



European Medicines Agency  
*Evaluation of Medicines for Human Use*

Doc. Ref.: EMEA/703892/2009

**ASSESSMENT REPORT**

**FOR**

**Sifrol**

International Nonproprietary Name: **pramipexole**

**Procedure No.: EMEA/H/C/000133/X/0051**

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.
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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK  
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45  
E-mail: [mail@emea.europa.eu](mailto:mail@emea.europa.eu) <http://www.emea.europa.eu>

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# **1. BACKGROUND INFORMATION ON THE PROCEDURE**

## **1.1 Submission of the dossier**

The applicant Boehringer Ingelheim International GmbH submitted on 28 October 2008 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Sifrol 0.26 mg, 0.52 mg, 1.05 mg, 2.1 mg and 3.15 mg prolonged-release tablets, pursuant to Annex II, point 2 iii and iv of the Commission Regulation (EC) No 1085/2003.

Boehringer Ingelheim International GmbH is the Marketing Authorisation Holder for Sifrol 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg and 1.1 mg tablets authorised on 14 October 1997 under part Part b of the Annex to Council Regulation No. (EEC) 2309/93 of 22 July 1993, as amended.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Steffen Thirstrup                      Co-Rapporteur: Jaana Kallio

### **Scientific Advice:**

The applicant did not seek scientific advice.

## **1.2 Steps taken for the assessment of the product**

- The application was received by the EMA on 28 October 2008.
- The procedure started on 19 November 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 February 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 February 2009.
- During the meeting on 16-19 March 2009, 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 20 March 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 April 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 11 June 2009.
- During the meeting on 22-25 June 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Sifrol on 25 June 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 23 June 2009.

## **2 SCIENTIFIC DISCUSSION**

### **2.1 Introduction**

Pramipexole is a nonergot dopamine agonist with full intrinsic activity. It shows high selectivity for interacting with receptors of the D2 subfamily, which consists of D2, D3 and D4 receptors. Pramipexole exhibits higher affinity for the D3 receptor subtypes than for D2 or D4 subtypes.

Pramipexole immediate release tablets have been authorized in the EU and USA since 1997. Immediate release tablets are indicated for the treatment of signs and symptoms of either early Parkinson's disease or advanced Parkinson's disease in combination with levodopa as well as for Restless Legs Syndrome. The immediate release tablets in Parkinson's disease have to be taken 3 times a day.

Boehringer Ingelheim has developed a prolonged-release tablets containing pramipexole that can be administered once daily. This alternative formulation is beneficial to patients with Parkinson's disease as this new pharmaceutical form will allow patients to treat their symptoms with a single daily dose, thereby increasing patient convenience and compliance. In addition, administration of the prolonged-release tablets results in a pharmacokinetic profile with less pronounced maximal plasma levels and more stable plasma levels over time.

This application was submitted under Article 8(3) of Directive 2001/83/EC as an extension to the marketing authorization for Sifrol 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg and 1.1 mg tablets (EU/1/97/050/001 - 012) marketed by Boehringer Ingelheim International GmbH to add a new pharmaceutical form associated with new strengths of pramipexole - 0.26 mg, 0.52 mg, 1.05 mg, 2.1 mg and 3.15 mg prolonged-release tablets.

### **2.2 Quality aspects**

#### **Introduction**

New pharmaceutical form of Sifrol is presented as prolonged-release tablets containing 0.26 mg, 0.52 mg, 1.05 mg, 2.1 mg or 3.15 mg of pramipexole (active substance) as the pramipexole dihydrochloride monohydrate salt. Excipients used in the preparation of prolonged-release tablets are well known excipients used in tablets preparations such as hypromellose, maize starch, carbomer 941, colloidal anhydrous silica and magnesium stearate.

Tablets are white to off-white and have different shape and embossing in order to differentiate strengths. Prolonged-release tablets 0.26 mg and 0.52 mg are of round shape, with bevelled edges, and have a code embossed (one side with the code P1 [(0.26 mg) and P2 (0.52 mg)], and one side with the Boehringer Ingelheim company symbol). Prolonged-release tablets 1.05 mg, 2.1 mg and 3.15 mg are white to off-white, of oval shape, and have a code embossed (one side with the code P3 [(1.05 mg), P4 (2.1 mg), and P5 (3.15 mg)], and one side with the Boehringer Ingelheim company symbol.

Sifrol prolonged-release tablets is packed in polyamide/aluminium/PVC blisters. Each blister strip contains 10 prolonged-release tablets. Cartons containing 1, 3 or 10 blister strips (10, 30 or 100 prolonged-release tablets).

#### **Active Substance**

The active substance used in this formulation is identical with the one used in the manufacture of the approved Sifrol presentations (EU/1/97/050/001 - 012).

## Medicinal Product

- Pharmaceutical Development

The objective of the development was to obtain a stable, extended release formulation containing pramipexole demonstrating adequate bioavailability for administration once daily.

Two different manufacturing technologies were investigated in the Phase I relative bioavailability study (formulation finding study): single unit extended release *matrix tablets* manufactured via a direct compression process-and multiple unit extended release *pellet formulation* filled in capsules.

The proposed formulation is a matrix single-unit prolonged-release tablet with pramipexole dihydrochloride monohydrate dispersed homogeneously throughout the matrix. Five dosage strengths have been developed based on the same formulation principle. The release mechanism of the active substance from the matrix is by diffusion and erosion mechanism. By the diffusion mechanism, gastro-intestinal fluids penetrate the insoluble matrix and diffuse back out together with dissolved substance. By the erosion mechanism, parts of the matrix surface separate from the core and the substance is directly exposed to the gastro-intestinal fluids. The *in-vitro* release characteristics of the active substance from the tablets are proportional to the square-root of time.

The commercial composition of all five dosage strengths has been based on the formulation which demonstrated the best *in-vivo* performance. This formulation was chosen for further development because found most suitable to achieve the intended *in vivo* profiles with a once daily application.

The formulation development for “in vitro /in vivo correlation” (IVIVC) studies was established at the lowest dose strength since single dosing of higher dose strengths to healthy subjects is not feasible due to tolerability. However, the fact that pramipexole is a BCS class 1 substance, the strictly linear kinetics of pramipexole and dose proportionality of the ER formulations allows the transfer to higher dose strengths.

As the *in vitro* dissolution profile of each of dosage strength must match the same specified dissolution profile optimization experiments for tailoring the release rate were performed in laboratory scale experiments. The resulting intended commercial formulations of all five dosage strengths are identical to the composition.

The same composition, design and operating principle of equipment and the same general manufacturing process has been utilized throughout pharmaceutical development at the development site and also for manufacturing of the primary stability batches and phase III clinical trial batches at the production site. The production site is the intended commercial manufacturing site. No changes were implemented for the manufacturing process of pramipexole dihydrochloride monohydrate used in phase III clinical studies compared to the primary stability batches as well as to the intended commercial manufacturing process at the manufacturing site.

- Adventitious Agents

None of the excipients present in the formulation are of animal or human origin. Magnesium stearate used in the manufacturing process of the medicinal product is of vegetal origin.

- Manufacture of the Product

The manufacturing process of the medicinal product comprises two main steps, i.e. dry-blending with a diffusion mixer and subsequent compression into tablets using a power assisted tablet press. The compressed tablets are packed in blisters in folded cardboard box.

Standard in-process controls are routinely performed during the manufacturing process to control the medicinal product quality. Acceptance criteria and specification limits have been set-up. The proposed in-process control tests are adequate to control the critical steps of the manufacturing process.

Prospective validation of the manufacturing process has been carried out with three production scale batches of each strength. The validation batches have been manufactured by the proposed commercial process. Acceptable validation results have been presented, demonstrating a robust process leading to a product complying with the set acceptance criteria. A homogeneous distribution of the active substance in the blend has been demonstrated. Segregation/deblending do not occur during the compression of tablets. Stratified assay and assay values are well within limits. The dissolution rate of the individual tablets all comply with the proposed criteria. Dissolution results for all strengths are all within the set limits.

- Product Specification

The product specification is a standard one for tablets and contains tests with suitable limits for appearance, identification (HPLC and UV), assay (HPLC), loss on drying, dissolution, uniformity of dosage units (HPLC) and degradation products (HPLC).

Full details of all analytical methods have been provided. All chromatographic procedures have been appropriately validated. Validations comply with the ICH harmonised Tripartite Guideline Q2(R1) Validation of Analytical Procedures: Text and Methodology. A summary of the validation results for the key methods: identification, dissolution, degradation, assay, and content uniformity have been provided.

The HPLC method for dissolution has been validated for specificity, linearity in the range, accuracy, repeatability and intermediate precision. Robustness in terms of filter validation and stability of sample and standard preparation has been investigated.

The HPLC method for degradation products has been validated with respect to the active, specified impurities and unspecified impurities for specificity/selectivity, accuracy, precision (repeatability and intermediate precision), linearity, range, limit of quantification, robustness and stability of solutions. Limit of quantitation and limit of detection have been determined.

The HPLC methods for assay and content uniformity have been validated with respect to specificity/selectivity, accuracy, precision (intermediate precision only), linearity, range, robustness and stability of solutions.

Batch analysis results have been provided for 54 batches, including development, clinical, validation and stability batches. The batches have been tested for compliance with the specifications in place at the time of testing. All results comply with the specification valid at the time of the testing. Results demonstrate compliance with the proposed specification and confirm consistency and uniformity of the product. The batch analysis data showed that prolonged-release tablets can be manufactured reproducibly according to the agreed finished product specification.

- Stability of the Product

For stability studies of the five developed dosage strengths of prolonged-release tablets 0.26 mg, 0.52 mg, 1.05 mg, 2.1 mg and 3.15 mg a bracketing approach was designed. In accordance with the ICH guideline "*Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products*" accelerated and long-term primary stability studies were based on three batches each of the lowest, medium and highest dosage strength, 0.26 mg, 1.05 mg, and 3.15 mg. In addition, one batch each of the intermediate dosage strengths 0.52 mg and 2.1 mg was tested.

The applicant performed also stressed stability testing. For stress stability testing, the samples were exposed in closed amber glass bottles (heat) and in open amber glass bottles (humidity). The results of the studies demonstrated that prolonged-release tablets have been found to be *slightly sensitive to heat* that are *sensitive to high humidity* indicating the need for a moisture protecting container/closure system.

In addition photostability testing has been performed. The samples were exposed 1) outside of the immediate pack, i.e. on glass dishes, of 2) in the immediate pack, i.e. in the proposed commercial container/closure system, which is an aluminium/aluminium blister. One batch each of the five dosage strengths has been tested. No significant changes or degradation were observed.

Based on the stability data the proposed shelf-life and storage conditions as defined in the SPC are acceptable.

### **Discussion on chemical, pharmaceutical and biological aspects**

The new pharmaceutical form – prolonged-release tablets with associated new strengths have been adequately described. The excipients used in the preparation of the product and the manufacturing process selected are appropriate. The results of the tests indicate that the medicinal product can be reproducibly manufactured and therefore the product should have a satisfactory and uniform performance in clinic.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve this as Follow-Up Measure after the opinion, within an agreed timeframe.

## **2.3 Non-clinical aspects**

### **Introduction**

This application is a line extension to the authorised medicinal product Sifrol. No specific non-clinical pharmacological and pharmacokinetic studies have been performed for pramipexole in the ER formulation.

