European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

Pramipexole Teva

International Nonproprietary Name: pramipexole

Procedure No. EMEA/H/C/000940

Assessment Report as adopted by the CHMP 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 84 16
E-mail: 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 Teva Pharma B.V. submitted on 22 October 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Pramipexole Teva, 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 mg, 0.18 mg, 0.35 mg and 0.7 mg 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 mg, 0.18 mg, 0.35 mg and 0.7 mg tablets**
- Marketing authorisation holder: **Boehringer Ingelheim International GmbH**
- Marketing authorisation number(s): **EU 1/97/050/001-006 and EU 1/97/050/011-012**

■ 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**

The Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur :	Dr. Tomas Salmonson
Pharmacovigilance Rapporteur :	Dr. Steffen 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.

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 22 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 25 March 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 July 2008.
- The summary report of the inspection carried out at the clinical site, and analytical, pharmacokinetics, statistical and report issuing site was issued on 08 April 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 05 September 2008.
- During the CHMP meeting on 22 to 25 September 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- During the meeting on 20 to 23 October 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 Pramipexole Teva on 23 October 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 22 October 2008

2 SCIENTIFIC DISCUSSION

2.1 Introduction

The medicinal product Pramipexole Teva is presented as tablets containing pramipexole dihydrochloride monohydrate. Pramipexole Teva tablets are available in the strengths 0.088 mg, 0.18 mg, 0.35 mg and 0.7 mg. The active ingredient is present in crystalline form.
Other ingredients include mannitol, microcrystalline cellulose, sodium starch glycolate, povidone, colloidal silicon dioxide, sodium stearyl fumarate and magnesium stearate.
The tablets are packaged in aluminium blister packs, the 90 tablets pack-size are packaged in High density polyethylene bottles with a child resistant polypropylene cap.

2.2 Quality aspects

Active Substance

The chemical name for pramipexole dihydrochloride monohydrate is (S)-2-amino-4,5,6,7-tetrahydro-6-(propylamino) benzothiazole dihydrochloride monohydrate. It is a white to off-white, crystalline powder soluble in methanol. The active substance has no polymorph forms.

The chemical structure of the active substance has been confirmed using analytical data by elemental analysis, IR absorption spectroscopy, UV absorption spectroscopy, ^{1}H NMR spectroscopy, mass spectrometry and optical isomerism. All data are consistent with the proposed structure.

- Manufacture

The active substance is manufactured by a one step process followed by a purification step. Detailed information about the manufacturing, validation and analytical controls of the active substance has been supplied in the form of an active substance master file (ASMF). The starting materials have been adequately characterized and the manufacturing process has adequately been validated.
All relevant impurities have been appropriately discussed and characterized. The levels of the impurities are considered acceptable and appropriate specifications have been set.
Information on stability studies conducted for pramipexole dihydrochloride monohydrate is provided.
Batches are stored for up to 18 months in long term stability condition, and up to 6 months in accelerated stability condition. The stability data support the proposed retest period.

- Specification

The active substance specifications include appropriate tests for appearance, identifications (UV and IR spectra, test for chlorides), organic impurities (HPLC), assay (titration), enantiomeric purity, sulphated ash, specific optical rotation, residual solvents, heavy metals and water content.
The impurity limits are acceptable and there is no concern in relation with safety or efficacy.
The batch analysis data support the proposed acceptance limits.

- Stability

Stability studies have been performed in accordance with the ICH requirements.
Long-term and accelerated stability studies have been conducted at 30ºC/65% RH during 66 months and at 40ºC/75% RH during 6 months. The test parameters evaluated in these studies were description, identity by IR, water content, specific optical rotation, enantiomeric purity by HPLC, chromatographic purity by HPLC and assay. The stability data provided justify the proposed retest period without special storage conditions.

Medicinal Product

- Pharmaceutical Development

The aim of the pharmaceutical development was to obtain an immediate-release tablet containing qualitatively and quantitatively the same active substance as the reference product already on the market Sifrol, and exhibiting the same bioavailability.

The formulation composition was based on the qualitative composition of the innovator product with minor changes in the excipients. All excipients are commonly used in the pharmaceutical industry.

- Adventitious Agents

None of the materials used in the manufacture of the medicinal product is of animal and/or human origin.

- Manufacture of the Product

Pramipexole Teva is manufactured by means of a wet granulation process, followed by drying of the wet granules, mixing with excipients and tabletting. The manufacturing process is regarded as a non-complex method.
The excipients used in the formulation comply with the monographs of the current Ph.Eur. Certificates of analysis for all excipients are provided.
All critical process parameters have been identified and controlled by appropriate in-process controls. The manufacturing process demonstrates to be reproducible and provides a finished product that complies with the finished product specifications.

- Product Specification

Appropriate medicinal product specifications have been set. The specifications for the finished product at release and shelf life are classical for this pharmaceutical form and include tests for appearance, identification and assay of the active substance, uniformity of dosage units, dissolution, degradants, water content, hardness, and microbial contamination. All tests included in the specification have been satisfactorily described and validated, according to the state of the art.
Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled. The specifications for dissolution, uniformity of dosage units and microbial contamination comply with the requirements of the Ph. Eur. for tablets.
Batch analysis data show that the proposed specifications are met.

