19 September 2013
EMA/703661/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Oprymea

International non-proprietary name: pramipexole

Procedure No. EMEA/H/C/000941/X/14

Note

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

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Table of contents

List of abbreviations

Active Pharmaceutical Ingredient	
ASM	Active Substance Manufacturer
BE	Bioequivalence
BSE	Bovine spongiform encephalopathy
CEP	Certificate of Suitability of the EP
CMS	Concerned Member State
CoA	Certificate of Analysis
DMF	Dimethylformamide
DL	Detection Limit
DSC	Differential scanning Calorimetry
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EP	European Pharmacopoeia
FT-IR	Fourrier transmission infra red (spectroscopy)
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
IPC	In-process control test
GC	Gas chromatography
ICH	International conference on harmonisation
IR	Infra-red
LoA	Letter of Access
LOD	Loss on Drying
LoD	Limit of detection
LoQ	Limit of Quantitation
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MS	Mass spectroscopy
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
PDE	Permitted Daily Exposure
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
QL	Quantitation limit
QOS	Quality Overall Summary
RH	Relative Humidity
RMS	Reference member state
RRt	Relative retention time
Rt	Retention time
SEM	Scanning electron microscopy
SmPC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis
TSE	Transmissible Spongiform Encephalopathy
UV	Ultra violet
XRD	X-Ray Diffraction

AE - Adverse event
ANOVA - Analysis of variance
AUC - Area under the plasma concentration versus time curve
AUCτ - The area under the plasma concentration versus time curve over the final dosing interval (τ)
BLQ - Below limit of quantification
BMI Body mass index
C_{avg} - Average concentration over the dosing interval, τ
CI - Confidence interval
C_{max} - Maximum measured plasma concentration
C_{min} - Concentration at the end of dosing interval
CV - Coefficient of Variation
EU European Union
FDA - Food and Drug Administration
%Fluc - Percent fluctuation
GCP - Good Clinical Practice
hr - Hour
ICH - International Conference on Harmonisation
IR - Immediate release
ISR – Incurred sample reanalysis
kg - Kilogram
kg/m2 - Kilogram per meter square
LLOQ – Lower Limit of Qualification
LSM - Least-squares means
Mg - Milligram
mL - Milliliter
PI - Principal Investigator
PK - Pharmacokinetic
PR - Prolonged-release
QA - Quality Assurance
QC - Quality Control
Qd - Per day
REC Research Ethics Committee
SD Standard deviation
SOP Standard operating procedure
t_{max} - Time of the maximum measured plasma concentration

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Krka, d.d., Novo mesto submitted on 04 January 2013 an application for an extension of the Marketing Authorisation to the European Medicines Agency (EMA) for Oprymea 0.26 mg, 0.52 mg, 1.05 mg, 1.57 mg, 2.1 mg, prolonged- release tablets, through the centralised procedure falling within the Article 19 (1) and Annex I (point 2 indent d) of the Commission Regulation (EC) No 1234/2008.

Krka, d.d., Novo mesto is already the Marketing Authorisation Holder for Oprymea 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg, 1.1 mg tablets (EMEA/H/C/000941/001-025).

Oprymea is used in the following indication:

Oprymea is indicated in adults for 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).

The application submitted is composed of administrative information, complete quality data and at least a bioequivalent study with the reference medicinal product Sifrol instead of non-clinical and clinical data.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Oprymea has been given a Marketing Authorisation in the EU on 12 September 2008.

Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Mette Tranholm.

- The application was received by the EMA on 04 January 2013.
- The procedure started on 30 January 2013.
- The Rapporteur's initial Assessment Report was circulated to all CHMP members on 19 April 2013.
- During the meeting on 27-30 May 2013, 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 30 May 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 July 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 August 2013.
- During the meeting on 16-19 September 2013, 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 Oprymea.

2. Scientific discussion

2.1. Introduction

Oprymea is indicated for 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).

Pramipexole is a synthetic amino-benzothiazole derivative (ATC Code: N04B C05). It has been shown to be a selective and specific full dopamine receptor agonist with high affinity and selectivity for the D2 receptor subfamily, and particularly the D3 receptor subtype. It is used in the management of Parkinson’s disease, alone or as an adjunct to levodopa therapy in more advanced stages of the disease.

Oprymea 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg and 1.1 mg tablets was authorised as a generic medicinal product containing pramipexole (as dihydrochloride monohydrate) as active substance. The reference product Sifrol 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg and 1.1 mg tablets was centrally authorised on 14 October 1997.