Non-clinical toxicology studies have been performed to qualify three potential degradation products of pramipexole ER tablets. These potential degradation products are CD10503, Product V and Product Z. CD10503 is specified with  $\leq 1.0\%$ , Product V and Product Z are covered under any unspecified degradation product with  $\leq 0.4\%$ . Therefore, the specified levels are below the qualification threshold according to the respective ICH guideline. However, as either structural elucidation, (DEREK-analysis gave an alert for mutagenicity for CD10503) or studies pertinent to pramipexole IR tablets indicated a mutagenic potential (Product V and Product Z), the degradation products have been toxicologically qualified accordingly. The MAH claimed that these degradation products are further degraded into known genotoxic substances (formaldehyde and catechol) for which exposures is much higher following consumption of foodstuff as compared to treatment with the maximum recommended human dose.

### **Pharmacology**

Not Applicable

### **Pharmacokinetics**

Not Applicable

### **Toxicology**

The non-clinical toxicology studies have been performed to qualify three potential degradation products of pramipexole ER tablets. These potential degradation products are CD10503, Product V and Product Z. CD10503 is specified with  $\leq 1.0\%$ , Product V and Product Z are covered under any unspecified degradation products with  $\leq 0.4\%$ . Therefore, the specified levels are below the qualification threshold according to the respective ICH guideline. However, the MAH has conducted several in vitro and in vivo genotoxicity studies due to the genotoxic potential of these degradation products.

The 13-week toxicity study in rats with CD 10503 indicated that there were no relevant differences between rats treated with pramipexole in combination with CD 10503 and rats administered 25 mg/kg pramipexole alone. Thus, this study is sufficient for qualifying CD10503 in relation to general toxicity up to a level of 10%. Most prominent clinical signs, such as decreased locomotor activity (Day 15-52), changing to increased locomotor activity (Day 53 until end of treatment) were observed in all test item treated animals. Most findings improved or disappeared until the end of the recovery period. Most findings described above were comparable to the 3-month oral toxicity studies with pramipexole [U87-1039] and were independent on the co-administered dose of CD 10503.

The MAH was subsequently asked by the CHMP to discuss in more detail about the differences in findings between this 13-week toxicity study and the earlier 3-month oral toxicity study with pramipexole.

In their response the MAH explained that the purpose of the 13-week study in Wistar rats with CD 10503 was to obtain data on the toxicity of pramipexole spiked with different levels of CD 10503 in comparison to pramipexole alone and to estimate the No Observed Adverse Effect Level (NOAEL) for CD 10503, and therefore to qualify CD 10503 according to the present guidelines. The study was not intended to compare the findings of pramipexole alone versus the previous 3-month study in Wistar derived strain of rats. In study U87-1039, the high-dose had been 25 mg/kg pramipexole. The same dose was administered in study U08-1790, either pramipexole alone or spiked with different levels of CD 10503. In both studies, relevant findings at this dose were:

- decreased and later on increased locomotor activity
- increased water consumption
- decreased body weight
- increased urinary volume
- decreased thymus weights and pituitary weights in female rats
- a moderate increase in mean absolute and relative weights of ovaries
- histopathological changes in the ovaries (minimal to moderate increase in number and size of corpora lutea) and the stomach (minimal to moderate erosions and/or hemorrhages)

As in other repeat-dose toxicity studies with pramipexole, these findings were mainly due to the exaggerated pharmacological effects of this very potent dopamine agonist. These findings were comparable a) comparing the groups treated alone with 25 mg/kg pramipexole from study U87-1039 versus study U08-1790 and b) no relevant differences between rats treated with pramipexole in combination with CD 10503 and rats administered 25 mg/kg pramipexole alone were noted in study U08-1790.

The CHMP concluded that according to the MAH, the 13-week toxicity study with pramipexole +/- CD10503 indicated comparable results with the earlier 3-month study with pramipexole in Wistar derived strain of rats (U87-1039) indicating that CD 10503 did not have a separate effect but all relevant findings were from pramipexole. No formal comparisons between studies have been presented e.g. in tabular format. However, based on the MAH's response the CHMP concluded that similar safety margins were fulfilled in both studies.

The MAH also proposed a hypothesis regarding the genotoxicity of CD10503 which the CHMP found reasonable. However, several issues needed further clarifications regarding presence and formation rate of formaldehyde in the final product, the purity of the batches of CD10503 used for the in vitro genotoxicity testing, and the validity of the in vivo micronucleus test. Furthermore, the MAH was asked to retest CD10503 and formaldehyde in a standard Ames test in accordance with the current guidelines.

In their response the MAH explained that pramipexole tablets contain HPMC (Hydroxy Propyl Methyl Cellulose). HPMC was identified as the only source which contains formaldehyde (FA) at trace level. The FA may either bind to pramipexole thereby forming CD 10503, or may be present as "free" FA in the medicinal product. Therefore, the total amount of FA which can be present in the final product is

directly linked to the FA content of the utilized excipient HPMC. For the determination of the total amount of FA in HPMC an analytical method was developed and validated. The data obtained through this analytical method was in the range from 10 to 19 ppm indicate a consistent PMC quality with respect to the FA level. The obtained data was also in concurrence with data reported in the literature where the same level of FA was determined in HPMC.

The level of FA in pramipexole tablets can be calculated from the concentration of FA in HPMC and the quantity of HPMC used for the manufacture of the tablets. In the response the MAH provided an overview of the various pramipexole tablet dosage strengths and the amounts of HPMC in their compositions. The MAH also provided an overview about the amount of FA per tablet and the maximum total daily intake of FA. These amounts were calculated under the provision that the HPMC contains 20 ppm which is a slightly higher concentration than the highest concentration of FA experimentally quantitated in HPMC. Taking into account the acceptable daily intake (ADI) for FA which is 10 mg/d, the intake of FA by administering pramipexole tablets is about 2200 times lower than the ADI.

The CHMP acknowledged that the MAH has calculated the content of formaldehyde in the medicinal product based on the amount of formaldehyde in HPMC, which was the only source identified. This approach is considered acceptable and the issue was seen as resolved.

The genotoxic potential of the degradation products V and Z is likely to be caused by the release of catechol from these degradation products. However, the MAH was asked by the CHMP to provide a detailed description of the proposed reaction and discuss the likelihood of this reaction occurring during storage.

The worst-case exposure to catechol is estimated to 16 µg/day in patients treated with pramipexole at the MRHD of 4.5 mg/day. This value is clearly well above the TTC limit of 1.5 µg/day for medicinal products intended for chronic treatment in a non-life-threatening disease. Nevertheless, catechol is naturally present in foodstuff and the estimated daily intake of catechol is above 1330 µg/day (calculated for a 50-kg patient based on data obtained from Canadian Authorities). Thus, the proposed specification for the degradation products V and Z is considered acceptable by the CHMP. Nevertheless, the MAH was asked to submit the Ames test conducted with catechol and the mixture of product V and Z.

The MAH responded with submitting the AMES test for the mixture of the degradation products V and Z. The MAH also provided the results for an AMES test for catechol that has been reported in the open literature. The mixture of Products V and Z as well as catechol were negative in the Ames test. The CHMP accepted the MAH response and considered this issue resolved.

## **2.4 Clinical aspects**

### **GCP**

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

### **Pharmacokinetics and Pharmacodynamics**

In support of the registration of an extended release formulation of pramipexole, the MAH submitted 6 clinical pharmacology studies:

- 248.560 is a single dose in vitro-in vivo correlation and food effect study in healthy Caucasians, that was not assessed further in this application
- 248.529 is a prototype formulation finding study that was not assessed further in this application.
- 248.524 is a clinical study of pramipexole (IR) and (ER) formulation in patients suffering from early Parkinson's disease. The PK data from this study has formed the basis for a population PK report
- 248.530 is a multiple dose study in healthy Caucasians studying dose-proportionality, bioequivalence and effects of food.

- 248.607 is a multiple dose study in healthy Japanese subjects studying dose proportionality, and comparative BA to immediate release tablets.
- 248.545 is a multiple dose study of QT effects of pramipexole (IR)

The bioavailability study in Japanese subjects (248.607) demonstrates a slightly lower bioavailability with respect to AUC for the ER formulation. The 90% CI values are within guideline specifications for bioequivalence. In Caucasians no difference with respect to AUC or C<sub>max</sub> could be demonstrated. T<sub>max</sub> at steady state was prolonged from 2 to 4 hours. There are no signs of dose-dumping. The effect of food during steady state has been studied. A slight increase in C<sub>max</sub> (20%) and AUC (13%) was observed. T<sub>max</sub> increased from 6 to about 8 hours. Fluctuation was significantly higher at steady state for the ER formulation. The fluctuations were higher in particular following food intake and in Japanese subjects. Subsequently the MAH was requested by the CHMP to discuss the possible clinical relevance of this.

In the response the MAH provided more details on the two trials 248.530 and 248.607. In summary, the fluctuation was overall not higher for pramipexole ER compared with IR in both healthy male subjects or male and female PD patients. Intake of food immediately before intake of pramipexole ER may increase C<sub>max</sub> and thereby the fluctuation. However, in the common clinical setting, as mirrored in the Phase III study 248.524 in which the study medication could be taken with or without food, concomitant food intake did not meaningfully affect the PK after pramipexole ER. Moreover, pramipexole ER was found to be non-inferior to pramipexole IR in the early PD trial 248.524. Lastly, the tolerability profile was comparable between the two pramipexole formulations at the same mean daily dose and dose distribution. Therefore, the possible higher fluctuations with pramipexole ER following food intake are according to the MAH not expected to be of any clinical relevance in PD patients.

The CHMP acknowledged that the difference in fluctuation between formulations, observed in healthy volunteers, appear likely due to differences in food intake between studies. In the study of Japanese subjects, food was administered 30 minutes prior to pramipexole resulting in slightly increased C<sub>max</sub> values as well as decreased C<sub>min</sub> values which may explain the increased fluctuation observed here. In clinical phase III trials with coadministration of pramipexole and food, no meaningful PK differences were observed. Simulated data in early Parkinson's disease patients does not suggest clinical meaningful differences in fluctuation between different ethnic groups. Tolerability profiles appeared similar between formulations.

Although acknowledging the MAH response the CHMP was still concerned about the possible clinical relevance of the noted food effect and requested the MAH to thoroughly discuss this in light of all efficacy and safety aspects and the MAH should discuss in detail if the ER formulation should be taken either without or with meal and what kind of fasting time would be needed after taking the ER formulation. Also the implications on the posology was to be commented on by the MAH and all relevant information should be reflected in the SPC. In particular, the following points were noted; Study 248.530: Conventional BE limits were not met in respect to C<sub>max,ss</sub>. Total pramipexole exposure and C<sub>max,ss</sub> increased with food about 20%. The food effect as observed now does not seem extremely large. However, possibly, the food effect may be underestimated as the intake of food was not performed for all five days during the food effect part of the study (4.5 mg ER active q.d fed on days 1 and 5, fasted for morning dose on other days). This issue was also to be addressed by the MAH when responding to the above questions. In addition, if the effect of food is considered to affect safety and/or efficacy, the MAH was to discuss whether a standardisation within the patient with respect to food intake would be a possible solution. Regarding study 248.607 the CHMP asked what were the calorie and fat contents of the light breakfast served 30 min before dosing. This information was to be discussed from a perspective to either suggest or not suggest a certain type of meal when taking pramipexole. Data on C<sub>max</sub> was also to be provided by the MAH to confirm bioequivalence between the test and reference product and to obtain additional information on the effect of food on C<sub>max</sub>.