- Stability of the Product

Long term (18 months at 25°C/60% RH) and accelerated stability (6 months at 40°C/75% RH) studies have been carried out according to the ICH requirements on at least two batches of each of the four strengths.
The parameters tested and analytical methods used were identical to those used for the release specifications. In all cases the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Pramipexole Teva is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorisation. There are no major deviations from EU and ICH requirements.

The Pramipexole Teva tablets intended for marketing are well suited; the manufacturing process is under control and ensures both batch to batch reproducibility and compliance with standard procedures and specifications; the analytical methods have been validated and seem to be suitable to ensure consistent quality of the active substance and the finished product, the synthetic pathway is presented and the structure and impurity profile are well characterised and in line with current ICH guidelines. The stability data on the active substance supports the proposed re-testing period.
The stability data of the finished product in the proposed packages support the shelf life stated in the SPC.
At the time of the CHMP opinion there were some unresolved minor quality issues which had no impact on the benefit/risk profile. The applicant committed in a letter of undertaking to provide the necessary information as follow up measures within an agreed timeframe.

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.
No ERA was submitted. Pramipexole Teva is unlikely to result in any significant increase in the combined sales volumes for all pramipexole containing products.
The non-clinical overview based on literature review is, thus, appropriate.

2.4 Clinical aspects

Introduction

The Rapporteur's assessment addressed pharmacokinetic data in respect of bioequivalence studies. One study (study 2007-1412) was submitted to support this indication.

GCP aspects

The bioequivalence study is stated to have been performed in accordance with GCP. The laboratory performing the clinical and analytical parts of the bioequivalence study has been inspected several times and has been found satisfactory. In connection with the examination of Pramipexole Teva, the CHMP asked for an inspection to be carried out of the conduct of the clinical study 2007-1412, in accordance with Article 57 of Council Regulation (EC) No 726/2004.
No critical or major deviations were found during the inspection. Based on these findings it was concluded that the study was in compliance with GCP.

Exemption

The applicant submitted only one comparative bio-availability study with 0.25 mg tablets to determine whether Pramipexole TEVA 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg Tablets to be licensed by TEVA Pharma B.V. demonstrate equivalent pharmacokinetic characteristics to the Boehringer Ingelheim International GmbH Sifrol 0.088 mg, 0.18 mg, 0.35 mg and 0.7 mg Tablets. However, the applicant

adequately justified the lack of the bioequivalence studies for the other strengths according to the requirements of the Guideline CPMP/EWP/QWP/1401/98 section 5.4.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study (study 2007-1412). The objective of this study was to evaluate the comparative bioavailability between Pramipexole TEVA 0.25 mg Tablets and Sifrol 0.18 mg Tablets, Boehringer Ingelheim International GmbH, after a single-dose in healthy subjects under fasting conditions.

Since this is a generic application, no further clinical studies were required and the applicant provided none. The clinical overview provided an adequate summary of the clinical data of pramipexole. It consisted of an overview of the published literature regarding clinical pharmacodynamics, pharmacokinetics, and efficacy and safety aspects of orally administered pramipexole hydrochloride.

Pharmacokinetics

- Methods

The applicant has submitted one bioequivalence study. The clinical part of the study was performed at Pharma Medica Research Inc. Toronto, Ontario, Canada. The bioanalysis, statistic and pharmacokinetic analyses were performed at Pharma Medica Research Inc., Ontario, Canada.

STUDY DESIGN

In study 2007-1412, the pharmacokinetics of pramipexole was investigated after a 0.25 mg single dose under fasting conditions in 24 healthy male and female healthy volunteers. Pramipexole was administered with 240 mL of room temperature potable water. Zofran (Ondansetron Hydrochloride) 8 mg was administered with 180 mL of room temperature potable water, approximately 1 hour prior to the administration of pramipexole. Blood samples were collected prior to drug administration and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30 and 36 hours after dosing in pre-chilled Vacutainers containing K2EDTA as anticoagulant. There was a 1-week washout between treatments.

TEST AND REFERENCE PRODUCTS

Pramipexole Dihydrochloride 0.25 mg Tablets, (Novopharm Limited, Canada).
Sifrol 0.18 mg Tablets (0.25 mg pramipexole dihydrochloride monohydrate containing 0.18 mg pramipexole), (Boehringer Ingelheim International GmbH, Germany).

POPULATION(S) STUDIED

The study population included non-smoking, male and female volunteers between 18-55 years of age with a BMI between 19 and 30 (inclusive), who were judged to be healthy based on a medical examination.
Of the 24 subjects who were included in the data analysis, 13 were caucasian, 8 were black, 2 were asian and 1 was hispanic. Thirteen (13) were female and 11 were male.

