European Medicines Agency
Evaluation of Medicines for Human Use

Doc. Ref: EMEA/441191/2008

ASSESSMENT REPORT

FOR

OPRYMEA

International Non-proprietary Name:
Pramipexole

Procedure No: (EMEA/H/C/941)

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

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 http://www.emea.europa.eu

© European Medicines Agency, 2008. Reproduction is authorised provided the source is acknowledged

TABLE OF CONTENTS

© EMEA 2008

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Krka, d.d., Novo mesto submitted on 31 October 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Oprymea, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

The legal basis for this application refers to Article 10(1).

The chosen reference product is:

■ Reference medicinal product which is or has been authorised for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: : **Sifrol 0.088/0.18/0.35/0.7/1.1mg tablets**
- Marketing authorisation holder: **Boehringer Ingelheim International GmbH**
- First authorisation: **14-10-1997**
- Member State (EEA)/Community: **EU registration**

■ Reference medicinal product authorised in the Community/Member State where the application is made:

- Product name, strength, pharmaceutical form: **Sifrol 0.088/0.18/0.35/0.7/1.1mg tablets**
- Marketing authorisation holder: **Boehringer Ingelheim International GmbH**
- Marketing authorisation number(s):**EU 1/97/050/001-012**

■ Medicinal Product used for bioequivalence study

- Product name, strength, pharmaceutical form: **Sifrol 0.18 mg tablets**
- Marketing authorisation holder: **Boehringer Ingelheim International GmbH**
- Member State of source: **Germany**

Rapporteur :	Dr. Thirstrup
Pharmacovigilance Rapporteur :	Dr. Thirstrup

Scientific Advice:
The applicant did not seek scientific advice at the CHMP.

Licensing status:

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

© EMEA 2008

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 31 October 2007.
- The procedure started on 21 November 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 08 February 2008.
- During the meeting on 19 March 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 March 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 April 2008.
- The Rapporteur circulated the Day 150 Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 06 June 2008.
- During the meeting on 23-26 June 2008, 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 on 26 June 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 20 June 2008.

© EMEA 2008

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Oprymea 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg and 1.1 mg tablets is a generic medicinal product containing Pramipexole as pramipexole dihydrochloride monohydrate as the active substance. The reference product Sifrol 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg and 1.1 mg tablets has been centrally authorised on 14 October 1997.

Pramipexole is a synthetic amino-benzothiazole derivative. It has been shown to be a selective and specific full DA receptor agonist with high affinity and selectivity for the DA D2 receptor subfamily, and particularly the D3 receptor subtype. Furthermore, Pramipexole is a non-ergot dopamine agonist with actions similar to those of Bromocriptine. It is used similarly in the management of Parkinson's disease, alone or as an adjunct to levodopa therapy in more advanced stages of the disease. Pramipexole is administered orally as the dihydrochloride monohydrate.

The efficacy and safety of Pramipexole has been demonstrated in randomised, placebo-controlled and comparative trials in motor symptoms of Parkison's disease. A summary of these studies may be found in the EPAR of Sifrol.

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).

2.2 Quality aspects

Introduction

Oprymea is presented as tablets containing 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg, 1.1 mg of Pramipexole base (as pramipexole dihydrochloride monohydrate) as active substance. The other ingredients are mannitol, maize starch, pregelatinised starch, povidone, silica colloidal anhydrous, magnesium stearate and purified water.
The tablets are marketed in alu/alu blister packs (Al/Al foil) consisting of cold formed OPA/Al/PVC film and heat sealing aluminium foil.

Active Substance

The active substance is Pramipexole dihydrochloride monohydrate and its chemical name is (S)-2-Amino-4,5,6,7-tetrahydro-N6-propyl-2,6-benzothiazolediamine dihydrochloride monohydrate according to the IUPAC nomenclature.
Pramipexole is white to off-white powder and it is produced and commercialized in the monohydrate pseudomorph form. Pramipexole soluble in methanol, freely soluble in water, slightly soluble in ethanol 95% (v/v), practically insoluble in dichloromethane.The above-mentioned active substance has one chiral centre and is used as a single enantiomer (S).