In summary the MAH responded as follows: In the phase I trial an average increase in C<sub>max</sub> of about 20 % (90 % CI = [113.9 – 126.8]) was observed after 4.5 mg pramipexole ER administration under steady state conditions in fed state. A C<sub>max</sub> increase of 24 % (90 % CI = [115.1 – 134.1]) was observed after single dose administration of 0.375 mg pramipexole ER immediately after the intake of a high fat

meal. The results indicate that the AUC remained within the 90 % CI limits of 80 – 125 % in comparison of the fed and fasted state in both lowest and highest dose strength after a single dose at steady state, which would suggest equivalent bioavailability. Referring to the study 248.530, the occurrence of adverse effects (AEs) in healthy male volunteers was observed numerically even lower in fed compared to fasted state. The comparison of AEs between the three treatments, 1.5 pramipexole IR tid fasted, 4.5 mg pramipexole ER qd after a high fat meal vs. 4.5 mg pramipexole ER qd fasted revealed a similar pattern of AEs.

The food had an effect only on absorption resulting in a higher  $C_{max}$ , but did not have an effect on elimination. After a single dose of 0.375 mg pramipexole ER the  $t_{1/2}$  and mean residence time (MRT) were not prolonged but were even slightly shorter in the fed state compared to fasted state (gMean  $t_{1/2}$  (% gCV) = 9.38 h (38.5%) and 8.40 h (9.79%) and MRT = 19.5 h (27.7%) and 17.3 h (7.02 %) under the fasted vs. fed conditions, respectively). In the multiple dose study 248.530, the pramipexole plasma concentration 23 hours after intake of 4.5 mg pramipexole ER with or without food was highly comparable and even slightly lower after a high fat meal compared to the fasted state (gMean  $C_{23,ss, fed}$  = 2.76 ng/mL (gCV= 43.1 %) vs. gMean  $C_{23,ss, fasted}$  = 2.82 ng/mL (gCV= 43.0 %). According to the MAH it therefore seems highly unlikely that the food effect would have been higher (higher accumulation) when the subjects had taken pramipexole ER under fed conditions over the whole 5-day treatment period.

In the phase III study 248.524 a PopPK covariate analysis did not reveal food to have a significant factor for PK after pramipexole ER administration to Parkinson's disease patients. In study 248.524 the food seemed to have only modest effect on the pramipexole plasma concentration after 2 and 4 hours from the pramipexole ER administration. The  $C_{2,ss}$ - and  $C_{4,ss}$ -value was on average 16 % and 4 %, higher in the fed state, respectively. Pramipexole ER  $t_{max}$  is close to the time point of  $C_{2,ss}$ -value measurement.

In the final analysis of study 248.524, adverse events did not occur more often in patients treated with pramipexole ER compared to pramipexole IR treated patients. This holds true also for Japanese patients of whom the vast majority had taken pramipexole ER and IR with food (final report 248.524). On the other hand food seemed to have also no effect on efficacy as pramipexole ER was as effective (non-inferior as measured by UPDRS part II and III total score change from baseline at week 33) as pramipexole IR in early Parkinson's disease (including patients of Japanese origin) as shown in the final report of the study 248.524.

The intake of a light breakfast immediately before pramipexole ER and IR administration in study 248.607 in healthy male Japanese subjects was required according to the Japanese pramipexole labelling. The calorie and fat content of the light breakfast served in study 248.607 was provided. The calorie content of the light breakfast was 542 kcal or 587 kcal and the fat content 24.8 g and 35.8g, respectively.

In contrast to the study in Caucasian volunteers 248.530 under fasted conditions the intake of a light breakfast before administration of pramipexole ER in the study in Japanese subjects led to a slightly higher  $C_{max,ss}$  of the ER-formulation compared with IR formulation (gMean ratio in Japanese subjects (fed) = 110.49 % vs. 95.38 % in Caucasian subjects (fasted)). However, in the Japanese study pramipexole ER was bioequivalent to same daily dose of pramipexole IR on  $AUC_{0-24,ss}$  and  $C_{max,ss}$  and the 90% CI did not exceed the standard upper limit of bioequivalence of 125 %. In addition,  $C_{min,ss}$  was not bioequivalent in this study. This was most likely due to the trial design of this phase I study (248.607) as food intake before administration of pramipexole ER seems to result in slightly lower  $C_{min,ss}$  for pramipexole ER but not for pramipexole IR (see also above food effect in study 248.530).

While study 248.530 investigated the bioavailability of pramipexole ER compared to pramipexole IR in the fasted state for both treatments, study 248.607 needs according to the MAH to be regarded as a relative bioavailability study comparing pramipexole ER with pramipexole IR under fed conditions. Though, no comparative trial on different type of meals was performed it seemed that the effect by a light meal was less compared to the effect of a high fat meal (gMean ratio in Japanese subjects after light meal = 110.49 % vs. 120.19 % in Caucasian subjects after a high fat meal). In the phase III trials

248.524 and 248.525 pramipexole ER could be taken with or without food without any limitation on the type of meal.

So, in summary the MAH made the following arguments in response of the CHMP question: When pramipexole ER was given immediately after a high fat, high caloric meal to healthy male subjects,  $C_{max}$  was increased on average by 20 % and 24 % after 4.5 mg pramipexole ER given at steady state or 0.375 mg pramipexole ER as single dose, respectively. The systemic bioavailability of pramipexole ER was not meaningfully affected by concomitant food intake. The AUC was bioequivalent whether pramipexole ER was given under fasted conditions or after a high fat meal. In phase III studies, patients were allowed to take pramipexole either with or without food. In this clinical setting, concomitant food intake increased pramipexole plasma concentrations by less than 20% and the data available do not provide any evidence for a positive or negative influence of any type of meal on the clinical efficacy or safety of pramipexole ER. Pramipexole ER can be, thus, taken with or without food and no specific instruction with regard to food intake is deemed necessary for the posology section of the SPC. The data itself are briefly described in the pharmacokinetic Section 5.2 of the SPC.

The CHMP acknowledged the thorough response from the MAH. However, the sentence “The food had an effect only to absorption resulting in a higher  $C_{max}$ , but did not have an effect on elimination.” needed further clarification. Significant differences were observed in  $C_{min,ss}$  and  $C_{pre,ss}$  with and without food in study 248.607 indicating some difference in elimination rate. It has been shown that in fed state, the elimination is somewhat faster. The CHMP considered that the fluctuations of pramipexole concentrations between  $C_{max}$  (higher with food) and  $C_{min}$  (lower with food) during ER formulation are even higher in fed state, which may have clinical relevance. Although the MAH adequately discussed the possibility of safety consequences of higher plasma pramipexole levels, the clinical significance of the lower  $C_{min,ss}$  and  $C_{pre,ss}$  observed for the drug’s efficacy during the pramipexole ER regimen in fed state was still to be further uncertain and therefore the CHMP requested the MAH to further discuss this.

In their response the MAH pointed out that the CHMP statement regarding significant differences were observed in  $C_{min,ss}$  and  $C_{pre,ss}$  with and without food in study 248.607 may potentially be based on a misunderstanding. In this study all volunteers took pramipexole IR and ER after meal. According to Japanese labelling also all Japanese patients in the Phase III efficacy trial 248.524 took medication after meal. It is of note, that the efficacy was comparable in this subgroup of Japanese patients compared to the whole population. Therefore, effects seen in the Japanese healthy volunteers (trial 248.607) seem to be of no practical clinical relevance. In both Phase I studies in Caucasian healthy volunteers the differences in  $C_{min}$  after administration of pramipexole ER in either fasted or fed state was always less than 20%. The MAH subsequently offered as a post approval-commitment to perform a further in-depth evaluation of the data of the Japanese study 248.607 in the light of potential ethnic differences, taking also efficacy and PK data of the currently ongoing Japanese Phase III trial 248.610 into account.

To the CHMP it was still unclear what the significance of the variability in PK along with food intake and interethnic differences is for the efficacy. The MAH suggestion for a post approval-commitment for further evaluation of these factors, taking into account also efficacy and PK data of the currently ongoing Japanese Phase III trial 248.610 was however considered acceptable and the issue was considered resolved (see section 2.7 for details).

The MAH also performed an extensive population PK analysis with all relevant data including data from healthy volunteers, treated patients in study 248.524 and data from a previous study in renally impaired patients. The CHMP concluded that the methodology is appropriately specified, documented, performed, evaluated and reported.

The CHMP also concluded that a two-compartment model with first order elimination was an adequate model describing pramipexole concentration-time profiles of early Parkinson’s disease patients (study 258.524). The absorption process of pramipexole IR formulation was depicted by the first order process with a lag time in absorption. For ER formulation, the absorption was described by a sequential model of zero and first order. Inter-individual variability was incorporated in the apparent

clearance of the ER and the IR formulations and in the apparent peripheral volume of distribution (V3/F) for the ER formulation.

Covariate analysis confirmed that CRCL has a clinically relevant effect on the clearance of pramipexole. The estimate of the typical CL/F was 29.2 L/h when CRCL was greater or equal to 121 mL/min. The typical individual CL/F is reduced linearly by 0.74% by reducing the CRCL by 1 mL/min. Body weight (BW) had an impact on V3 for pramipexole ER. The relationship between body weight and V3/F was described by a proportional linear model. The estimate of the typical V3/F for a 75 kg patient was 313 L. A change in 1 kg body weight changes V3/F by 2.26%. Other intrinsic factors, like sex, age or race did not significantly affect the pharmacokinetics of pramipexole.

The MAH has performed an adequately designed, conducted and reported study on the effect of pramipexole 2.25 and 4.5 mg daily on QT interval. The results demonstrate that pramipexole at the suggested clinical dose interval does not affect the QT interval.

Following their assessment of PK data the CHMP also requested that all known drugs using the same active renal secretory mechanism as pramipexole should be evaluated in the literature and these should be listed as interacting substances in the product information.

The MAH responded that there are only a few studies published showing a clinically relevant interaction between two drugs at the renal tubular human organic cation transporter (hOCT2). Relevant effects of a > 20% reduction in (renal) clearance are mainly reported for cimetidine (see table below). Cimetidine (300 mg q.i.d) has been shown to decrease pramipexole clearance (~ renal clearance) by about 34 % in a drug-drug interaction study using pramipexole IR. Amantadine has been shown to decrease pramipexole clearance by about 24 % in Japanese Parkinson's disease patients. However, this effect could not be repeated using pramipexole ER in a most recent study. In a recent paper levofloxacin was shown to exert only negligible effects on the PK of the hOCT2 probe procainamide. Average procainamide clearance was reduced by 22 % and AUC by about 21 %. Ranitidine and cimetidine have almost the same Km- and IC<sub>50</sub>-values, but the therapeutic dose of the former is less than 50 % of the cimetidine dose. Based on aforementioned ranitidine and levofloxacin are not expected to affect the pramipexole renal clearance.