The applicant applied for an extension of marketing authorisation in order to add to prolonged-release tablets in the following strengths: 0.26 mg, 0.52 mg, 1.05 mg, 1.57 mg and 2.1 mg. In addition, the applicant took the opportunity to introduce some minor editorial and typographic changes in Module 3.S.

Prolonged-release tablets are beneficial to patients with Parkinson’s disease as they can be administered once daily, thereby increasing patient convenience and compliance. In addition, administration of prolonged release tablets results in a pharmacokinetic profile with less pronounced maximum plasma levels and more stable plasma levels over time.

To support the application, the MAH submitted data from dissolution and bioequivalence studies. In the bioequivalence studies, Krka’s pramipexole prolonged release tablets were compared to Sifrol prolonged release tablets.

2.2. Quality aspects

2.2.1. Introduction

The medicinal product is presented as prolonged-release tablets containing 0.26 mg, 0.52 mg, 1.05 mg, 1.57 mg and 2.1 mg of the active substance pramipexole (as dihydrochloride monohydrate).

Other ingredients are: hypromellose, maize starch, silica, colloidal anhydrous and magnesium stearate. The prolonged-release tablets are packed in OPA/Alu/DES/PE-Alu blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

The active substance used in the prolonged-release tablets (0.26 mg, 0.52 mg, 1.05 mg, 1.57 mg and 2.1 mg), pramipexole, is the same active substance as the one approved for the currently authorised Oprymea tablets (0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg and 1.1 mg). Nevertheless, the applicant resubmitted the Module 3.S since some minor editorial and typographic changes.were introduced.

2.2.3. Finished medicinal product

Pharmaceutical development

The aim of the pharmaceutical development was to develop a product essentially bioequivalent to the reference product, Sifrol prolonged-release tablets. In this context, the applicant developed a pharmaceutical formulation that is very similar to the reference product.The pharmaceutical development took into consideration that the active substance is BCS class 1.

During development a range of release-rate controlling excipients were investigated and also different manufacturing processes such as wet granulation and direct compression were studied. Several pharmaceutical compositions of pramipexole were investigated during finished product development. It was noted that the active substance is slowly released by diffusion and erosion from the single unit matrix in the reference product and the Krka medicinal product.

In order to insure comparable performance between Oprymea prolonged-release tablets and the reference product, the MAH performed two *in vivo* pilot bioequivalence studies. These pilot studies were conducted under fasting and fed conditions with two different formulations. According to the results the proposed formulations were found to be bioequivalent to the reference product. Based on these results, one of the formulations was chosen for further development.

All strengths of the proposed Krka pramipexole prolonged-release tablet formulation were tested *in vivo* in order to prove the bioequivalence (BE) with the reference medicinal product under single dose fasting and fed (high fat) and steady state conditions. The compositions of the batches used for BE studies are identical to the product final formulation. Based on the results of pilot bioequivalence studies the most suitable dissolution method was developed. This method was further used as a supportive tool for the product development.

The effect of particle size of the active substance was also evaluated. Formulations with the same composition and active substance with different particle size were tested. The effect of hardness and compression speed on the properties of tablets was studied during the pharmaceutical development. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The finished product is packed in blister packs consisting of OPA/Alu/DES/PE-Alu blisters. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The proposed commercial manufacturing process involves standard technology using standard manufacturing processes such as mixing, blending, compressing, packaging. Furthermore, the equipment used is commonly available in the pharmaceutical industry. A detailed manufacturing description and flow scheme have been provided. The process is considered to be a standard manufacturing process, but considering the finished product is a specialised pharmaceutical form (low dose, prolonged-release tablets), process validation data to cover the proposed batch size is provided.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Results on process validation for pilot scale batches and production scale batches, covering the proposed batch size range, have been provided.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visually), uniformity of dosage (Ph Eur), identification (HPLC and UV), impurities (HPLC), dissolution (Ph Eur), assay (95% - 105%, HPLC) microbiological quality (Ph Eur). The finished product specifications are standard for prolonged-release tablets. All tests included in the specification have been satisfactorily described and validated. Appropriate data have been presented to justify the specifications. Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety.

Batch analysis results are provided for three pilot batches of each strength and first production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three pilot scale batches of all strengths of finished product stored under long term conditions for twelve months at 25 ºC / 60% RH and for up to six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The

batches of medicinal product are representative to those proposed for marketing and were packaged as proposed for marketing.

Samples were tested for appearance, assay, impurities, dissolution and microbiological quality.

