] | S.E. |
| Baseline | 636 | 3.30 | 0.028 | 639 | 3.29 | 0.030 | 636 | 3.27 | 0.030 |
| Week 4 | 597 | 3.01 | 0.043 | 581 | 2.36* | 0.048 | 567 | 2.31* | 0.050 |
| Week 12 | 553 | 2.93 | 0.047 | 553 | 2.40* | 0.051 | 517 | 2.34* | 0.053 |

| | Continuation with Long term Prucalopride Treatment | | |
|---|---|---|---|
| | N | Mean[#] | S.E. |
| Month 3 | 1322 | 1.95 | 0.033 |
| Month 6 | 1076 | 1.81 | 0.034 |
| Month 9 | 915 | 1.74 | 0.036 |
| Month 12 | 780 | 1.69 | 0.038 |
| Month 15 | 681 | 1.68 | 0.040 |
| Month 18 | 509 | 1.67 | 0.045 |

[#] Values range from 0 to 4 and lower values indicate improvement - more satisfaction.
* $p<0.001$ vs placebo
Source: Module 5.3.5.3/DEFF 10.1.1.A and DEFF 10.1.1.C

Across all of these Phase II/III studies, the reported withdrawal rate due to inadequate response was 19% (489/2595). However, sub-analysis of the data shows that the 19% of patients who withdrew due to lack of efficacy during the open label phase, comprised 16% that were shown to be non-responders during the double blind phase. Thus only 3% of responders withdrew due to lack of efficacy after up to two and half years of treatment.

This appears to be further supported by the fact that in responders, symptoms reportedly return to baseline when treatment is stopped. Therefore patients are unlikely to develop tolerance during long term treatment. The SPC text has been amended accordingly. In addition, the applicant commits to provide further controlled data to study the long-term efficacy/safety of Prucalopride (FUM).

- Clinical studies in special populations

*Elderly*

A Phase III study in an elderly population (PRU-INT-12) evaluated the effects of 3 doses of Prucalopride (1, 2 and 4 mg o.d.). Details of the trial are provided in the section "Dose response studies".

*Population with "Opioid-Induced Constipation"*

Five studies, including one pilot study, were performed in patients with opioid-induced constipation. These are summarised in the table 18 below. Due to halting of the programme, only one of the studies was completed (PRU-INT-8).

**Table 19: Summary of Phase II/III double-blind placebo-controlled trials in patients with opioid-induced constipation**

| | | |
|---|---|---|
| PRU-USA-8<br>Phase II | A pilot study of once-daily oral Prucalopride capsules vs. placebo in opioid-induced constipation in cancer patients. | N=5 (5)<br>Placebo, 2 mg, 4 mg/<br>4 weeks |
| PRU-INT-14<br>Phase II | A double-blind, placebo-controlled trial to evaluate the efficacy and safety of Prucalopride in patients with chronic cancer pain, suffering from opioid-induced constipation. | N=53 (52)<br>Placebo, 2 mg, 4 mg/<br>4 weeks |
| PRU-INT-8<br>Phase II | 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 | N=196 (196)<br>Placebo, 2 mg, 4 mg/<br>4 weeks |
| PRU-USA-27<br>Phase II | A study of once-daily oral Prucalopride tablets vs. placebo in patients with opioid-induced constipation. | N=88 (84)<br>Placebo, 2 mg, 4 mg/<br>4 weeks |
| PRU-INT-17<br>Phase II | A study to evaluate the long-term tolerability and safety and the pattern of use of Prucalopride in patients with chronic pain (cancer and non-cancer pain), suffering from opioid-induced constipation. | N=96<br>1 to 4 mg/<br>12 months |

N = number randomised patients, between brackets the number of ITT patients

PRU-INT-8 was a multicentre, double-blind, randomised, placebo-controlled, parallel-group study to evaluate the efficacy, safety and the effects on quality of life of Prucalopride 2 and 4 mg in men and women with chronic non-cancer pain, suffering from opioid-induced constipation. The study consisted of a 2-week drug free run-in phase (baseline), followed by a randomised, 4-week, double-blind treatment phase. Prucalopride was given orally o.d. In this population, the primary efficacy parameter was the proportion of patients with an increase of ≥1 in the average weekly frequency of SCBM, whereas the proportion of subjects with ≥3 SCBM per week was considered the key secondary parameter.