**Clinical studies which reported a > 20 % reduction in renal clearance of presumed substrates of hOCT2 after co-medication with presumed inhibitors of hOCT2**

Affected substrate	Inhibitor	% reduction in renal clearance
Metformin	Cimetidine	27
Procainamide	Cimetidine	44
N-acetylprocainamide	Cimetidine	24
Quinidine	Cimetidine	33
Ranitidine	Cimetidine	40
Pindolol	Cimetidine	39 (R); 30 (S)
Pilsicainide	Cimetidine	28
Zidovudine	Cimetidine	56
Triamterene	Ranitidine	51
Procainamide	Levofloxacin	26
N-acetylprocainamide	Levofloxacin	21
Procainamide	Trimethoprim	47
N-acetylprocainamide	Trimethoprim	13
Zidovudine	Trimethoprim	48
Pramipexole	Amanatadine	24 <sup>1</sup>
Pramipexole	Cimetidine	34 <sup>2</sup>

<sup>1</sup>significant co-variate in a PopPK model

Recently, Giacomini et al. proposed a ratio of  $> 10$  of unbound  $C_{max}$  over  $IC_{50}$  for an inhibitor of hOCT2 to exert clinically relevant effects. Accordingly, Zolk et al. proposed a list of drugs which was ordered based on the ratio of unbound plasma concentration ( $C_{u,p}$ ) /  $IC_{50} \times 1000$ . This resulted in the case of cimetidine in a ratio of  $10.7 \times 10^4$  and all drugs with a ratio  $> 10^4$  are provided in a table below as drugs potentially interacting with pramipexole via hOCT2 in the kidney. Drugs with a  $C_{u,p}/IC_{50}$  ratio  $< 5 \times 10^4$  are expected to reduce pramipexole clearance by less than 20 %, which would be of no clinical relevance.

**Unbound plasma concentration:  $IC_{50}$  ratio ( $C_{u,p}/IC_{50}$ ) of drugs acting on the human OCT2 transporter**

Compound	$C_{u,p}/IC_{50}$ (x 1000)
Chlorpromazine	65.3
Cimetidine	107
Disopyramide	30.5
Doxepin	21.5
Fenfluramine	93.6
Metformin	21.2
Mexiletine	90.8
Propafenone	10.5
Quinidine	35.1
Trimethoprim	14.3

Table adapted from Zolk et al., 2008

Drawn from the results presented in the table above only chlorpromazine, fenfluramine and mexiletine need to be considered in addition to cimetidine and amantadine. However, chlorpromazine is not excreted renally as the parent compound; chlorpromazine undergoes oxidative metabolism and conjugation. The metabolites and conjugates are unlikely to affect the tubular hOCT2. Fenfluramine is no longer marketed and can be, thus, neglected as drug potentially affecting the clearance of pramipexole in a clinically relevant setting.

In summary the MAH argued that of the marketed drugs which may meaningfully affect the pharmacokinetics of pramipexole via inhibition of active tubular secretion cimetidine, amantadine and mexiletine needs to be mentioned in the SPC of pramipexole.

The CHMP acknowledged the MAH response, but argued that the justification by the MAH for selecting substances as clinically meaningful inhibitors of pramipexole clearance is not fully comprehensive. It was still unclear to the CHMP why e.g. trimethoprim and ranitidine have not been selected although they cause significant clearance reduction of HOCT2 probe drugs in clinical studies. The MAH was therefore requested to provide further justifications.

The MAH responded that although trimethoprim and ranitidine have been reported to have a  $> 20$  % reduction in renal clearance on other substrates, the MAH expects these substances to reduce pramipexole clearance by less than 20%, which would be of negligible clinical relevance. The statement in question in Section 4.5 of the SPC is currently phrased in a way that specific substances mentioned would be examples for an overall principle rather than an exhaustive list. It is the understanding of the MAH that the most important and most prominent substances in terms of clinical relevance should serve as examples. However, if an exhaustive list is required instead, the MAH would be prepared to offer a post-approval commitment for an in-depth evaluation of all potential substances and to implement an exhaustive list of substances in the SPC in a subsequent variation application.

The CHMP concluded that examples of interacting agents may not be enough, since the PK variability may be relevant for efficacy. The fact that the MAH would be prepared to offer a post-approval commitment for an in-depth evaluation of all potential substances interacting with pramipexole is considered acceptable (see section 2.7 for more details). The MAH is also requested to take a proactive role for evaluating interactions of pramipexole with commonly used hOCT2-inhibitors like ranitidine and trimetoprim.

The influence of the inter-individual and inter-ethnic genetic variation in transporter hOCT2 structure and function may also have substantial effect on inter-individual variation in C<sub>max</sub>, C<sub>min</sub> and AUC values of hOCT2 substrates. The MAH was therefore requested by the CHMP to follow the literature in this field and be aware that any treatment failure or toxicity symptom may be related to this variability. The MAH was further asked if the patients in the relevant studies could be genotyped for the most commonly existing polymorphisms of hOCT2.

The MAH explained in their response that they understand that these considerations raised are relevant for pramipexole itself, independent of the prolonged-release tablet formulation applied for. Any inter-individual and interethnic genetic variation among patients is taken into account by titrating pramipexole to an individual dose level balancing efficacy and tolerability. The MAH offered to perform a review of the relevant literature on a regular basis and provide updates with each PSUR/RMP as a post-approval commitment.

The CHMP concluded that the simple guidance for the use of pramipexole of the MAH that “any inter-individual and interethnic genetic variation among patients is taken into account by titrating pramipexole to an individual dose level balancing efficacy and tolerability” may not be enough for relevant safety and efficacy of modern drug treatment. The MAH however offered to perform a review of the relevant literature on genetic variation in transporter hOCT2 on a regular basis and provide updates with each PSUR/RMP as a post-approval commitment (see section 2.7 for details). This was considered to be an acceptable approach by the CHMP. In addition the MAH was requested to also take an active role in genotyping the relevant hOCT2 variants in each population in future studies.

### **Clinical efficacy**

The efficacy and safety of pramipexole (PPX) has previously been demonstrated in clinical studies, and the IR tablets are registered with the indication treatment of patients with early and advanced Parkinson’s disease (PD).

Three clinical studies were planned for PPX ER including 2 phase III studies to evaluate safety and efficacy in early (248.524) and advanced PD (248.525); and a study to evaluate the switch between PPX IR and PPX ER to determine dose and safety (248.636).

In their application the MAH submitted the results of bioequivalence study 248.530, interim safety data from the planned phase III studies and interim efficacy analysis on treatment of early PD (248.524) and the switch study (248.636) in support of the clinical efficacy. Following a request from the CHMP the MAH submitted the final data from the two pivotal Phase III trials (248.524 in early PD and 248.525 in advanced PD).

### Main clinical studies

#### **Discussion on interim results from Study 248.524**

The primary efficacy study for the present application was study 248.524. This study was planned as a randomised, double-blind, placebo-controlled, parallel group study of early PD. The objective of the study was to evaluate superiority of PPX ER to placebo at week 18 and non-inferiority of PPX ER to PPX IR at week 33. It was planned to include 500 patients in the study, but for the submitted interim analysis only the first 250 randomised patients were analysed by the pre-specified primary hypotheses. To secure data integrity and to keep blinding at the study level, PAREXEL was involved in the interim analyses and interim study report, and the study team had no access to the results of these interim analyses. Since it had been decided that efficacy data was not needed for this application, the data

should be considered supportive only. The study is ongoing and the updated data should eventually be available according to the pre-specified plan for analysis.

The study design was in accordance with current standards to investigate PD and the demographic data for the patients were representative for the intended target population:

**Demographic data, treated set at first interim analysis, week 18**

		Placebo	PPX ER	PPX IR	Total
Number of patients		50	106	103	259
Sex					
Male	N (%)	23 (46)	62 (58)	59 (57)	144 (56)
Female	N (%)	27 (54)	44 (42)	44 (43)	115 (44)
Age	mean (SD)	63.2 (8.7)	61.6 (9.4)	62.0 (8.3)	62.1 (8.8)
Age classes					
Age < 65 years	N (%)	23 (46)	57 (54)	57 (55)	137 (53)
Age ≥ 65 years	N (%)	27 (54)	49 (46)	46 (45)	122 (47)
Race					
Caucasian	N (%)	32 (64)	67 (63)	62 (60)	161 (62)
Asian	N (%)	18 (36)	39 (37)	41 (40)	98 (38)
BMI [kg/m <sup>2</sup> ]	mean (SD)	26.7 (4.4)	26.0 (4.7)	26.2 (4.5)	26.2 (4.5)

**Selected PD-related baseline characteristics, treated set at first interim analysis, week 18**

		Placebo	PPX ER	PPX IR	Total
Number of patients		50	106	103	259
Duration	mean (SD)	0.8 (1.1)	1.1 (1.3)	0.9 (1.2)	0.9 (1.2)
Duration <2 y	N (%)	42 (84)	76 (72)	83 (81)	201 (78)
PD pre-treated	N (%)	7 (14.0)	10 (9.4)	7 (6.8)	24 (9.3)
Hoehn&Yahr Staging 2-3	N (%)	36 (72)	75 (71)	76 (74)	187 (72)
UPDRS					
Part II+III total score	mean (SD)	30.1 (17)	30.4 (13)	28.2 (12)	29.5 (14)

The CHMP noted that there were a different gender distribution in the placebo group (46% males) compared to the PPX groups (58%). The significance of this is difficult to evaluate. The up-titration phase was 7 weeks, and the dose was increased in all patients who were not at least “a little better”, and the increase stopped if adverse events were not tolerable. The maintenance phase was up to 11 weeks for the week 18 interim analysis.

The primary outcome was UPDRS parts II+III.

- The primary endpoint at week 18 would be considered met (PPX ER effective), if the UPDRS Part II+III score was significantly better for PPX ER than for placebo, and
- UPDRS Part II+III scores at week 18 and week 33 were similar for the PPX groups by a descriptive analysis.

Secondary efficacy criteria included: Clinical and Patient Global Impression of Improvement, proportion of patients improved, Quality of life scales, etc.

The primary endpoint at week 18 was met as shown in the table below.

**UPDRS Part II+III total score, 18 weeks treatment, FAS 1 (LOCF)**

Primary endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. Placebo	PPX IR vs. placebo
No of patients	50	102	101		
Baseline, Mean (SD)	30.1 (17.0)	30.5 (13.6)	28.3 (12.0)		
Week 18, Mean (SD)	24.0 (14.9)	21.3 (14.0)	19.3 (9.8)		
LS Mean Change (SE)-ANCOVA*	-5.1 (1.3)	-8.1 (1.1)	-8.4 (1.1)	0.0282	0.0153
LS Mean Change (SE)-MMRM*	-4.0 (1.2)	-8.0 (1.0)	-8.0 (1.0)	0.0016	0.0014

\*ANCOVA and MMRM with factors treatment and country and covariate baseline.