The analytical procedures used are stability indicating. One pilot batch of each strength has been investigated regarding photostability as defined in the ICH Guideline on photostability Testing of New Drug Substances and Products. No major changes were observed and reported.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Data on development, manufacture and control of this pharmaceutical form has been presented in a satisfactory manner. The new pharmaceutical form was developed since it is beneficial to patients with Parkinson's disease as they can be administered once daily, thereby increasing patient convenience and compliance. The applicant developed a pharmaceutical formulation that is very similar to the reference product.All strengths of the proposed Krka pramipexole prolonged-release tablet formulation are bioequivalent to the reference medicinal product. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the medicinal product should have a satisfactory and uniform clinical performance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the data provided, the quality of this medicinal product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment (ERA) was submitted. This was justified by the applicant as the introduction of Oprymea manufactured by Krka d.d. Novo mesto is considered unlikely to result in any significant increase in the combined sales volumes for all parmipexole containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for prolonged release tablets containing pramipexole. To support the marketing authorisation application the applicant conducted five bioequivalence studies with cross-over design under both fasting and fed conditions.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment, the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1 in its current version is of particular relevance.

GCP

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

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

Exemption

In line with the Note for guidance on modified release oral and transdermal dosage forms: section II (pharmacokinetic and clinical evaluation), CPMP/EWP/280/96, prolonged release formulations can be assessed as bioequivalent on the basis of single and multiple dose studies which are designed to demonstrate, amongst other, that performance of the test and the reference formulation is equivalent after single dose and at steady state. In line with the Note as well as the biowaiver criteria laid down in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1), the MAH applied to waive the need for conducting additional bioequivalence studies including multiple dose studies involving all strengths at steady state.

All strengths of the pramipexole prolonged-release tablet formulation are manufactured by the same manufacturing process, the qualitative composition of the different strengths is the same, the amount of the active substance is less than 5 % of the tablet core weight, and the amount of a filler is changed to account for the change in amount of active

The MAH furthermore confirmed to have conducted appropriate in vitro dissolution studies confirming the adequacy of waiving additional in vivo bioequivalence testing. Upon request of the CHMP, the MAH submitted comparative between strength in vitro dissolution data in three relevant dissolution media using paddle apparatus and dissolution rotation speed.

Calculation of the f2 factor in accordance with criteria of the Guideline on the Investigation of Bioequivalence demonstrates similarity of profiles between all strengths of the pramipexole prolonged-release tablets formulation. The MAH concluded that the pharmacokinetics of pramipexole in the prolonged release formulations were linear and all the stipulated conditions of the dose proportionality rule were fulfilled as well as similar dissolution profiles between all strengths were demonstrated.

The CHMP considered the justification to be acceptable and agreed with the MAH's conclusions.

Clinical studies

To support this application, the MAH submitted the results of 5 bioequivalence studies with the test pramipexole prolonged release tablets formulation in comparison to Sifrol prolonged release tablets (see table 1 for an overview of the studies conducted)

Table 1. Tabular overview of clinical studies

Strength	Single dose fasting	Single dose fed	Strength
0.26 mg	12-368		
0.52 mg	12-365	12-366	
1.05 mg	12-369		
1.57 mg			12-370

2.4.2. Pharmacokinetics

Methods

Study design

Three of the bioequivalence studies were standard single dose fasting studies. One study was conducted under fed conditions and one study, where the highest strengths (1.57 mg and 2.1 mg) were used, was conducted as a multiple dose study first assessing the 1.57 mg dosage strength and subsequently the 2.1 mg strength.

The studies were conducted as open label, two periods, two sequences, crossover, controlled, randomised trials.

Specific design aspects by study type (single dose fasting, single dose fed and multiple dose fasting) are summarized below:

- Single dose studies under fasting conditions

Food and fluid intake:

After at least 10 hours of fasting, each subject received one dose of pramipexole prolonged-release tablets, administered with 240 ml of water.

Sampling schedule:

Blood samples for the analyses of pramipexole were collected before administration and at several points in time up to 48 hours post administration of a single-dose tablet with 240 ml of water.

- Single dose study under fed conditions

Drug intake procedures:

On the treatment days, after at least 10 hours of fasting and 30 minutes after the start of serving of a standardized high-fat high-calories breakfast (900 kcal, 16% from protein, 27% from carbohydrates and 57% from fat), each subject received one dose of pramipexole 0.52 mg prolonged-release tablet, administered with 240 ml of water.