The data showed an improvement in the percentage of patients that had an improvement of ≥1 SCBM per week with a response of 35.9% of patients on Prucalopride 2 mg and 40.3% on Prucalopride 4 mg, vs. 23.4% on placebo. Differences between both Prucalopride 2 mg (p=0.021) and 4 mg (p=0.002) groups and placebo were significant at Week 1 but not during subsequent weeks and overall for Weeks 1 through 4. The difference in response rates between the placebo group and the Prucalopride 4 mg group was 17% (uncorrected p=0.043) over the entire treatment period (Weeks 1-4).

*Patients with Multiple Sclerosis or Spinal Cord Injury*

Three studies were conducted in patients with multiple sclerosis or spinal cord injury. These are tabulated below.

**Table 20: Summary of Phase II/III trials in patients with multiple sclerosis or spinal cord injury**

| | | |
|---|---|---|
| PRU-BEL-18<br>Phase II | A double-blind placebo-controlled trial to evaluate safety and tolerability and pilot efficacy of R093877 in subjects with constipation due to MS | N=22 (22)<br>Placebo, 1 mg, 2 mg/<br>4 weeks |
| PRU-DEN-2<br>Phase II | A double-blind placebo-controlled trial to evaluate safety and tolerability and pilot efficacy of R093877 in subjects with constipation subsequent to SCI | N=23 (22)<br>Placebo, 1 mg, 2 mg/<br>4 weeks |
| PRU-INT-9<br>Phase II | A study to evaluate the long-term tolerability, safety and efficacy of oral Prucalopride administered to patients with constipation due to SCI or MS | N=22 (22)<br>1 mg, 2 mg/<br>12 months |

N = number randomised patients, between brackets the number of ITT patients

- Supportive studies

Numerous supportive studies, both controlled and uncontrolled, were performed to demonstrate efficacy of prucalopride. The findings of these additional studies are consistent with the results of pivotal and other studies discussed above.

**Clinical safety**

- Patient exposure

Clinical Safety includes the safety data from 82 completed clinical studies: 47 Phase I studies, 25 Phase II studies, and 10 Phase III studies. In the Phase II/III double-blind placebo-controlled program, studies were performed in adults with chronic constipation (2717 on Prucalopride), of which 564 were elderly (>65 years). Special studies in elderly included 405 patients. Additional studies were performed in special subpopulations such as patients with constipation due to multiple sclerosis (MS; n=22) and spinal cord injury (SCI; n=23) and patients with chronic cancer and non cancer pain, suffering from opioid-induced constipation (n=341).

Total exposure in a double-blind placebo-controlled setting in patients with chronic constipation included 2717 patients treated with Prucalopride over a median of 57 days (range 1 to 140 days) and 1369 patients were on placebo, with a total exposure to Prucalopride of 406 patient years..

Exposure to the recommended dose of 2 mg in adults added up to 165 years (n=938). Total exposure in the elderly added up to 63 years (n=534), and exposure in elderly to the 1 mg recommended dose added up to 8 years (n=113).

A total of 2595 patients with chronic constipation were treated with Prucalopride in the open-label studies. The mean treatment duration was 284.4 days (40.6 weeks). A total of 1490 patients were treated for 6 months or longer, and 869 patients were treated for more than 1 year (>365 days). The maximum treatment duration was 952 days (136 weeks, or 2.6 years).

A summary of the various datasets is presented in the following table:

**Table 21: Summary of the overall patient exposure from various datasets**

| **Population** | **Number of patients** | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Placebo** | **PRU 0.5 mg** | **PRU 1.0 mg** | **PRU 2.0 mg** | **PRU 3.0 mg** | **PRU 4.0 mg** | **All PRU** |
| Phase I volunteers, oral | 269 | | | | | | 797 |
| Phase I volunteers, i.v./s.c. | 60 | | | | | | 80 |
| Phase II/III DBPC chronic constipation | 1369 | 110 | 308 | 938 | | 1361 | 2717 |
| Phase II/III DBPC opioid-induced constipation | 116 | | | 112 | | 109 | 221 |
| Phase II/III DBPC MS and SCI | 15 | | 15 | 15 | | | 30 |
| Phase II DBPC postoperative ileus, i.v./s.c. | 100 | 92 | 11 | 89 | | 91 | 283 |
| Phase II/III open chronic constipation | | | 218 | 1007 | 223 | 1147 | 2595 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Phase II open opioid-induced constipation | | | 17 | 31 | 10 | 50 | 108 |
| Compassionate use | | | 37 | 54 | 14 | 114 | 219 |