- **Manufacture**

Pramipexole is synthesised in three reactions steps. The manufacturing process has been adequately described. Critical parameters have been identified and adequate in-process controls included. Specifications for starting materials, reagents, and solvents have been provided. Adequate control of critical steps and intermediates has been presented. The active substance is purified by recrystallisation in ethanol and the crystallised active substance is finally packed in HDPE containers lined primarily with transparent and secondary with black polythene bags.
Structure elucidation has been performed by ultraviolet spectroscopy, infrared absorption spectroscopy, ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy, and mass spectroscopy. The molecular weight was

© EMEA 2008

determined by mass spectroscopy. The proposed molecular structure was confirmed by X-ray powder diffraction.

- **Specification**

The active substance specifications include tests for identification (IR/HPLC), water (PhEur), optical rotation (PhEur), HCl content (potentiometric titration), sulphate ash (PhEur), heavy metals (PhEur), impurities (HPLC), assay, residual solvents (GC) and enantiomeric purity (HPLC).
It was verified that all specifications reflect the relevant quality attributes of the active substance. The analytical methods, which were used in the routine controls, were well described and their validations are in accordance with the relevant ICH Guidelines.
Impurities were described, classified as process related impurities and possible degradation products, and specified. Residual solvents were satisfactorily controlled in the active substance according to the relevant ICH requirements. Certificates of analyses for the active substances were provided and all batch analysis results comply with the specifications and show a good uniformity from batch to batch.

- **Stability**

The stability results from long-term accelerated and stress studies were completed according to ICH guidelines demonstrated adequate stability of the active substance. The active substance is not susceptible to degradation under the influence of light exposure. However, degradation was observed at oxidative, basic conditions and strong acidic conditions. Following some degradation studies it was concluded that the R-isomer is not a degraded impurity of the active substance. The results of the long-term and accelerated studies fulfil the proposed specification and for that reason support the proposed retest period.

Medicinal Product

- **Pharmaceutical Development**

All information regarding the choice of the active substance and the excipients are sufficiently justified.
The main aim of the applicant was to develop a medicinal product bioequivalent to the reference product (Sifrol). Therefore, several compositions of pramipexole tablets were prepared and carefully studied during the laboratory formulation studies. The selection of excipients was based not only on the reference product but also on the results from lab scale formulations.
Different technological processes such as direct tabletting, dry granulation and wet granulation were tested during the development. Taking into account the low content of the active substance in the tablet it was decided to select the wet granulation.
Based on formulation used for bioequivalence, the other strengths were developed. Dissolution profiles for all strengths are very similar and also compared to Sifrol.

- **Manufacture of the Product**

The proposed commercial manufacturing process involves standard technology using standard manufacturing processes such as mixing, blending, wet granulation and compressing.
Furthermore, the equipment used is commonly available in the pharmaceutical industry. It was demonstrated that there are no critical steps in the manufacturing process.
The batch analysis results show that the medicinal product can be manufactured reproducibly according the agreed finished product specifications.

- **Product Specification**

The medicinal product specifications were established according the ICH guidelines and include the following tests: appearance, content uniformity (Ph Eur), uniformity of mass (Ph Eur), identification (UV and HPLC), impurities (HPLC), dissolution, assay (HPLC) and microbial limits (Ph Eur).
All analytical procedures that were used for testing the medicinal product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines.

© EMEA 2008

Batch analysis data on three production scale batches of each strengths confirm satisfactory uniformity of the product at release.

- **Stability of the Product**

The stability studies were conducted according to the relevant ICH guidelines. Three pilot scale batches of each strength have been stored at long term, intermediate and accelerated conditions in the proposed market packaging.
One production batch per strength was stored for photostability at ICH conditions.
Based on the available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product. Therefore, this medicinal product should have a satisfactory and uniform performance in the clinic. Dissolution results indicate comparability with the reference product (Sifrol) and this is confirmed by in-vivo bioequivalence results (see the clinical part of the report). At the time of the CHMP opinion, there were a number of minor unresolved quality issues, which do not have an impact on the Benefit/Risk ratio of the product. The applicant gave a letter of undertaking and committed to resolve these as follow up measures following the marketing authorisation, within agreed timeframes.

2.3 Non-Clinical aspects

No further studies are required and the applicant justified why new data were not provided.
Pharmacodynamic, pharmacokinetic and toxicological properties of pramipexole dihydrochloride are well known. As pramipexole is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. The overview based on literature review is appropriate.

2.4 Clinical Aspects

Introduction

The Applicant addressed pharmacokinetic data in respect of bioequivalence studies.