Negative changes imply improvement in UPDRS Part II+III total score

Four patients in the PPX ER group and 2 in the PPX IR group were excluded from FAS 1 due to UPDRS Part II+III values were only partial or missing for baseline or for treatment period. Due to the small number, this has probably no influence on the result. The test for superiority of PPX ER over placebo remained statistically significant after different sensitivities analyses. The results were also supported by most of the secondary endpoints. The significance of concomitant PD therapy (levodopa) started during the study period, primarily in the placebo group was discussed. The primary endpoint was also met at week 33. The analysis was made on the FAS 2 (Observed Cases), the argument being that the patients included with an LOCF analysis was withdrawn before week 18:

**Maintenance of effect in UPDRS Part II+III total score at week 18 and week 33, FAS 2 (OC)**

Primary endpoint (maintenance of effect)	Placebo	PPX ER	PPX IR
No of patients	18	35	31
Baseline, Mean (SD)	23.6 (13.5)	31.3 (13.9)	29.0 (14.5)
Week 18, Mean (SD)	19.3 (12.7)	19.5 (12.5)	17.1 (10.9)
Change from baseline Mean (SD)	-4.2 (7.0)	-11.8 (8.1)	-11.9 (8.8)
Week 33, Mean (SD)	20.9 (12.9)	19.8 (13.4)	17.1 (10.3)
Change from baseline Mean (SD)	-2.7 (6.7)	-11.5 (8.5)	-11.9 (9.6)

Negative changes imply improvement in UPDRS Part II+III total score

Even though the primary endpoint was met, there are several problems with the analysis at week 33. The numbers in the groups are small and resulted in several imbalances compared to week 18; concerning gender, age and race. The UPDRS Part II+III values are almost identical at the two time points for all 3 groups, but it is noted that the largest difference is the baseline for the placebo group.

Subgroups analyses were attempted for the first interim analysis (248.524 at week 18, FAS 1 set). For the second interim analysis there number of patients were too too the small in the subgroups. Most of the differences were not consistent and seemed due to chance. However, two findings seem more robust and of potential significance: The influence of PPX dose level on the placebo corrected mean improvement in UPDRS Part II + III score between baseline and week 18. The differences in mean change from baseline were statistically significant for the high dose category, while no improvement was seen for the medium and low dose groups. The CHMP therefore concluded that only doses >3mg/d seemed to be effective. In addition, a better response was seen in patients <65 years of age.

**Discussion on interim results from Study 248.636**

This study was planned as a double-blind, double-dummy, randomized, two parallel groups, multinational multi-centre study evaluating the switch from PPX IR to PPX ER or IR with or without dose adaptation over a 9-week DB treatment phase. The sample size was calculated to be able to claim non-inferiority/equivalence for 2 treatment group. Using a one-sided significance level of 0.05 and about 80% power, a sample size of 120 patients was found to be sufficient. The inclusion and exclusion criteria were standard and the study design was in accordance with current standards to investigate PD. The demographic data for the patients were representative for the intended target population and similar to the study group of 248.524. The duration of the disease was 0-5 years for 85% of the population. The study has been completed according to the plans. Only a single of the 156 randomised patients were not available for analysis.

The primary efficacy endpoint was the proportion of patients successfully switched from PPX IR to PPX ER or IR at the end of the maintenance phase. A successful switch (PPX ER non-inferior to PPX IR) was defined as less than 15% worsening of the UPDRS II+III score after the switch (with a possible dose adaption). The result was:

**Proportion of patients switched from PPX IR to ER or IR after possible dose adaptation, FAS (LOCF)**

	PPX ER	PPX IR	PPX Total
N	103	52	155
Number (%) of patients successfully switched	87 (84%)	49 (94%)	136 (88%)
Number (%) of patients not successfully switched	16 (16%)	3 (6%)	19 (12%)
Difference (%) of successfully switched patients PPX ER – PPX IR	-9,8%		
95% Confidence interval*	-18.8,1.7		

\*The confidence interval is based on the Wilson score interval

Since the lower bound of the 95% confidence interval was -18.8%, non-inferiority between PPX ER and PPX IR could not be demonstrated. Further analysis of the dose adaptation showed that 83 of the 87 successfully switched patients were successfully switched without dose adaptation and only an additional 4 were successfully switched after a dose adaptation.

The CHMP considered that although the majority of patients (84%) could be successfully switched from PPX IR to PPX ER, non-inferiority was not demonstrated, superiority of IR being most likely. The MAH was therefore requested to provide an analysis of the mean UPDRS II+III scores to evaluate whether the IR form is indeed superior. The role of adverse effects for the failures of switch from IR to ER should be discussed. If the question is resolved, it must be clearly stated in the SPC, that about 15 % of patients cannot be switched to PPX ER.

In their response the MAH elaborated on the non-inferiority testing, role of adverse events and impact on SPC wording. Further detail on this is provided under the respective heading below. The MAH started by emphasising that the primary objective of the study to demonstrate that patients can be safely switched overnight on a 1:1 mg basis from pramipexole IR to pramipexole ER was clearly achieved. One-hundred out of 104 (96.2%) pramipexole ER patients compared to 49 out of 52 (94.2%) pramipexole IR patients completed the 9-week study, supporting the fact that patients can be safely switched from pramipexole IR to ER. No patient stopped the trial prematurely due to lack of efficacy. In each treatment group, only one patient prematurely discontinued the trial due to a drug-related adverse event.

#### Non-inferiority testing

In the 248.636 switch study, a successful switch (from open-label PPX IR to double-blind PPX ER or PPX IR) was defined as no worsening of the UPDRS II+III score by more than 15% from baseline and no drug-related adverse events (AE) leading to withdrawal. The between groups difference (ER vs. IR) in percentage of patients successfully switched was -9.76%. So, formally, non-inferiority between pramipexole ER and IR could not be demonstrated using the pre-defined non-inferiority margin of -15% for the lower bound of the 95% CI. However, as the 95% CI ([-18.81, 1.66]) included the zero value, superiority of pramipexole IR over pramipexole ER cannot be concluded either. Overall comparable efficacy between ER and IR is further supported by the fact that, on all secondary efficacy endpoints, pramipexole ER showed a numerically better efficacy than pramipexole IR in study 248.636:

- CGI-I responder rates: 87.4% vs. 78.8% for ER vs. IR, respectively
- PGI-I responder rates 81.6% vs. 71.2% for ER vs. IR, respectively
- Adjusted mean improvement from baseline in the UPDRS II+III score: -1.6 points vs. -0.5 points for ER vs. IR, respectively.

No formal test of non-inferiority for the absolute mean change (in points) of the UPDRS Part II+III was implemented in the 248.636 trial protocol, as the main objective of this study was to prove the safety of an overnight switch from pramipexole IR to ER, as explained above. In addition, it was assumed that a formal test of non-inferiority based on a between-group difference of -3 points would have required more patients than planned in this trial. The trial report displays an adjusted between-group difference of -1.1 points in favour of pramipexole ER for the change from baseline in the UPDRS II+III score and a 95% CI of this between-group difference of [-2.8, 0.6]. The lower bound of the 95% CI (-2.8 points) was higher than the non-inferiority margin of -3 points (between-group difference) as pre-defined in trial 248.524. Consequently, with the same non-inferiority margin of -3 points than in trial 248.524, non-inferiority between pramipexole ER and IR would have been established also in the switch trial. These data were not used for a statement of non-inferiority in the trial report, as a post-hoc defined non-inferiority margin can only be used for hypotheses generation.

A test for superiority of pramipexole IR versus ER based on UPDRS Part II+III score would not provide a significant result, because the adjusted mean improvement in the pramipexole ER group was numerically higher than in the pramipexole IR group (PPX ER: -1.6 points, PPX IR: -0.5 points). The fact that formally the non-inferiority margin was not met is clearly linked to the choice of a relative change instead of an absolute change for the non-inferiority margin. As stated above, with the same

non-inferiority margin of -3 points as pre-defined in trial 248.524, the non-inferiority between pramipexole ER and IR would have been established in Trial 248.636 as well.

#### Role of adverse effects

Patients reporting a drug-related adverse event (AE) leading to withdrawal were considered as not successfully switched. The fact that formally non-inferiority (using the pre-defined margin of -15%) between pramipexole ER and IR could not be demonstrated is not due to differences in the percentages of patients prematurely withdrawn due to a drug-related AE, as only one (1.0%) of 104 patients switched to pramipexole ER was prematurely withdrawn due to a drug-related AE (vertigo and nausea), and this patient was not included in the efficacy analysis (FAS, LOCF) as he had no post-baseline efficacy data. In consequence, none of the 16 pramipexole ER patients considered as not-successfully switched was considered as such due to a drug-related AE leading to premature discontinuation. All (16) pramipexole ER patients considered as not-successfully switched were considered as such due to a worsening of UPDRS II+III score of more than 15% from baseline.

#### Impact on SPC wording

All patients can be switched safely overnight from pramipexole IR to pramipexole ER at the same daily dose, as demonstrated in the Switch Trial, where all (104) pramipexole ER patients were switched from pramipexole IR (OL) to pramipexole ER (DB). Four (3.8%) pramipexole ER patients and 3 (5.8%) pramipexole IR patients discontinued prematurely the trial. None of them discontinued prematurely due to lack of efficacy. If needed, the pramipexole dose could be adjusted after switching from pramipexole IR to pramipexole ER. The benefit of a dose adaptation was clearly shown, as 12 of the 17 pramipexole ER patients who increased the pramipexole dose were considered as successfully switched after dose increase, while only 5 of 17 could not be considered as successfully switched during the duration of the trial despite a dose increase. Efficacy was maintained in 87 of 103 patients switched to pramipexole ER. Out of these 87 patients, 82.8% did not change their dose, 13.8% increased and 3.4% decreased their dose. In half of the 16 patients who did not meet the criterion for maintained efficacy on UPDRS Part II+III score, the change from baseline was considered not clinically relevant. Only one patient switched to pramipexole ER experienced a drug-related adverse event leading to withdrawal. Therefore, the MAH is of the opinion that the SPC should not contain any statement that a certain percentage of patients cannot be switched from pramipexole IR to pramipexole ER. However, the MAH suggested adding a statement to the posology section of the SPC (4.2) that a dose adjustment may be required after switching from pramipexole IR to pramipexole ER tablets.

The CHMP acknowledged the MAH response and agreed this issue can be resolved with an amendment to the SPC as suggested by the company below (section 4.2 and 5.1):

*4.2 Patients already taking {TRADE NAME} tablets may be switched to {TRADE NAME} prolonged-release tablets overnight, at the same daily dose. After switching to {TRADE NAME} prolonged release tablets, the dose may be adjusted depending on the patient's therapeutic response (see section 5.1).*

*5.1 Efficacy was maintained in 87 of 103 patients switched to {TRADE NAME} prolonged-release tablets. Out of these 87 patients, 82.8% did not change their dose, 13.8% increased and 3.4% decreased their dose. In half of the 16 patients who did not meet the criterion for maintained efficacy on UPDRS Part II+III score, the change from baseline was considered not clinically relevant. Only one patient switched to {TRADE NAME} prolonged-release tablets experienced a drug related adverse event leading to withdrawal.*

The subgroup analyses in study 248.636 further suggested that switching might be more difficult in patients  $\geq 65$  years of age and in patients on levodopa therapy. Since no data concerning pramipexole prolonged-release in advanced PD patients were available, the CHMP requested the MAH to discuss whether ER should be restricted to the population  $< 65$  years and the indication should be restricted only to “signs and symptoms for early PD”.

In response the MAH elaborated further on data from study 248.636 with regards to analyses based on age and on concomitant intake of L-Dopa. A summary of this discussion is included below.