DBPC: double-blind placebo-controlled, PRU: Prucalopride, s.c.: subcutaneous(ly)

- Adverse events

  - **Overall Adverse Event Profile - Relationship to Treatment**

All events with a numerical difference of ≥0.5% higher incidence rate in the combined Prucalopride treatment groups vs. placebo, listed in descending order of the difference in frequency between all-Prucalopride and placebo, shows that the AEs of headache, nausea and diarrhoea occurred at a clearly higher rate than placebo (>8%) in the active treatment groups. However, it is notable that this higher incidence is mainly driven by the occurrence of AEs on Day 1 of treatment. Without the events on Day 1, the differences between placebo and all treatment groups are markedly less as shown in the Table 22 below.

**Table22: Chronic constipation: adverse events after Day 1 occurring more frequently in the combined Prucalopride groups than on placebo in all double-blind placebo-controlled Phase II/III studies**

| | **Placebo N=1369** | **All PRU N=2717** |
|---|---|---|
| **Preferred term** | **n (%)** | **n (%)** |
| Total no. of patients with AE >Day 1 | 803 (58.7) | 1626 (59.8) |
| Headache | 144 (10.5) | 307 (11.3) |
| Nausea | 94 (6.9) | 233 (8.6) |
| Diarrhoea | 42 (3.1) | 163 (6.0) |
| Vomiting | 30 (2.2) | 84 (3.1) |
| Dizziness | 23 (1.7) | 67 (2.5) |
| Abdominal pain upper | 35 (2.6) | 88 (3.2) |
| Fatigue | 20 (1.5) | 54 (2.0) |
| Abdominal pain | 113 (8.3) | 176 (6.5) |
| Bowel sounds abnormal | 4 (0.3) | 18 (0.7) |
| Pollakiuria | 3 (0.2) | 26 (1.0) |
| Pyrexia | 2 (0.2) | 23 (0.9) |
| Flatulence | 48 (3.5) | 89 (3.3) |
| Muscle spasms | 15 (1.1) | 32 (1.2) |
| Palpitations | 9 (0.7) | 26 (1.0) |

Approximately 50% of all the AEs of nausea, diarrhoea and headache in the Prucalopride 2 mg and 4 mg groups occurred on the first day of treatment. For abdominal pain, this percentage was somewhat lower, i.e. 32-36%. The onset of these AEs in the placebo group was mostly after the first week of treatment. The duration of the most common AEs did not significantly differ between placebo and Prucalopride treatment groups.

The most frequently reported AEs associated with Prucalopride treatment are headache and GI symptoms (nausea, diarrhoea and abdominal pain). These AEs are expected from the type of medicinal product and occur predominantly in the first few days of treatment. They are generally mild to moderate in severity and the proportion of patients discontinuing due to these events appears to be low.

- **Adverse Events of Special Interest**

Palpitations

A significant proportion of palpitations in the double-blind studies occurred on Day 1 or 2 of Prucalopride treatment when compared to placebo. The absence of ECGs in the majority of patients who had palpitations does not allow for definite conclusions regarding the mechanism of palpitations. However, the Phase I studies indicate that the first day of treatment is accompanied by a several beat-per-minute increase in heart rate. It is likely that the combination of first day effects of increased heart rate, moderate to severe GI symptoms and/or headache contribute to the occurrence of palpitations in certain patients.

However, it would appear that in some patients, palpitations are a noticeable symptom particularly at the higher 4 mg dose. The associated potential risk is difficult to ascertain. From the available data, there seems to be no evidence to suggest that they are linked to more significant cardiovascular adverse events. Nevertheless, it seems appropriate to keep the incidence of palpitations and any possible association with other more serious cardiovascular events under review post-authorisation.