GCP aspects

BE study as well as analytical testing were conducted at CRO outside EU. Both clinical and analytical sites have been inspected by an EU Member State Inspection Authority in November 2006. No critical or major findings were reported from this inspection.

Exemption
A biowaiver for the 0.088mg, 0.35mg, 0.7mg and 1.1mg strengths was sought by the applicant and justification, in accordance with section 5.4 of the Bioequivalence guideline (Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98), was provided.
This was accepted because all conditions of guideline have been fulfilled:

- the same manufacturing site and manufacturing process is used for all strengths
- pharmacokinetic is linear
- the qualitative components of different strengths are the same
- the composition of all strengths is proportional
- the dissolution profile is similar for all five strengths

Clinical studies

© EMEA 2008

To support the application, the applicant has submitted one bioequivalence study. The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study to determine whether Oprymea 0.18 mg tablet demonstrates equivalent pharmacokinetic characteristics to the Boehringer Ingelheim Ingelheim GmbH brand Sifrol 0.18 mg tablets.

Pharmacokinetics

- Methods

STUDY DESIGN

The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 7 days between the two administrations. The dose of 0.18 mg was administered in each period.

Subjects were confined to the clinical facility at least 10 hours prior to drug administration and until after the 24-hour blood draw in each period.
After a supervised overnight fast a controlled meal was served not less than 4 hours post dosing and controlled meals thereafter were served at appropriate times thereafter, during each period. Subjects were served identical meals post-dose at each period. Fluids were not permitted from 2 hours before dosing to 2 hours after dosing, but water was permitted *ad libitum* at all other times.
Subjects were beforehand informed about restrictions in intake or use of xanthine or xanthine related compounds, energy drinks, alcohol, grapefruit or pomelo products, natural food supplements, vitamins, and use of illicit drugs or any tobacco products during the study.

Blood samples were collected pre-dosing and at 0.333, 0.667, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.0, 12.0, 16.0, 20.0, 24.0 and 36.0 hours post administration of a single-dose 0.18mg tablet with 240 ml of water for the analyses of pramipexole.
The study was in compliance with GCP, as claimed by the applicant.

TEST AND REFERENCE PRODUCTS

Oprymea tablets 0.18mg by KRKA has been compared to Sifrol 0.18mg tablets by Boehringer Ingelheim pharma.

POPULATION(S) STUDIED

Twenty-four healthy (20 Caucasian, 1 Black and 3 American Hispanic) 9 male and 15 female subjects participated in the study. Nineteen subjects completed the study and data from these 19 subjects were used for pharmacokinetic and statistical evaluation.
Two subjects droped-out: one subject did not show up for confinement period 2, and the other decided to withdraw for personal reasons.
Three subjects withdrew: one due to difficulty to install catheter, one due to vomiting (before Tmax) and another one due to vomiting (before 2x Tmax).

ANALYTICAL METHODS

The blood samples were analyzed by LC-MS/MS method for detection of pramipexole.
Linear concentration range: 9.93pg/mL to 993.00pg/mL. LOQ: 9.99pg/mL.
The method has been sufficiently validated.
Due to sensitivity of pramipexole to light (UV), blood samples were processed under conditions that minimised their exposure to light.
Duration of sample storage: 49 days.
Demonstrated stability of analyte in matrix: 62 days at -20°C.

PHARMACOKINETIC VARIABLES

© EMEA 2008

Choice of primary variables and secondary PK variables:
The parameters calculated were AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, K_{el}, residual area and $t_{½}$ el.
Primary variables: AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}.

Method of assessment of pharmacokinetic parameters: SAS® (release 8.02 for Windows).

STATISTICAL METHODS

ANOVA was performed on the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.
The ANOVA model included sequence, subject nested within sequence, period and treatment.
Non-parametric test was carried out on tmax (Wilcoxon's Signed-Rank test).

Criteria for conclusion of bioequivalence:
Formulations were considered bioequivalent if the calculated 90% CI for the C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ parameters fell within the 80-125% limits.

- Results

The bioequivalence results for pramipexole of the test and reference product are shown in the Table 1 and 2 below.