#### Analyses based on age

Percentage of patients successfully switched by age groups (sub-group analysis): Of the 103 pramipexole ER patients, 55 patients were younger than 65 years and 48 patients were 65 years or older. Results of the sub-group efficacy analysis by age category are given below:

- In patients younger than 65 years, 45 of 55 (81.8%) were successfully switched
- In patients of at least 65 years, 42 of 48 (87.5%) were successfully switched The percentage of patients successfully switched to pramipexole ER was therefore slightly larger in patients of at least 65 years (87.5%) compared to patients younger than 65 years (81.8%). However, the difference is considered not clinically relevant and is deemed to be due to the small number of patients included in this sub-group analysis.

Influence of age as a co-variate in the model:

In order to show the influence of age on the primary endpoint, the ANCOVA analysis was modified by adding age as a covariate similar to UPDRS Part II+III score at baseline. There was no effect from age as a covariate ( $p=0.1839$ ). When using age groups ( $<65$ ,  $\geq 65$  years) as a factor into the model, age was also non-significant ( $p=0.5914$ ).

From the data on change in UPDRS II+III score by age groups, the MAH concluded that switching from pramipexole IR to pramipexole ER is possible in all patients independent of age group ( $<65$  or  $\geq 65$  years).

#### Analyses based on concomitant intake of L-Dopa:

Out of 103 pramipexole ER patients, 55 patients were concomitantly treated with L-Dopa, while 48 patients did not receive a concomitant treatment with L-Dopa. Results of the sub-group efficacy analysis by concomitant intake of L-Dopa are given below:

- In patients concomitantly treated with L-Dopa, 45 of 55 (81.8%) were successfully switched
- In patients not concomitantly treated with L-Dopa, 42 of 48 (87.5%) were successfully switched

The percentage of patients successfully switched to pramipexole ER was therefore slightly lower in patients receiving a concomitant treatment with L-Dopa (81.8%) compared to patients not concomitantly treated with L-Dopa (87.5%). However, the difference is considered not clinically relevant and is deemed to be due to the small number of patients included in this sub-group analysis. With pramipexole ER, the mean and median improvements from baseline in the UPDRS II+III score were comparable in patients with or without L-Dopa (-1.36 vs. -1.69, respectively).

#### Analyses based on age and concomitant intake of L-Dopa

Descriptive statistics are provided below in Table 29: 4 for the change in UPDRS II+III in the four following sub-groups of patients:

- Patients  $< 65$  years and treated with L-Dopa
- Patients  $< 65$  years and not treated with L-Dopa
- Patients  $\geq 65$  years and treated with L-Dopa
- Patients  $\geq 65$  years and not treated with L-Dopa

Table 29: 4

Descriptive statistics for UPDRS Part II+III stratified by age and use of L-dopa

Distributions of age and L-Dopa categories		Treatment group							
		Pramipexole ER				Pramipexole IR			
		Change from baseline				Change from baseline			
		N	Mean	SD	Median	N	Mean	SD	Median
< 65 years	Without L-Dopa	33	-1.7	4.4	-1.0	15	0.9	5.3	0.0
	With L-Dopa	22	-1.2	5.8	-1.0	25	0.5	4.5	0.0
≥ 65 years	Without L-Dopa	15	-1.7	4.4	-1.0	9	-2.0	3.1	-2.0
	With L-Dopa	33	-1.5	5.7	-1.0	27	-1.5	3.6	0.0

In the pramipexole ER group, improvements from baseline were observed in these four subgroups of patients, independent of age or of a concomitant treatment with L-Dopa.

The CHMP agreed with the MAH that switching from pramipexole IR to pramipexole ER is possible in patients independent of age group and concomitant treatment with L-Dopa.

In addition, with regards to the results of study 248.636, the CHMP requested the MAH to discuss the reasons why the predefined non-inferiority margin of -15% was not reached in the study. The CHMP especially wanted the MAH to elaborate on of there could be some safety related reasons explaining this failure.

The MAH responded that in the 248.636 study, successful switch from open-label pramipexole IR to double-blind pramipexole ER or IR was defined as no worsening of the UPDRS II+III score by more than 15 % from baseline and no drug-related adverse events (AE) leading to withdrawal. The sample size was based on being able to claim non-inferiority in percentages of patients with a worsening in UPDRS II+III score from baseline  $\leq 15\%$  after being switched. A sample size of 120 patients (PPS) was expected to be sufficient for testing the following two hypotheses: 1) Assuming a non-inferiority margin of 15% and a success rate of 95% in the IR group and 91.5% in the ER group (i.e. expected between-group difference of -3.5%). 2) Assuming a non-inferiority margin of 20% and a success rate of 90% in the IR group and 85% in the ER group (i.e. expected between-group difference of -5%).

Considering the bioequivalence data from Phase I trial, it was assumed that switching at same total daily dose, without a worsening  $>15\%$  from baseline in the UPDRS II+III score, should be possible in at least 85% patients in the ER group, and that the expected between-group difference should not be greater than -5%. The observed between groups difference was -9.76 %, i.e. larger than expected.

In most patients with a relative change from baseline  $>15\%$ , the absolute difference compared to baseline in the UPDRS II+III score was small and not clinically relevant ( $\leq 5$  points) and the patient was still considered well-controlled (based on PGI-I and/or CGI-I). Four (3.8%) pramipexole ER patients and 3 (5.8%) pramipexole IR patients discontinued prematurely the trial. None of them discontinued prematurely due to lack of efficacy.

The absolute change in the UPDRS II+III score (adjusted mean) from baseline to Week 9 was larger in pramipexole ER group (-1.6 points) compared to pramipexole IR group (-0.5 points), resulting in an adjusted mean difference between the two groups of -1.1 points, and a 95% CI of [-2.8, 0.6]. It should be noted that this CI does not include the value “-3 points”, which was the predefined non-inferiority margin between pramipexole ER and IR, for the final non-inferiority test in the early PD trial 248.524. This non-inferiority margin of -3 points in early PD patients was agreed by Health Authorities with the MAH during a meeting with the Rapporteur on September 28th 2006. The lower bound of the 95% CI for the between-group difference in the adjusted mean change from baseline in the UPDRS II+III score was -2.8 points. Therefore, with the same non-inferiority margin of -3 points as predefined in trial 248.524, the non-inferiority of pramipexole ER versus IR would have been established in the

switch trial. On all secondary endpoints in Trial 248.636 (change in UPDRS II+III score, UPDRS II and III separately, CGI-I and PGI-I responder rates), the efficacy was always numerically better in the pramipexole ER group, compared to the pramipexole IR group.

The fact that formally non-inferiority (using the pre-defined margin of -15%) between pramipexole ER and IR could not be demonstrated is not due to differences in the percentage of patients prematurely withdrawn due to a drug-related AE, as only one (1.0%) of 104 patients switched to pramipexole ER was prematurely withdrawn due to a drug related AE (vertigo and nausea), and this patient was not included in the efficacy analysis (FAS, LOCF) as he had no post-baseline efficacy data. In the not-successfully switched pramipexole ER patients, only one patient did not increase the dose due to an adverse event (hypotension). In consequence, none of the 16 pramipexole ER patients considered as not-successfully switched was considered as such due to a drug-related AE leading to premature discontinuation. All (16) pramipexole ER patients considered as not-successfully switched were considered as such due to a worsening of UPDRS II+III score of more than 15 % from baseline. The fact that formally the non-inferiority margin was not met is clearly linked to the choice of a relative change instead of an absolute change for the non-inferiority margin. As stated above, with the same non-inferiority margin of -3 points as pre-defined in trial 248.524, the non-inferiority between pramipexole ER and IR would have been established in Trial 248.636 as well.

The CHMP acknowledged the MAH response and considered the argumentation on this issue acceptable, the reason for the not met non-inferiority criteria being more due to the selection of relative change instead of an absolute change for the non-inferiority margin. The CHMP confirmed that the latter choice of the non-inferiority margin for the absolute change -3 points was previously agreed by Health Authorities during a meeting with the Rapporteur on September 28th 2006. The CHMP therefore considered this issue partly resolved. The  $C_{max}$ ,  $C_{min}$ ,  $C_{pre}$ , AUC and Clr, SrClr values of the patients not successful in switch should however be presented by the MAH and compared with those of patients successful in switch.

The MAH responded that the requested PK data are unfortunately not available for the switch study, as no blood samples for the purpose of PK investigations have been collected in this study. The only PK data in patients available were collected in study 248.524, including Asian and Japanese patients, where pramipexole ER could be taken with or without food. If any further analyses of the available PK data beyond those already presented and discussed are deemed as useful by the CHMP, the MAH requested a clear guidance on the kind of analyses to be provided.

The CHMP considered the MAH response acceptable and issue resolved.

The CHMP further concluded that in the overall data provided with this application, equivalent efficacy between the test and the reference product could not be proven. Evidence of efficacy and safety relative to the IR formulation has not been confirmed for the ER formulation relative to the IR formulation. From the data available the following was established:

- Study 248.524. There is initial evidence of efficacy of the PR formulation against placebo.
- No efficacy data are available from the on going Study 248.525.
- Study 248.636 ("Switch trial") design is not ideal to compare formulations, and formally non-inferiority between pramipexole ER and pramipexole IR cannot be concluded.

The MAH was subsequently requested to comment and to provide further data.

In their response the MAH submitted the final results from the two pivotal Phase III trials (248.524 in early PD and 248.525 in advanced PD) which had been completed and analysed. The final results from these studies are summarised below.

#### **Final results from Study 248.524 in early PD**

This trial was powered to test for both superiority of pramipexole ER over placebo and noninferiority between pramipexole ER and IR (2:2:1 randomisation ratio for PPX ER: PPX IR: PBO). A total of 539 patients were treated for up to 33 weeks in this trial (PPX ER: 223, PPX IR: 213 and PBO: 103). Doses were flexibly up-titrated, based on efficacy and tolerability. The mean (SD) final pramipexole

dose was comparable in the two pramipexole groups (PPX ER: 2.90 (1.41) mg/day, PPX IR: 2.93 (1.40) mg/day). Superiority of pramipexole ER over placebo was demonstrated after 18 weeks of treatment (interim cut-off, confirmatory analysis) and after 33 weeks of treatment (final cut-off, descriptive analysis). Non-inferiority between pramipexole ER and pramipexole IR was demonstrated after 33 weeks of treatment (final cut-off, confirmatory analysis).

#### Demonstration of superiority of pramipexole ER over placebo

Superiority of pramipexole ER over placebo was demonstrated after 18 weeks of treatment (interim cut-off, confirmatory analysis). The descriptive analysis after 33 weeks of treatment has confirmed superiority of pramipexole ER over placebo, as summarised further below:

At the final (33-week) analysis, superiority of pramipexole ER over placebo was shown on both the primary and the key secondary efficacy endpoints (descriptive tests), in the FAS (LOCF) population. Adjusted mean change from baseline to Week 33 in the UPDRS II+III score of -8.6 points, -8.8 points and -3.8 points for pramipexole ER, pramipexole IR and placebo, 0.26 mg, 0.52 mg, 1.05 mg, 2.1 mg, and 3.15 mg prolonged-release tablets respectively ( $p=0.0001$  for PPX ER vs. placebo, and  $p<0.0001$  for PPX IR vs. placebo); CGI-I response rate of 29.4% in the placebo group, compared to 43.3% in the pramipexole ER group and 46.1% in the pramipexole IR group ( $p=0.0256$  for PPX ER vs. placebo, and  $p=0.0078$  for PPX IR vs. placebo); PGI-I response rate of 21.4% in the placebo group, compared to 34.4% in the pramipexole ER group and 33.3% in the pramipexole IR group ( $p=0.0148$  for PPX ER vs. placebo, and  $p=0.0193$  for PPX IR vs. placebo).