Atrial Rhythm-Related Events

Most of atrial rhythm-related events involved various types of sinus or supraventricular tachycardia, and other related arrhythmias. The majority of affected patients had underlying cardiovascular disease, and/or use of medications that also predisposes to cardiac arrhythmias. The onset of symptoms was not early in the treatment course and was scattered throughout the treatment period in both the double-blind and open-label studies. Most cases that were identified from current Prucalopride database are probably consistent with the disorders expected in the underlying patient population.

QT Prolongation

Certain 5-HT$_4$ receptor antagonists such as Cisapride are known to induce QTc prolongation, which in some instances lead to ventricular arrhythmias and sudden deaths.

Data from the two QT studies(PRU-GBR-9 and PRU-GBR-10) in the current application appear to show that prucalopride may not induce QTc prolongation. However the design of these studies did not conform to the current ICH guidelines. As such, they were probably not sensitive enough pick up small evidence of QT prolongation.

However, data from the various studies appear to show that the influence, if any, of Prucalopride on QT interval and other ECG variables is negligible. This is supported by the reassuring results of the recently submitted new properly designed additional QT study with an active comparator which showed that Prucalopride has no effect QT interval.

Ischaemic-Related Events

In the double-blind studies, the number of cardiovascular ischaemic-related events was low (0.2% of all Prucalopride-treated patients) and incidences were comparable between the Prucalopride groups and placebo (0.1 %). There was 1 death due to a cardiovascular ischaemic-related event in the placebo group. The overall incidence of serious events was the same: 1 on placebo and 1 on 4 mg Prucalopride.

In the open-label studies, when a correction was made for exposure, the incidence of cardiovascular ischaemic events was similar when compared to the placebo group of the double-blind studies (1.0% and 0.9%, respectively).

A detailed review of the data seems to indicate that a small possible causal relationship between Prucalopride treatment and such ischaemic events cannot be excluded completely. Taking into account the general limitations of the clinical trial safety data to detect such rare events, it is appropriate to continue to monitor this class of events carefully during the post-authorisation phase.

- Serious adverse event/deaths/other significant events

An overview of the serious adverse events (SAEs), deaths from the double-blind studies is presented in Table 23 below.

**Table 23: Summary of SAEs, Deaths and Discontinuations due to SAEs from double-blind placebo-controlled studies in chronic constipation- all-subjects population**

| | Placebo N=1369 | PRU 0.5 mg N=110 | PRU 1 mg N=308 | PRU 2 mg N=938 | PRU 4 mg N=1361 | All PRU N=2717 |
|---|---|---|---|---|---|---|
| Parameter | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| SAEs (incl. post study) | 26 (1.9) | 2 (1.8) | 9 (2.9) | 19 (2.0) | 28 (2.1) | 58 (2.1) |
| Deaths (incl. post study) | 1 (0.1) | 0 (0.0) | 1 (0.3) | 1 (0.1) | 0 | 2 (0.1) |

The frequency of serious adverse events was relatively low. In the double- blind controlled studies, the incidences of these events were largely comparable between prucalopride and placebo.

The incidence of SAEs with Prucalopride in the open-label studies was higher (9.5%) than in the double-blind placebo-controlled studies. However, this is likely to be a consequence of the longer duration of treatment. Considering all patients treated with Prucalopride, no single SAE preferred term was reported by more than 1% of the patients. The most commonly reported SAEs were within the system organ class of surgical and medical procedures, with hysterectomy (0.7%) being the most commonly reported SAE preferred term, but these were not treatment related. The most commonly reported treatment-related SAEs were in the system organ class of GI disorders (1.9% overall), and the most commonly reported SAE preferred term within this class was abdominal pain, reported by 0.4% of patients. There were 4 deaths reported in the open-label studies. None of the cases were considered related to treatment by the investigator

- Laboratory findings

Overall, the incidence of adverse events concerning abnormal laboratory test results was low in both placebo and Prucalopride treated patients. This applies to both the double blind and open label studies. No clinically relevant differences in laboratory related AEs between Prucalopride and placebo were observed

Possibly prolactin-related AEs (i.e., tumours, prolactin-related events, or clinical manifestations of increased prolactin secretion) were observed in 13 (0.5%) Prucalopride-treated patients with chronic constipation (compared with 7 [0.5%] placebo-treated patients. The most common AEs were breast tenderness (0.2% on Prucalopride and 0.1% on placebo) and breast pain (0.1% and 0.3%, respectively. The majority of events was mild or moderate; 1 placebo-treated patient and 2 patients in the 2 mg group had an event of severe intensity.