Sampling schedule:

Blood samples were collected pre-dosing and at administration and at several points in time up to 48 hours post administration of a single-dose of 0.52 mg prolonged release tablet with 240 ml of water.

- Multiple dose study under fasting conditions

Drug intake procedures:

Study subject entered firstly an up-titration period of 9 days, immediately followed by a multiple dose cross-over study (cross-over 1) evaluating the bioequivalence of test product A and reference formulation B (1.57 mg of Pramipexol prolonged release tablets). Cross-over study 1 were immediately followed by the second cross-over study (cross-over 2) evaluating the bioequivalence of test formulation C and reference formulation D (2.1 mg of Pramipexol prolonged release tablets), ending with a down titration of 4 days.

After uptitration period subjects received an oral dose of the assigned formulations with 240 mL.

There was no washout between periods. The first dose in each period was administered under fed conditions and all other doses under fasting conditions.

The study terminated after adequate downtitration.

Sampling schedule:

Blood samples for the analyses of pramipexole were collected before administration and at several points in time up to 24 hours post administration on pre-specified days.

Serial blood samples were collected at the following time points

- Predose on Days 12-30;
- Postdose on Days 14, 19, 24, and 29 at several points in time up to 24 hours.

Test and reference products

Each strength of Oprymea, prolonged-release tablets, manufactured by KRKA, d.d., Novo Mesto, Slovenia has been compared with the corresponding strength of the reference product, Sifrol, prolonged-release tablets of Boehringer Ingelheim, Germany, in the five bioequivalence studies.

Batches used are described below by study:

- Studies 12-365 and 12-366:
  - Test products batch No.: 1228 07 P003 0512, re-test date: 22.09.2012, assay 100%. Batch size: 100,000 prolonged release tablets.
  - Reference product batch No. 106190, batch size NA, exp. date 08/2014, assay 100%.
- Study 12-368
  - Test product batch No.: 1228 06 P003 0512, re-test date: 22.11.2012, assay 101%, batch size: 100,000 prolonged release tablets
  - Reference product batch No. 106191, batch size NA, exp. date 08/2014, assay 99%.
- Study 12-369
  - Test products batch No.: 1228 08 P001 0512, re-test date: 23.09.2012, assay 100%, batch size: 100,000 prolonged release tablets.
  - Reference product batch No. 109053, batch size NA, exp. date 01/2015, assay 98%.
- Study 12-370
  - Test product: 1.57 mg prolonged-release tablets batch No. 1228 11 P001 **0512, re-test date: 23.01.2012, assay 102%, Batch size: 100,000** prolonged release tablets; 2.1 mg prolonged-release tablets batch No 1228 09 P001 0512, re-test date: 23.01.2012, assay 102%, Batch size: 100,000 prolonged release tablets.
  - Reference products: 1.57 mg prolonged-release tablets batch No. 108720A, batch size NA, exp. date 11/2014, assay: NA; 2.1 mg prolonged-release tablets batch No. 105486, batch size NA, exp. date 07/2014, assay: NA.

Population(s) studied

All studies were conducted in healthy male volunteers. All single dose studies were conducted in 24 study subjects while the multiple dose study was performed in 36 subjects. In the multiple dose study, 32 subjects completed crossover 1 and 34 completed crossover 2. One Subject dropped out on day 2 of period 1 (crossover 1) as a result of withdrawing his informed consent. Subject 22 was dropped by on day 13 of period 1 (crossover 1) due to a swollen painful right knee which required treatment. Subjects 24 and 29 both did not have any pharmacokinetic blood samples on day 19 of period 2 (crossover 1) due to adverse events.

Analytical methods

For studies: 12-365, 12-366, 12-368 and 12-368 HPLC-MS/MS (high performance liquid chromatography- mass spectroscopy) method for detection of Pramipexole was used(linear concentration range: 10 pg/mL to 10500 pg/mL; limit of quantitation: 10 pg/mL). The method has been sufficiently validated and the handling of samples in the studies are considered acceptable.

For study 12-370 a similar validated LC-MS/MS (liquid chromatography- mass spectroscopy) method for detection of pramipexole was used (linear concentration range: 30 pg/mL to 7500 pg/mL; limit of quantitation: 30 pg/mL). The method has been sufficiently validated.

Pharmacokinetic Variables

In the single dose studies the following parameters were evaluated:

- Area under the plasma concentration curve from administration to last observed concentration at time t: AUC_{0-t},
- Area under the plasma concentration curve extrapolated to infinite time: $AUC_{0-\infty}$,
- Maximum plasma concentration: C_{max},
- Time until Cmax is reached: t_{max},
- Elimination rate constant: $K_{el,}$ and
- Plasma concentration half-life: $t_{½\ el}$.