Table 1. Pharmacokinetic parameters

Parameters	**Oprymea 0.18 mg tablets (A)**			**Sifrol 0.18 mg tablets (pramipexole) (B)**		
	Mean	**SD**	**CV (%)**	**Mean**	**SD**	**CV (%)**
AUC_{0-t} (pg/ml/h)	6304.12	1175.43	18.65	6164.38	1041.96	16.90
$AUC_{0-\infty}$ (pg/ml/h)	6737.07	1288.58	19.13	6605.78	1132.09	17.14
C_{max} (pg/ml)	463.42	73.28	15.81	463.31	74.93	16.17
Residual area (%)	6.33	2.55	40.19	6.61	2.18	32.91
t_{max} (h)	2.86	1.15	40.25	2.39	0.82	34.41
t_{max*} (h)	2.67	1.34	-	2.33	0.67	-
K_{el} (h^{-1})	0.0786	0.0128	16.30	0.0784	0.0098	12.46
$K_{1/2\ el}$ (h)	9.06	1.59	17.51	8.97	1.11	12.38
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours, calculated by the linear trapezoidal method **C_{max}** maximum plasma concentration **T_{max}** time for maximum concentration **$T_{1/2}$** half-life **K_{el}** elimination rate constant						

**Medians and interquartile ranges are presented*

Table 2. Pramipexole 0.18 mg tablets (A) *vs* Sifrol 0.18 mg tablets (pramipexole) (B)

	$AUC_{0-\tau}$ **pg/ml/h**	**$AUC_{0-\infty}$** **pg/ml/h**	**C_{max}** **pg/ml**

© EMEA 2008

Ratio [1]	101.99%	101.72%	99.84%
90% Geometric C.I. [2]	98.47% to 105.65%	98.15% to 105.42%	94.60% to 105.37%
Intra-Subject CV	6.24%	6.32%	9.56%

[1] *Calculated using least-squares means according to the formula:* $e^{(Pramipexole\ 0.18\ mg\ tablets\ (A)\ -\ Sifrol®\ 0.18\ mg\ tablets\ (B)}\ X\ 100$

[2] *90% Geometric Confidence Interval using ln-transformed data*

Safety evaluation:
A total of 62 post-dose adverse events were reported by 21 of the 24 subjects who received at least 1 dose of the study medication. Twenty-six Adverse Events (AEs) were reported from subjects having received treatment A (test: Oprymea) and 36 AEs were reported from subjects having received treatment B (reference: Sifrol). Twenty-eight AEs were graded as mild, 28 were graded as moderate and 3 were graded as severe (two cases presented vomiting and one syncope).
No serious adverse events occurred during the study. The most commonly reported adverse event was 'somnolence' which was reported by 50% of all subjects.

- Conclusions

Based on the presented bioequivalence study Oprymea 0.18 mg tablet is considered bioequivalent with Sifrol 0.18 mg tablet.

Pharmacodynamics

No pharmacodynamic studies were performed.

Additional data

Dissolution studies:
Comparative dissolution data have been generated for the test and reference products using the following dissolution method:
Apparatus: II (paddle), 500ml 0.1N HCl, 50 rpm with HPLC/UV-263nm detection.
More than 80% are dissoluted after 5 minutes in this media and also in media at higher pH. All strengths show the same fast dissolution.

The composition of the batch used for BE studies is identical to the applied product.

Discussion on Clinical aspects

Based on the presented bioequivalence study Oprymea 0.18 mg tablet is considered bioequivalent with Sifrol 0.18 mg tablet. A biowaiver for not testing the 0.088mg, 0.35mg, 0.7mg and 1.1mg strengths was accepted, in accordance with section 5.4 of the Bioequivalence guideline (Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98).

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

© EMEA 2008

2.5 Pharmacovigilance

- **PSUR**

The PSUR submission schedule for Oprymea should follow PSURs submission schedule for the reference medicinal product.

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system has deficiencies that should be addressed as part of the follow up measures.

- **Risk Management Plan**

A Risk Management Plan has not been submitted. Since the application concerns a generic of reference medicinal product for which no safety concerns requiring additional risk minimization activities have been identified, a Risk Management Plan is not required.

- **User consultation**

The Package leaflet with a few minor exceptions has been harmonised with the originator PL.

2.6 Overall conclusions, benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

The application contains adequate quality, non clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.

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.

Recommendation

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).
Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Oprymea in the above mentioned indication was favourable and therefore recommended the granting of the marketing authorisation.

© EMEA 2008