As only a few prolactin samples in the clinical database, it is not possible to conclude whether or not there is a signal of increased prolactin secretion in some patients. Prolactin levels should therefore be monitored in future clinical studies.

- Safety in special populations

Prucalopride is not recommended for use in the paediatric population as efficacy and safety studies have not yet been performed.

Overall, the analysis of the global safety database did not provide any evidence for an impact of old age on the safety profile on Prucalopride. The differences seen in the variety of events and the increase in SAEs in elderly patients are attributable to the normal background in this age group.

Although no additional risk appears to be attributed to male gender, the number of male subjects investigated is limited.

- Safety related to drug-drug interactions and other interactions

Limited interactions were observed in 2 interaction studies: 1) Prucalopride enhanced the systemic exposure of erythromycin by about 30%, and 2) on co-administration with ketoconazole, Prucalopride plasma levels were increased by 40%. Although neither of these findings are likely to have major safety implications, they were unexpected and could not readily be explained.

The data relating to pregnancy appear to indicate that Prucalopride may be associated with abortion and possibly foetal malformation. It is noteworthy that 8 of the 32 women who became pregnant during the development programme were using oral contraceptives and 3 of these were taking antibiotics that may have contributed to contraceptive failure. However, the contribution of Prucalopride in these eight patients could not be excluded as no pharmacokinetic interaction study involving oral contraceptives has been performed. Hence, the applicant commits to submit an interaction study with oral contraceptives (FUM).

- Discontinuation due to adverse events

In phase 1 studies, AEs leading to treatment discontinuation were infrequent (0.6% during treatment with Prucalopride compared with 0.7% in the placebo group). The most commonly reported AEs were gastrointestinal disorders (0.5% and 0.7%, respectively).

In the double-blind placebo-controlled Phase II/III studies, overall, 7.1% of Prucalopride-treated patients prematurely discontinued due to AEs, compared to 2.8% of placebo-treated patients. The most commonly reported AEs leading to discontinuation were gastrointestinal disorders (i.e. reported by 5.0% of patients treated with Prucalopride and 1.5% in the placebo group) and headache (2.3% and 0.4%, respectively). The incidence of these AEs tended to increase with dose. There was no clinically relevant difference between men and women with respect to the overall incidence (8.6% and 6.9%) or nature of AEs leading to discontinuation

In phase II/III open-label studies, overall, 8.3% of Prucalopride-treated patients prematurely discontinued due to AEs. As in the double-blind placebo-controlled studies, the most common AEs leading to discontinuation were gastrointestinal_disorders i.e. reported by 3.6% patients and headache by 1.3% patients. There was no difference between men and women with respect to the overall incidence (8.3% for both men and women) or nature of AEs leading to discontinuation

In summary, as expected, events that most frequently led to discontinuation were headache, diarrhoea, nausea, and abdominal pain with each of these being more common in the 4 mg group than in the 1 or 2 mg group.