The primary parameters assessed were: AUC_{0-t} and $C_{max.}$

In the multiple dose study the following parameters were assessed:

- AUC_{0-t},
- C_{max},
- Minimum plasma concentration C_{min},
- Mean plasma concentration C_{avg},
- %Fluctation,
- Swing (($C_{max} – C_{min}$) /C_{min}*100), and
- tmax.

The primary parameters assessed were: AUC_{0-t}, C_{max} and $C_{min.}$

Statistical methods

In the single dose studies Latin square ANOVA was performed on the ln-transformed C_{max} and AUC_{0-t}. The ANOVA model included sequence, period and treatment as fixed effects with subject nested within sequence.

In the multiple dose study separate analyses of variance (ANOVA) were performed on the ln-transformed AUC_T, C_{min}, and C_{max} for each crossover (*Crossover 1 and Crossover 2*). The ANOVA model included group sequence, period nested within group, formulation, and formulation*group interaction as fixed effects, and subject nested within group*sequence as a random effect.

Criteria for conclusion of bioequivalence for single dose studies: The 90% confidence interval (CI) of the ratio between test and reference for AUC and C_{max} were to be inside the range 0.8-1.25.

Criteria for conclusion of bioequivalence for the multiple dose (steady state) study: The 90% CI of the ratios of LSM (*Least Square Mean*) of AUC_{0-t}, C_{max} and C_{min} of the test to reference formulation were to be within 0.8-1.25.

Results

Results from the individual studies for the primary assessment parameters are presented in the below tables:

- Study 12-365 – Single dose study with 0.52 mg pramipexole under fasting conditions

Table 2. Study 12-365 - pharmacokinetic parameters

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test product	**Reference Product**
$AUC_{(0-t)}$	15356.147 (±3702.898)	15283.731 (±3448.860)
$AUC_{(0-\infty)}$	16954.013 (±5170.551)	16580.726 (±4344.449)
Cmax	610.262 (±91.340)	591.028 (±104.417)
tmax[1]	10.000 (4.000, 20.000)	10.000 (3.000, 20.000)

[1] Median (Min, Max)

Table 3. Study 12-365 - statistical analysis (ln transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0-t)}$	100.215	95.877 - 104.748	8.944
Cmax	103.716	98.889 - 108.778	9.635

[1] Estimated from the Residual Mean Squares.

- Study 12-366 – Single dose study with 0.52 mg pramipexole under fed conditions

Table 4. Study 12-366 - pharmacokinetic parameters

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test Product	**Reference Product**
$AUC_{(0-t)}$	13349.133 (±2611.904)	13848.331 (±2378.579)
$AUC_{(0-\infty)}$	14031.109 (±2757.677)	14481.829 (±2459.539)
Cmax	636.041 (±124.325)	657.550 (±119.540)
tmax[1]	7.500 [4.000, 14.000]	7.000 [5.000, 14.000]

[1]Median (Min, Max)

Table 5. Study 12-366 - statistical analysis (ln transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0-t)}$	96.076	90.565 - 101.922	11.959
Cmax	96.560	91.953 - 101.398	9.887

[1]Estimated from the Residual Mean Squares.

- Study 12-368 – Single dose study with 0.26 mg pramipexole under fasting conditions

Table 6. Study 12-368 - pharmacokinetic parameters

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test Product	**Reference Product**
$AUC_{(0-t)}$	6585.613 (±1637.478)	6844.859 (±1758.940)
$AUC_{(0-\infty)}$	7303.406 (±1975.054)	7433.408 (±2126.869)
Cmax	262.746 (±57.652)	272.791 (±55.308)
Tmax[1]	10.000 (3.000, 16.000)	9.000 (4.000, 20.000)

[1]Median (Min, Max)

Table 7. Study 12-368 - statistical analysis (ln transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0-t)}$	96.627	87.767 - 106.380	19.105
Cmax	95.925	88.763 - 103.665	15.367

[1]Estimated from the Residual Mean Squares.