#### Demonstration of non-inferiority between pramipexole ER and IR

The non-inferiority hypothesis comparing pramipexole ER to pramipexole IR was tested using a non-inferiority margin of -3 points for the between-group difference in the change from baseline to Week 33 of the UPDRS II+III score.

#### Demonstration of non-inferiority between pramipexole ER and IR at the final (33-week) analysis with regards to the primary efficacy endpoint (UPDRS II+III score)

The adjusted mean change from baseline to Week 33 in the UPDRS II+III score was -8.6 points for pramipexole ER and -8.8 points for pramipexole IR, a between-group difference of -0.2 points and a 95% CI of this difference of [-2.2; 1.7], in the PPS (OC) population. The lower bound of this 95% CI (-2.2 points) was higher than the pre-defined non-inferiority margin of -3 points. These non-inferiority data are further supported by the CGI-I and PGI-I responder rates, showing an overlap between the 95% CI for CGI-I and PGI-I responder rates in the pramipexole ER and IR groups: CGI-I responder rate: Pramipexole ER: 43.3%, 95% CI [36.5, 50.3] Pramipexole IR: 46.1%, 95% CI [39.2, 53.2] 0.26 mg, 0.52 mg, 1.05 mg, 2.1 mg, and 3.15 mg prolonged-release tablets.

PGI-I responder rate:

Pramipexole ER: 34.4%, 95% CI [28.1, 41.2]

Pramipexole IR: 33.3%, 95% CI [27.0, 40.2]

The CHMP acknowledged the data submitted by the MAH and concluded that both primary and secondary efficacy analyses confirm efficacy of ER against placebo and non-inferiority against IR in PD.

#### **Final results from Study 248.525 in advanced PD:**

This trial was powered to test for superiority of pramipexole ER over placebo (1:1:1 randomisation ratio for PPX ER: PPX IR: PBO). A total of 517 patients were treated for up to 33 weeks in this trial (PPX ER: 164, PPX IR: 175 and PBO: 178). Doses were flexibly up-titrated, based on efficacy and tolerability. The mean (SD) final pramipexole dose was comparable in the two pramipexole groups (PPX ER: 2.76 (1.44) mg/day, PPX IR: 2.77 (1.42) mg/day). This 33-week study was concluded after the last patient completed 18 weeks of treatment. Superiority of pramipexole ER over placebo was assessed after 18 weeks of treatment (confirmatory analysis) and after 33 weeks of treatment (descriptive analysis).

### Demonstration of superiority of pramipexole ER over placebo

Superiority of pramipexole ER over placebo was demonstrated after 18 weeks of treatment on both primary and key secondary efficacy endpoints (confirmatory analysis). Adjusted mean change from baseline to Week 18 in the UPDRS II+III score of -11.0 points, -12.8 points and -6.1 points for pramipexole ER, pramipexole IR and placebo, respectively ( $p=0.0001$  for PPX ER vs. placebo, and  $p<0.0001$  for PPX IR vs. placebo).

Adjusted mean change from baseline in percentage off-time of -13.3 points, -15.9 points and -8.8 points for pramipexole ER, pramipexole IR and placebo, respectively ( $p = 0.0122$  for PPX ER vs. placebo, and  $p < 0.0001$  for PPX IR vs. placebo). The corresponding adjusted mean changes in hours were -2.1 hours, -2.5 hours and -1.4 hours for pramipexole ER, pramipexole IR and placebo, respectively ( $p = 0.0199$  for PPX ER vs. placebo, and  $p < 0.0001$  for PPX IR vs. placebo).

The descriptive analysis, after 33 weeks of treatment, also demonstrated superiority of pramipexole ER over placebo. Adjusted mean change from baseline to Week 33 in the UPDRS II+III score of -11.1 points for pramipexole ER, -11.5 points for pramipexole IR, and -6.8 points for placebo; ( $p=0.0135$  for PPX ER vs. placebo, and  $p=0.0051$  for PPX IR vs. placebo).

### Demonstration of comparable efficacy of pramipexole ER and IR

This trial was not designed nor powered for a formal non-inferiority test between pramipexole ER and IR. Overall, there was no clinically relevant difference in terms of efficacy between pramipexole ER and pramipexole IR (numerical comparison). The change from baseline in the UPDRS II+III score was clinically relevant for both formulations. As there is an overlap in the 95% CIs for the adjusted mean change from baseline to week 33 in the UPDRS II+III score for the two pramipexole groups (ER: [-13.7, -8.4], IR: [-14.0, -9.0]), it cannot be concluded that either formulation is superior.

### Demonstration of equivalent safety of pramipexole ER and IR

In this trial, adverse events were reported less frequently in the pramipexole ER group (54.9%) compared to the pramipexole IR group (64.0%). Dizziness was reported less frequently in the pramipexole ER group (4.9%) compared to the pramipexole IR group (10.3%). Otherwise, the safety profile of pramipexole ER and IR tablets was comparable, at comparable daily doses and duration of treatment.

The CHMP acknowledged the data submitted by the MAH and concluded that both primary and secondary efficacy analyses confirm efficacy and safety of ER against placebo and non-inferiority against IR in late PD.

### **Clinical safety**

The safety and tolerability profile of PPX ER were similar to the profile of PPX IR both when used to treat patients with early PD not on levodopa and when used to treat patients with advanced PD on concomitant levodopa. PPX ER does not appear to differ from PPX IR in regards to the frequency of overall adverse events, serious adverse events, adverse events leading to drug discontinuation; frequency of common adverse events; or frequency of adverse events of special interest. In an active-control clinical trial, only one of 104 (1.0%) patients discontinued drug treatment due to an adverse event when blindly switched overnight from PPX IR to PPX ER at the same daily dose. No new or unexpected safety or tolerability issue emerged during the clinical development program of PPX ER.

### Patient exposure

The safety data presented are presented pooled from the placebo-controlled studies 248.524 and 248.525 for the patients treated up to 18 weeks. A total of 1015 patients were treated in these trials: 370 PPX ER, 377 PPX IR and 268 placebo patients. In active controlled trials and open-label trials an additional 104 and 329 patients, respectively were exposed to PPX ER. Thus, 803 patients were exposed to adequate doses of PPX ER for an estimated 180 patient-years for safety evaluation.

### Adverse events

For none of the adverse events there were any significant differences between PPX ER and PPX IR. Of the patients in the PPX ER groups 66.7% reported AE compared to 60.2% in the placebo groups.

The most common frequent AEs was as follows:

#### **Frequency of adverse events (%)**

	PPX ER	PPX IR	Placebo
Somnolence	20.5	21.4	12.7
Nausea	15.2	15.0	6.6
Constipation	10.5	10.9	3.6
Dyskinesia	9.5	8.6	3.6
Dizziness	6.2	12.7	6.6
Hallucinations	4.3	5.9	0.6
Vomiting	2.4	5.0	1.8

Only 6.2% of the AEs in the PPX ER patients were rated as severe. Sleepiness, orthostatic hypotension and abnormal behaviour were defined as AEs of special interest in the PPX ER development program, but the frequencies were general low and no significant differences were seen between PPX ER, PPX IR and placebo groups.

#### Serious adverse events and deaths

The frequency of severe AE were similar for all 3 groups and only 5 patients with hallucinations requiring hospitalisation were considered drug-related (3 ER and 2 IR patients). Two deaths are described, one from lip/oral cancer and one from a rectal cancer, neither was considered drug-related.

#### Laboratory findings

None reported.

#### Safety in special populations

Paediatric patients and pregnant women were not treated, so no data on these groups can be given. No clinically data is reported for renally and hepatically impaired patients, so the same recommendations as for PPX IR were recommended by the CHMP.

#### Immunological events

None reported.

#### Safety related to drug-drug interactions and other interactions

None reported, but only few were expected, and data for PPX IR was considered sufficient.

#### Discontinuation due to AES

Relatively few patients discontinued due to AE:

#### **Frequency of adverse events leading to discontinuation (%)**

	PPX ER	PPX IR	Placebo
Hallucinations	0.5	1.8	0
Nausea	1.0	0.9	0.6
Somnolence	0.5	1.4	0

Overall, AEs were of mild or moderate intensity. The CHMP concluded, that PPX is very similar to PPX IR with regards to adverse events, and no new or unexpected adverse event have been reported in the studies on PPX ER presented.

## **2.5 Pharmacovigilance**

### **Detailed description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the legislative requirements. The Pharmacovigilance system also provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

In view of addition of a new pharmaceutical form associated with additional strengths, the periodic safety update reports will be submitted every six months during two years, once a year for the following two years and thereafter at three-yearly intervals.

### **Risk Management Plan (RMP)**

With this application the MAH submitted a Risk Management Plan (RMP) for pramipexole prolonged-release tablets.

Pramipexole prolonged-release tablets is an extended release formulation of pramipexole immediate release (pramipexole IR) which was approved in the EU more than ten years ago. The MAH has used the data on the safety of pramipexole IR as well as data from the clinical development program of pramipexole ER.

In assessing the RMP the CHMP considered that information on toxicity, general pharmacology, drug interactions and other toxicity related information for pramipexole was lacking and therefore asked the MAH to update the RMP with this information. The CHMP also requested the MAH to present the RMP in a stand alone format since several of the sections of the RMP initially submitted used previous PSURs of pramipexole IR as references. The MAH responded by submitting an updated version of the RMP. The CHMP concluded that the updated RMP contains the relevant information regarding general pharmacology, drug interactions and other toxicity related information for pramipexole.

The MAH also did not include the established risks of pramipexole treatment in the RMP initially submitted, but discussed only newly identified risks in detail. The MAH was therefore requested by the CHMP to provide more extensive information.

In response the MAH submitted a list and subsequent text parts with details of identified potential risks associated with pramipexole treatment regardless of the fact that these risks have been mentioned in previous pramipexole immediate release RMP's were prepared and included in section 1.5.2.10-1.5.2.20, 1.10, 2.2-2.6, and 7 of the updated RMP, Module 1.8.2. the CHMP considered the updated sections acceptable.

The MAH was also requested by the CHMP to elaborate on how the design of the packaging, the PIL and the SPC reduces the risk of medication error and to explain how the risk of medication errors will be further monitored. In their response the MAH explained that in order to minimise the occurrence of medication errors such as inadequate frequency of dosing or crushing of the pramipexole prolonged-release tablets, potentially carrying a risk of overdose, the packaging and tablet design is aimed to ensure a clear differentiation of the two pramipexole formulations by health care professionals, patients and care givers. The prolonged release tablets are different in shape, size, and embossing compared to the immediate release tablet and will not contain a break score. The name and strength of the product appearing on each blister that in addition is of different size compared to the immediate release tablets allows an identification of the formulation also in case the blister will not be stored in the original pack by the patient. The proper naming, design and packaging of the product and the physician (SPC) and patient (PL) labeling documents, allows an identification of the products diversity and are regarded as adequate measures to minimize medication errors.