## 2.5 Pharmacovigilance

**Detailed description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

## Risk Management Plan

The MAA submitted a risk management plan

**Table 24. Summary of the risk management plan**

| Safety concern | Proposed pharmacovigilance activities (Routine and additional) | Proposed risk minimization activities (Routine and additional) |
|---|---|---|
| **Important identified risks** | | |
| Palpitations | Routine pharmacovigilance;<br>Special focus on surveillance: monthly review of line listing, CV SOC; monthly case series review for risk factors, change in severity, and outcome;<br>Special questionnaire for follow up of palpitation cases. | The SmPC will include text in Section 4.8 regarding palpitations and recommending that the patient seeks physician advice. |
| Headache | Routine pharmacovigilance. | The SmPC includes headache as an adverse effect in Section 4.8. |
| **Important potential risks** | | |
| Cardiovascular ischaemic events | Routine pharmacovigilance;<br>Special focus on surveillance: monthly review of line listing, CV SOC; monthly case series review for risk factors, and outcome;<br>Special questionnaire for follow up of cardiovascular ischaemic events;<br>Epidemiology study (THIN database). | The SmPC includes text in Section 4.4 stating that patients with severe and clinically unstable concomitant cardiovascular disease have not been studied and caution should be exercised when prescribing the drug to patients with these conditions. In particular the drug should be used with caution in patients with a history of arrhythmias or uncontrolled cardiac disease. |
| QT prolongation and related ventricular arrhythmias | Routine pharmacovigilance | The SmPC will include text in Section 4.4 stating that patients with severe and clinically unstable concomitant cardiovascular disease have not been studied and caution should be exercised when prescribing the drug to patients with these conditions. In particular the drug should be used with caution in patients with a history of arrhythmias or uncontrolled cardiac disease. |
| Syncope | Routine pharmacovigilance; | No specific labelling in SmPC |
| Potential for overdose/ abuse/misuse (in patients dosing like laxatives | Routine pharmacovigilance;<br>Monthly review of numbers of cases for real time assessment of off-label use. | The tablets are packaged in alu/alu calendar blisters as primary packaging, making the accidental or purposeful (over)ingestion of tablets unlikely. Additionally, the tablets are dispensed in packages of 28, allowing for monitoring of monthly usage via prescription refills.<br>The SmPC will include text in section 4.2 stating that Prucalopride should be used at the recommended dose of 1 tablet per day and that due to the specific mode of action of Prucalopride, exceeding the daily dose will not increase efficacy. |

| | | |
|---|---|---|
| Potential for off-label paediatric use | Routine pharmacovigilance;<br>Monthly review of numbers of cases for real time assessment of off-label use. | The SmPC will include text in section 4.2 stating that the safety and efficacy of Prucalopride in children younger than 18 years have not yet been established. |
| **Important missing information** | | |
| Safety in pregnant women | Routine pharmacovigilance;<br>Targeted follow up of all pregnancy cases (reminder system in database);<br>Epidemiology Study (THIN database). | The SmPC will include text in section 4.6 that experience with Prucalopride during pregnancy is limited. Cases of spontaneous abortion have been observed during clinical trials, although, in the presence of other risk factors, the relationship to Prucalopride is unknown. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Resolor is not recommended during pregnancy. Women of childbearing potential should use effective contraception during treatment. |
| Efficacy and safety in chronic constipation in paediatric patients | Routine pharmacovigilance. | The SmPC will include text in section 4.2 that safety and efficacy of Prucalopride in children younger than 18 years have not yet been established. Currently available data are described in section 5.2.<br>Additionally, a PIP is in the process of being prepared and will be submitted in 2009. |
| Safety in patients with hepatic impairment | Routine pharmacovigilance;<br>Hepatic impairment study. | The SmPC will include text in section 4.2 recommending a dosage reduction in patients with severe hepatic impairment and stating that no information is available in mild and moderate hepatic impairment. If necessitated by the outcome of the hepatic impairment study, this language will be adjusted. |
| Safety in patients with severe and unstable cardiovascular disease | Routine pharmacovigilance;<br>Special focus on surveillance: monthly review of the line listing, CV SOC, monthly case series review for risk factors, severity, and outcome;<br>Special questionnaire for follow up of cases | The SmPC will include text in section 4.4 stating that patients with severe and clinically unstable concomitant cardiovascular disease have not been studied and caution should be exercised when prescribing the drug to patients with these conditions. In particular the drug should be used with caution in patients with a history of arrhythmias or uncontrolled cardiac disease |
| Drug interaction with oral contraceptives | Routine pharmacovigilance;<br>Drug-drug interaction study | No specific labelling in SmPC |

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

## 2.6 Overall conclusions, risk/benefit assessment and recommendation

### Quality

The active substance and finished product have been adequately described. The excipients used in the preparation of the finished product and the manufacturing process selected are typical of an immediate release tablet. The film-coated tablets provide taste-masking and colour differentiation between the tablet strengths.

The results of the tests indicate that the active substance and the finished product can be reproducibility manufactured and therefore the product should have a satisfactory and uniform performance in the clinic.

### Non-clinical pharmacology and toxicology

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and toxicity to reproduction and development. An extended series of safety pharmacology studies with special emphasis on cardiovascular parameters showed no relevant changes in haemodynamic and ECG derived parameters (QTc) with the exception of a modest increase in heart rate and blood pressure observed in anaesthesized pigs after i.v. administration, and an increase in blood pressure in conscious dogs after bolus i.v. administration, which was not observed either in anaesthetized dogs or after oral administration in dogs reaching similar plasma levels.