- Study 12-369 – Single dose study with 1.05 mg pramipexole under fasting conditions

Table 8. Study 12-369 - pharmacokinetic parameters

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test product	**Reference Product**
$AUC_{(0-t)}$	29500.163 (±5553.973)	30788.212 (±6488.406)
$AUC_{(0-\infty)}$	31417.939 (±5965.169)	32958.014 (±7611.419)
Cmax	1251.304 (±250.256)	1248.934 (±299.962)
Tmax[1]	10.000 (6.000, 14.000)	9.000 (3.000, 16.000)

[1] Median (Min, Max)

Table 9. Study 12-369 - statistical analysis (ln transformed values)

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Ref**	**Confidence Intervals**	**CV%[1]**
$AUC_{(0-t)}$	95.840	89.774- 102.316	12.927
Cmax	100.776	92.147- 110.213	17.762

[1] Estimated from the Residual Mean Squares.

- Study 12-370 – Multiple dose study with 1.57 and 2.1 mg pramipexole under fasting conditions

Table 10. Study 12-370 - pharmacokinetic parameters for 1.57 mg strength

Pharmacokinetic parameter		
	Test product	**Reference Product**
Geometric Mean (Geometric CV%)		
AUC_{τ} (pg·hr/mL)	57274 (13.6)	57345 (16.1)
C_{max} (pg/mL)	3099 (11.8)	2975 (16.1)
C_{min} (pg/mL)	1695 (19.3)	1706 (28.3)
C_{avg} (pg/mL)	2386 (13.6)	2389 (16.1)
Median (Min - Max)		
t_{max} (hr)	6.02 (2.05 - 16.00)	7.03 (2.00 – 16.05)
Arithmetic Mean ± SD		
Fluc (%)	58.8 ± 13.9	52.4 ± 23.6
Swing (%)	84.8 ± 26.4	83.4 ± 76.6

- Study 12-370 - pharmacokinetic parameters for 2.1 mg strength

Pharmacokinetic parameter		
	Test product	Reference Product
Geometric Mean (Geometric CV%)		
AUC_τ (pg·hr/mL)	76870 (13.7)	79715 (14.7)
C_{max} (pg/mL)	4081 (12.7)	4122 (12.9)
C_{min} (pg/mL)	2157 (25.3)	2403 (17.1)
C_{avg} (pg/mL)	3203 (13.7)	3322 (14.7)
Median (Min - Max)		
t_{max} (hr)	5.99 (3.00 – 12.99)	6.00 (2.00 – 15.98)
Arithmetic Mean ± SD		
Fluc (%)	59.2 ± 19.3	51.6 ± 14.3
Swing (%)	95.7 ± 58.9	73.7 ± 28.9

Table 11. Study 12-370 - statistical analysis for 1.57 mg strength (ln transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	90% Confidence Intervals	CV%[1]
C_{max} (pg/mL)	103.96	99.55 - 108.56	10.2
C_{min} (pg/mL)	99.29	93.39 - 105.57	14.5
AUC_τ (pg·hr/mL)	99.63	96.56 - 102.80	7.37

[1]Estimated from the Residual Mean Squares.

Table 12. Study 12-370 - statistical analysis for 2.1 mg strength (ln transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	90% Confidence Intervals	CV%[1]
C_{max} (pg/mL)	99.06	96.00 - 102.21	7.62
C_{min} (pg/mL)	90.11	84.68 - 95.88	15.2
AUC_τ (pg·hr/mL)	96.43	93.58 - 99.36	7.30

[1]Estimated from the Residual Mean Squares.

Safety data

Only minor adverse events were reported by the MAH to have been observed during the conduct of the single dose studies using 0.26 mg, 0.52 and 1.05 mg prolonged release tablets (*dizziness and headache*). In the multiple dose study performed with 1.57 mg and 2.1 mg formulations, a total of 538 mild to moderate adverse events were reported by 35 of the 36 subjects (97%) enrolled. Of these, 323 events occurred during the crossover periods and 215 events occurred during the up-titration and down-titration phases. The occurrences of adverse events were comparable across test and reference treatments for both dose levels of pramipexole.

Conclusions

For all studies, the calculated 90% confidence interval of the geometric mean ratios of test versus reference product for the primary pharmacokinetic parameters (single dose: C_{max} and

$AUC_{(0-t);}$ steady state: C_{max}, C_{min} and AUC_{0-t}) lie within the accepted range of 0.8-1.25 (80.00-125.00%). Therefore, based on the presented bioequivalence study(ies) Oprymea prolonged release tablets (0.26, 0.52, 1.05, 1.57 and 2.1 mg) is considered bioequivalent with Sifrol prolonged release tablets.