The CHMP concluded that the MAH is taking the risk of medication error seriously and has given much consideration regarding the design and labelling of the product. Furthermore, a sufficient description of the monitoring of medication errors has been provided. The committee subsequently considered the issue resolved.

### Summary of safety concern and planned Pharmacovigilance actions

Identified risks will be followed up by the MAH in terms of updated frequency estimation from the MAH's clinical trial database (project database). Planned and ongoing Pharmacovigilance activities to characterise the potential risks include clinical trials. No important missing information had been identified. The table below summarises the planned actions according to the important risks.

Table Summary of the risk management plan:

Safety issue	Proposed pharmacovigilance activities (Routine and Additional)	Proposed risk minimisation activities (Routine and Additional)
<p>Binge eating, Compulsive shopping, Pathological gambling, Hypersexuality and other Abnormal behaviour</p>	<p>Routine pharmacovigilance</p> <p>Continued pooled analysis of controlled clinical trial data base including new PD IR, PD ER and RLS studies as soon as available. PERIODIC REVIEW IN PSUR</p> <p>Trial 248.619 (DOMINION): cross-sectional, retrospective screening and case-control study in PD patients treated with pramipexole and other antiparkinson drugs, completed</p> <p>Trial 248.659: Observational RLS study, ongoing</p>	<p>Routine risk minimisation activities.</p> <p>The following information is included in section 4.4 of the SmPC (Special warnings and precautions for use):</p> <p><i>Impulse control disorders and compulsive behaviours: Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson’s disease, including {TRADE NAME}. Furthermore, patients and caregivers should be aware of the fact that other behavioural symptoms of impulse control disorders and compulsions such as binge eating and compulsive shopping can occur. Dose reduction/tapered discontinuation should be considered.</i></p> <p><i>Behavioural symptoms of impulse control disorders and compulsions are described as common, compulsive shopping, hypersexuality, pathological gambling as uncommon and binge eating as psychiatric disorders with unknown frequency in section 4.8 of the SmPC (Undesirable effects).</i></p> <p>Furthermore the following information is provided in Section 4.8 of the SmPC (Undesirable effects):</p> <p><i>Impulse control disorders and compulsive behaviours: Patients treated with dopamine agonists for Parkinson’s disease, including {TRADE NAME}, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation (see also section 4.4).</i></p> <p><i>In a cross-sectional, retrospective screening and case-control study including 3,090 Parkinson’s disease patients, 13.6% of all patients</i></p>

		<p>receiving dopaminergic or non-dopaminergic treatment had symptoms of an impulse control disorder during the past six months. Manifestations observed include pathological gambling, compulsive shopping, binge eating, and compulsive sexual behaviour (hypersexuality). Possible independent risk factors for impulse control disorders included dopaminergic treatments and higher doses of dopaminergic treatment, younger age (<math>\leq 65</math> years), not being married and self-reported family history of gambling behaviours.</p>
Suicide-related behaviour	Routine pharmacovigilance PERIODIC REVIEW IN PSUR	NONE
Augmentation, post treatment worsening after withdrawal and rebound in RLS patients	<p>Routine pharmacovigilance PERIODIC REVIEW IN PSUR</p> <p>Trial 248.629: randomised, double-blind, placebo-controlled, dose titration trial with pramipexole to investigate the long-term efficacy, safety and tolerability in patients with RLS; completed</p>	<p>Routine risk minimisation activities.</p> <p>The following information is included in section 4.4 of the SmPC (Special warnings and precautions for use):</p> <p><i>Augmentation: Reports in the literature indicate that treatment of Restless Legs Syndrome with dopaminergic medicinal products can result in augmentation. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. The controlled trials of {TRADE NAME} in patients with Restless Legs Syndrome were generally not of sufficient duration to adequately capture augmentation phenomena. The frequency of augmentation after longer use of {TRADE NAME} and the appropriate management of these events have not been evaluated in controlled clinical trials.</i></p>
SIADH	<p>Routine pharmacovigilance</p> <p>Planned pooled analysis of controlled clinical trial data concerning SIADH PERIODIC REVIEW IN PSUR</p>	NONE.
Delirium/Mania	<p>Routine pharmacovigilance</p> <p>Planned pooled analysis of controlled clinical trial data</p>	NONE.

	concerning delirium/mania PERIODIC REVIEW IN PSUR	
Dyspnoea	Routine pharmacovigilance Continued pooled analysis of controlled clinical trial data base including new PD IR, PD ER and RLS studies as soon as available. PERIODIC REVIEW IN PSUR	Routine risk minimisation activities. <i>Dyspnoea</i> is described as uncommon respiratory, thoracic, and mediastinal disorders in section 4.8 of the SmPC (Undesirable effects).
Pneumonia	Routine pharmacovigilance Continued pooled analysis of controlled clinical trial data base including new PD IR, PD ER and RLS studies as soon as available. PERIODIC REVIEW IN PSUR	Routine risk minimisation activities. <i>Pneumonia</i> is described as uncommon infection in section 4.8 of the SmPC (Undesirable effects).
Bronchitis	Routine pharmacovigilance Continued pooled analysis of controlled clinical trial data base including new PD IR, PD ER and RLS studies as soon as available. PERIODIC REVIEW IN PSUR	NONE.
Cardiac failure	Routine pharmacovigilance Continued pooled analysis of controlled clinical trial data base including new PD IR, PD ER and RLS studies as soon as available. PERIODIC REVIEW IN PSUR	NONE.
Retinal degeneration	Routine pharmacovigilance Trial 248.538: randomised, parallel group, ophthalmologic safety study, ongoing	Routine risk minimisation activities. The following information is included in section 4.4 of the SmPC (Special warnings and precautions for use): <i>Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occur.</i> The following information is included in section 5.3 of the SmPC (Preclinical safety data): [...] <i>at doses of 2 mg/kg (of salt) and higher, pramipexole was associated with retinal degeneration in albino rats. The latter finding was not observed in pigmented rats, nor in a 2-year albino mouse carcinogenicity study or in any other species investigated.</i>
Decreased appetite/Anorexia	Routine pharmacovigilance	NONE
Skin melanoma	Routine pharmacovigilance	NONE
Diplopia	Routine pharmacovigilance	Routine risk minimisation activities.

		<i>Visual disturbance including vision blurred and visual acuity reduced is described as common eye disorder in section 4.8 of the SmPC (Undesirable effects). Diplopia is considered as covered by this description.</i>
Photopsia	Routine pharmacovigilance	Routine risk minimisation activities. <i>Visual disturbance including vision blurred and visual acuity reduced is described as common eye disorder in section 4.8 of the SmPC (Undesirable effects). Photopsia is considered as covered by this description.</i>
Fibrotic events	Routine pharmacovigilance	NONE.
Substance abuse/Drug dependence	Routine pharmacovigilance	NONE
Response-based behaviour	Routine pharmacovigilance	NONE.
Hyperreflexia	Routine pharmacovigilance	NONE
Dystonia	Routine pharmacovigilance	NONE.
Overdose	Routine pharmacovigilance PERIODIC REVIEW IN THE BI GLOBAL DRUG SAFETY DATABASE	Routine risk minimisation activities. The following information is included in section 4.9 of the SmPC (Overdose): <i>There is no clinical experience with massive overdose. The expected adverse reactions would be those related to the pharmacodynamic profile of a dopamine agonist, including nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension. There is no established antidote for overdose of a dopamine agonist. If signs of central nervous system stimulation are present, a neuroleptic agent may be indicated. Management of the overdose may require general supportive measures, along with gastric lavage, intravenous fluids, administration of activated charcoal and electrocardiogram monitoring.</i>

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. The safety specification and planned Pharmacovigilance activities are considered adequate.

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

### **Quality**

The new pharmaceutical form – prolonged-release tablets with associated new strengths have been adequately described. The excipients used in the preparation of the product and the manufacturing process selected are appropriate. The results of the tests indicate that the medicinal product can be reproducibly manufactured and therefore the product should have a satisfactory and uniform performance in clinic.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve this as Follow-Up Measure after the opinion, within an agreed timeframe.

### **Non-clinical pharmacology and toxicology**

No specific non-clinical pharmacological and pharmacokinetic studies have been performed for pramipexole in the ER formulation. Non-clinical toxicology studies have been performed to qualify three potential degradation products of pramipexole ER tablets. These potential degradation products are CD10503, Product V and Product Z. Several in vitro and in vivo genotoxicity studies were conducted by the MAH due to the genotoxic potential of these degradation products. The genotoxic potential was indicated in either structural elucidation or in studies pertinent to pramipexole IR tablets. The MAH proposed a hypothesis regarding the genotoxicity of CD10503 which the CHMP found reasonable. Data indicates that CD 10503 did not have a separate effect but all relevant findings were from pramipexole being a very potent dopamine agonist. The genotoxic potential of the degradation products V and Z is likely to be caused by the release of catechol from these degradation products. The mixture of Products V and Z as well as catechol were negative in the Ames test.

### **Efficacy**

The efficacy and safety of pramipexole (PPX) has previously been demonstrated in clinical studies, and the IR tablets are registered with the indication treatment of patients with early and advanced Parkinson's disease (PD).

Although efficacy was established in the pivotal clinical trials (248.524 in early PD and 248.525 in advanced PD) there were a few issues that needed to be resolved. Following assessment the CHMP still did not find it clear what the significance of the variability in PK along with food intake, interactions and interethnic differences is for the efficacy. The MAH therefore committed to perform a further evaluation of these factors, taking into account also efficacy and PK data of the currently ongoing Japanese Phase III trial 248.610. In addition, examples of interacting agents may not be enough in the SPC, since the PK variability may be relevant for efficacy. The MAH therefore committed to perform an in-depth evaluation of all potential substances interacting with pramipexole and also to take a proactive role for evaluating interactions of pramipexole with commonly used hOCT2-inhibitors like ranitidine and trimetoprim. The MAH also committed to review relevant literature on genetic variation in transporter hOCT2 on a regular basis and provide updates with each PSUR/RMP.

### **Safety**

Overall, Adverse Events were of mild or moderate intensity. The CHMP concluded, that pramipexole prolonged-release tablets is very similar to pramipexole immediate release tablets as to adverse events, and no new or unexpected adverse event have been reported in the studies on PPX ER presented.

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.

### **Risk-benefit assessment**

Although the benefits of pramipexole prolonged-release tablets seem limited, the formulation is effective in the intended population, however, in a clinical setting, a proportion of PD patients (about 15%, compared to 6% in the IR group) did not meet the criterion for maintained efficacy on UPDRS Part II+III score even after dose adaptation. In half of these patients the difference in efficacy on UPDRS part II and III score was not considered to be clinically relevant. This is however adequately reflected in section 4.2 and 5.1 of the SPC. From a clinical perspective the risk associated with pramipexole prolonged-release tablets is similar to the risk for pramipexole immediate release tablets, thus acceptable. The overall Benefit/Risk of Sifrol is therefore 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 decision that the risk-benefit balance of Sifrol extended release tablets in the treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa) or in combination with levodopa, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or "on off" fluctuations) was favourable and therefore recommended the granting of an extension of the marketing authorisation.