Initial concerns were raised with regards to the genotoxicity and carcinogenic potential. However, considering the extensive genotoxicity testing performed, the weight of evidence shows that Prucalopride raises no genotoxic concern. Also, it is plausible that the mechanism causing the liver and thyroid tumours in the rat carcinogenicity study is the classical "enzyme induction mechanism". This is species specific and the observed liver and thyroid tumours are not considered relevant for humans.

### Efficacy

The results from the pivotal studies for both the ITT and per protocol patient population show that Prucalopride at a dose of 2 mg o.d. produces statistically significant effects in patients with chronic constipation most of whom were dissatisfied with their previous treatment. Each of the 3 pivotal studies individually showed a statistically significant improvement in the primary endpoint (≥3 SCBM per week for 12 weeks), with 23.6% of patients achieving this response level on Prucalopride 2 mg vs. 11.3% in the placebo group. In addition, an improvement of ≥1 SCBM per week and ≥1 point on the PAC-QOL satisfaction score are additional measures of clinical benefit.

Long term efficacy appears to be maintained as shown by the sub-analysis which seem to indicate that only 3% of patients who respond during the first three months of treatment are likely to discontinue due to lack of response during the course of two and half years of treatment. Tolerance is therefore unlikely to develop during long term treatment. Nevertheless, further controlled long-term treatment data will be gathered following Marketing Authorisation, as an agreed follow-up measure.

However, the pivotal studies were conducted almost exclusively in (Caucasian) women. This raises concerns that the drug has not been sufficiently evaluated in men. However, with regards to PK, PD and safety data, the effect of Prucalopride is similar in both males and females compared with placebo. The small number of subjects in double blind studies may explain the lack of statistical significance of the 2 mg dose which is further compounded by the higher proportion of male patients with severe constipation at baseline in this subgroup. This limitation of data in men will need to be further addressed by the provision of new relevant efficacy data. The applicant commits to a post-authorization efficacy study in males (FUM).

**Safety**

In clinical studies, the most commonly reported adverse events associated with Prucalopride treatment are headache and gastrointestinal complaints (nausea, diarrhoea and abdominal pain). The long-term safety data did not reveal the emergence of any new safety issues. Numerous preclinical concerns have been identified, including findings of hyperprolactinemia in rodents. Because there are so few prolactin samples in the clinical database, it is not possible to conclude whether or not there is a signal of increased prolactin secretion in some patients. Thus, prolactin levels should be monitored in future clinical studies.

Data from the various studies appear to show that the influence, if any, of Prucalopride on QT interval and other ECG variables is negligible. This is supported by the reassuring results of a newly submitted properly designed QT study which showed that Prucalopride has no effect on QT interval.

With regards to ischaemic- related events, the available data seem to indicate that a possible causal relationship with Prucalopride treatment cannot be completely ruled out. Taking into account the general limitations of the clinical trial safety data to detect such rare events, it is essential to continue to monitor these events carefully.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The user testing report submitted is adequate and in accordance with current recommendations.

**Risk-benefit assessment**

*Benefits*

Prucalopride appears to significantly improve bowel movement symptoms (including consistency, straining during defecation). It also shortens the time to first SCBM and reduces the use of laxatives. When all bowel movements were considered, Prucalopride decreased stool hardness and severe straining, apparently without increasing the number of watery stools. The patients' satisfaction with treatment and the perception of constipation symptom severity also improved.

*Risks*

The potential risks due to ischaemic- related and pro-arrhythmic events, if any, appear negligible and manageable. However, precautionary appropriate pharmacovigilance activities have been put in place.

Missing information for relevant populations, such as paediatric patients, pregnant women and patients with impaired hepatic function have been addressed in the Risk Management Plan. In addition, it is noted that the pivotal studies were conducted almost exclusively in women, meaning that efficacy has not sufficiently been demonstrated in men. This limitation of data in men will need to be further addressed by the provision of new relevant efficacy data. Also, controlled safety /efficacy data are limited to 12 weeks of treatment. This prompted the commitment to further gather relevant data on the long-term benefit of Prucalopride.

*Balance*

The benefit-risk balance of Resolor is considered positive.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

**Recommendation**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Resolor indicated for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief was favourable and therefore recommended the granting of the marketing authorisation.