The results of multiple dose study 12-370 with 1.57 and 2.01 mg formulations can be extrapolated to the other strengths included in this application, in line with the conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6, and the Note for guidance on modified release oral and transdermal dosage forms: section II (pharmacokinetic and clinical evaluation), CPMP/EWP/280/96.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available for Oprymea prolonged release tablets. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

The CHMP considered that the 5 bioequivalence studies, submitted in support of this application, have been performed in accordance with principles of GCP and GLP and were generally designed, conducted and analysed in accordance with current EU guidelines regarding the performance of bioequivalence studies.

The bioanalytical methods used for detection of pramipexole were both developed based on literature references. Overall, the CHMP considered the applied methods as acceptable. Full and partial validations have been performed including the lower limit of quantitation. Adequate stability data were presented indicating that samples were stable at the end of the analysis period and that the results are therefore valid. The sampling time of up to 48 hours for the single dose studies was also considered acceptable to ensure measurements over 4-5 half-lives based on an elimination half-life of approximately 10-12 hours. Likewise, the collection of samples 24 hours post dose on days 14, 19 and 21 was considered acceptable for measurements of steady state pharmacokinetics.

The MAH's justification for a biowaiver, as supported by in vitro dissolution data on similarity between additional strengths applied for and the strengths investigated in bioequivalence studies, was considered acceptable by the CHMP. Hence, the CHMP considered the absence of bioequivalence studies at steady state with 0.26, 0.52, and 1.05 mg tablets acceptable.

The CHMP furthermore noted that in line with the Note for guidance on modified release oral and transdermal dosage forms: section II (pharmacokinetic and clinical evaluation), for single unit prolonged release formulations with multiple strengths a single dose study under fasting conditions is required for each strength. However, due to dose related safety concerns for the

two highest strengths (1.57 and 2.1 mg, respectively) when given to a volunteer without prior up-titration, no single dose studies were conducted with the two highest strengths.

Similarly, the Note for guidance on modified release oral and transdermal dosage forms requires that bioequivalence studies for prolonged release formulations under fed conditions, should be conducted with the same strength as those of the pivotal bioequivalence studies. However, the CHMP noted that the effect of food was only investigated in the 0.52 mg strength and that no such study was conducted for the highest strength used for single dose studies under fasting conditions. The MAH explained that the 0.52 mg strength was selected over the 1.05 mg strength due to safety concerns for the healthy volunteers. While the scientific literature only reports clinically not relevant food effects on Cmax for the reference product, a slight increase in Cmax (20%) and AUC (13%) was observed at the time of EU approval of Sifrol prolonged release tablets. The MAH judged that for pramipexole 1.05 mg prolonged-release tablets already a 25% increase in the exposure could be problematic with regards to safety.

The CHMP considered that the MAH's justification to omit certain bioequivalence studies with higher strengths of the prolonged-release formulation under fasting and fed conditions for safety reasons was acceptable. In particular, the CHMP noted that the two highest strengths were investigated in bioequivalence studies under steady state conditions and that, as for all studies conducted, the pre-set bioequivalence criteria (standard acceptance criteria) were met.

2.4.6. Conclusions on clinical aspects

Pre-set bioequivalence criteria were met for all bioequivalence studies presented in support of this application. Hence, the CHMP considered that Oprymea prolonged release tablets (0.26, 0.52, 1.05, 1.57 and 2.1 mg) was bioequivalent to the reference product Sifrol prolonged release tablets (26, 0.52, 1.05, 1.57 and 2.1 mg).

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

Based on the PRAC review of the Risk Management Plan version 1.1, the PRAC considers by consensus that the risk management system for Pramipexole (Oprymea) in the treatment of sign 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), is acceptable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 2.1 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Binge eating, compulsive shopping, pathological gambling, hypersexuality and other abnormal behaviour Dyspnoea Pneumonia Decreased appetite Diplopia
Important potential risks	Suicide-related behaviour SIADH Delirium/Mania Bronchitis Cardiac failure Retinal degeneration Skin melanoma Photopsia Fibrotic events Substance abuse/Drug dependence Response-based behaviour Hyperreflexia Dystonia Overdose Medication error (pramipexole prolonged-release tablets)
Missing information	None

The PRAC agreed.

Pharmacovigilance plans

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine pharmacovigilance was sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

There is no risk minimisation activities proposed beyond routine risk minimisation as stated in the product information (Summary of Product Characteristic and Patient Information Leaflet)

Table: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures
Binge eating, compulsive shopping, pathological gambling, hypersexuality and other abnormal behaviour	Section 4.4 of the SPC: Impulse control disorders. Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating andcompulsive eating can occur in patients treated with dopamine agonists including Oprymea. Dose reduction/tapered discontinuation should be considered if such symptoms develop. Furthermore the following information is provided in Section 4.8 of the SPC: The following adverse reactions are expected under the use of Oprymea: abnormal dreams, amnesia, behavioural symptoms of impulse control disorders and compulsions such as binge eating, compulsive shopping, hypersexuality and pathological gambling; cardiac failure, confusion, constipation, delusion, dizziness, dyskinesia, dyspnoea, fatigue, hallucinations, headache, hiccups, hyperkinesia, hyperphagia, hypotension, inappropriate antidiuretic hormone secretion, insomnia, libido disorders, nausea, paranoia, peripheral oedema, pneumonia, pruritus, rash and other hypersensitivity; restlessness, somnolence, sudden onset of sleep, syncope, visual impairment including diplopia, vision blurred and visual acuity reduced, vomiting, weight decrease including decreased appetite, weight increase. Impulse control disorders. Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Oprymea (see section 4.4). In a cross-sectional, retrospective screening and case-control study including 3,090 Parkinson's disease patients, 13.6% of all patients receiving dopaminergic or nondopaminergic 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 (≤ 65 years), not being married and self-reported family history of

Safety concern	Routine risk minimisation measures
	gambling behaviours.
Dyspnea	*Dyspnea is d*escribed as uncommon Respiratory, thoracic, and mediastinal disorders in Section 4.8 of the SPC (Undesirable effects)
Pneumonia	*Pneumonia* is described as uncommon infection in Section 4.8 of the SPC (Undesirable effects)
Decreased appetite	*Weight decrease including decreased appetite* is described as common ADR (under Investigations) in Section 4.8 of the SPC (Undesirable effects)
Diplopia	*Visual impairment including diplopia, vision blurred and visual acuity reduced* is described as common Eye disorders in Section 4.8 of the SPC (Undesirable effects)
Cardiac failure	*Cardiac failure* is described as uncommon Cardiac disorders in Section 4.8 of the SPC (Undesirable effects). Furthermore the following information is included in Section 4.8 of the SPC: Cardiac failure. In clinical studies and post-marketing experience cardiac failure has been reported in patients with pramipexole. In a pharmacoepidemiological study pramipexole use was associated with an increased risk of cardiac failure compared with non-use of pramipexole (observed risk ratio 1.86; 95% CI, 1.21-2.85).
Retinal degeneration	The following information is included in Section 5.3 of the SPC (Preclinical safety data): A carcinogenicity study showed that, 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.
Photopsia	Visual impairment including diplopia, vision blurred and visual acuity reduced is described as common Eye disorders in Section 4.8 of the SPC (Undesirable effects). Photopsia is considered as covered by this description
Overdose	Section 4.9 of the SPC (Overdose): 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.

Safety concern	Routine risk minimisation measures
Medication error (pramipexole prolongedrelease tablets)	Additional instructions on the outer carton of the prolonged-release tablets: Once daily. Swallow whole, do not chew, divide or crush. Section 4.2 of the SPC for prolonged-release tablets: Oprymea prolonged-release tablets are a once-a-day oral formulation of pramipexole. Method of administration The tablets should be swallowed whole with water, and must not be chewed, divided or crushed. The tablets may be taken either with or without food and should be taken each day at about the same time. The following information is included in Section 3 of the PIL for prolonged-release tablets (together with a pictogram): Take Oprymea prolonged-release tablets only once a day and each day at about the same time. You can take Oprymea with or without food. Swallow the tablets whole with water. Do not chew, divide or crush the prolonged release tablets. If you do, there is a danger you could overdose, because the medicine may be released into your body too quickly.

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

PSUR submission

Since the entry into force of the Pharmacovigilance legislation 2010/84/EU, the marketing authorisation holder shall refer to the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal and shall submit periodic safety update reports for this medicinal product if required.

User consultation

The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance pramipexole; the MAH's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

Five bioequivalence studies were provided in support of this application. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Oprymea prolonged release tablets met the protocol-defined criteria for bioequivalence when compared with the reference product Sifrol. The point estimates and their 90% confidence intervals of the geometric mean ratios of test versus reference product for the primary pharmacokinetic parameters (single dose: C_{max} and $AUC_{(0-t);}$ steady state: C_{max}, C_{min} and AUC_{0-t}) were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

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

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Oprymea 0.26 mg, 0.52 mg, 1.05 mg, 1.57 mg, 2.1 mg, prolonged- release tablets in the indication in adults for 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).

It is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- Periodic Safety Update Reports

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included

in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.