ANALYTICAL METHODS

Pramipexole was analysed in plasma by liquid-liquid extraction followed by reversed phase LC-MS/MS.
Data on long-term storage stability was missing in both the within-study and pre-study analytical report. The longest period for sample storage was fifty (50) days (June 07, 2007 – July 27, 2007). This period was stated to be covered by a long term stability program; however the CHMP asked the applicant to submit the long-term stability data supporting stability during long-term storage of samples.
Data on storage stability was submitted by the applicant and showed that Pramipexole was stable in EDTA treated plasma for at least 139 days at -20ºC.
The CHMP considered the issue resolved, as the storage stability data covered the storage period of the BE study.

PHARMACOKINETIC VARIABLES

The parameters calculated were AUC_{0-t}, $AUC_{0-\infty,}$ C_{max}, T_{max}, K_{el}, T_{half}.

STATISTICAL METHODS

Descriptive statistics were calculated by treatment for the estimated pharmacokinetic parameters. Analysis of Variance (ANOVA) was also carried out on the natural log-transformed AUC_t, AUC_{inf}, Cmax, and untransformed K_el and t1/2 data. Values for the T_{max} parameter were analyzed by a nonparametric approach. Based on the log-transformed parameters, the following criteria were used to evaluate the bioequivalence between the test and reference products:
The 90% confidence intervals of the relative mean AUC_t, AUC_{inf} and C_{max} of the test to reference products should be between 80% and 125%.

- Results

All 24 participants completed the study.

Note that Test Product (A) was Pramipexole Dihydrochloride 0.25 mg Tablets (Novopharm Limited, Canada), and Reference Product (B) was Sifrol 0.18 mg Tablets (0.25 mg pramipexole dihydrochloride monohydrate containing 0.18 mg pramipexole) (Boehringer Ingelheim International GmbH, Germany).

The results are presented in Table 1 below.

Table 1 Main pharmacokinetic parameters and their 90% confidence intervals

Parameters	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
	Treatment A	Treatment B			
AUC_{0-t} (ng*h/mL)	9.7463 9.8452 (14)	9.3579 9.4683 (16)	104.15	99.51 - 109.01	9
$AUC_{0-\infty}$ (ng*h/mL)	10.4613 10.5598 (14)	10.0698 10.1930 (16)	103.89	99.20 - 108.80	9
C_{max} (ng/mL)	0.8607 0.9138 (38)	0.8139 0.8492 (33)	105.74	97.68 - 114.47	16
T_{max} (h)[a]	2.43 (35)	2.53 (34)	-	-	-
K_el (1/h)[a]	0.0786 (18)	0.0785 (18)	-	-	-
T_{half} (h)[a]	9.09 (1 8)	9.13 (19)	-	-	-

[a]Presented as arithmetic mean (CV%) only

A statistically significant difference (p=0.05) was detected between the two periods of the study in the analysis of K_el (p=0.0105) and T_{hal}f (p=0.0091) parameters. The least-squares means of the formulation effect were adjusted for the period effect therefore the final results are not influenced by the statistically significant period effect noticed for K_el and half-life parameters.

Safety evaluation:

There were 60 adverse events (AEs) involving 24 subjects in the study.
A summary of the AEs by severity and relation to the drug and necessity for treatment is presented in the table below.

	Severity			Relation to the Drug				Intervention	
Treatment Group	Mild	Mod	Severe	Unrelated	Unlikely	Possible	Probable	Required Drug Therapy	Required Non-Drug Therapy
A	28	0	0	7	4	17	0	0	2
B	31	1	0	5	2	25	0	0	1
Total	**59**	**1**	**0**	**12**	**6**	**42**	**0**	**0**	**3**

No serious AEs were reported during the conduct of this study.
None of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results.

Treatment A
There were 28 Adverse Events associated with Treatment A, which consisted of:
• Creatine increase (8)
• Headache (4)
• Somnolence (4)
• Leukocytosis (3)
• Urin abnormalities (3)
• Diarrhea (2)
• Edema peripheral (1)
• Hypertension (1)
• Pain Abdominal (1)
• GGTP increase (1)

Treatment B
There were 32 Adverse Events associated with Treatment B, which consisted of:
• Creatinine increase (8)
• Somnolence (7)
• Headache (5)
• Urine abnormalities (3)
• Diarrhea (3)
• Eosinophilia (1)
• Hypertension (1)
• Tachycardia (1)
• Pain (1)
• Asthenia (1**)**
• Fever (1)

- Conclusions

Bioequivalence has been shown between the generic product and the reference innovative product..

Pharmacodynamics

No pharmacodynamic studies were conducted by the applicant.

Discussion on Clinical aspects

The efficacy, safety and clinical pharmacology of the active ingredient pramipexole dihydrochloride monohydrate are already well established and documented for the original medicinal product Sifrol. The submitted bioequivalence study is designed and reported in accordance with the relevant EU note for guidance. The data of this study sufficiently demonstrate that the tested formulation intended for marketing is bioequivalent to the innovator product. The bioequivalence demonstrated for tablets of the strength 0.25 mg may be extrapolated also to strengths 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg. The validity of the BE data was confirmed following the positive outcome of a GCP inspection conducted at the clinical and analytical sites.

Post marketing experience

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

2.5 Pharmacovigilance

- **PSURs**

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

- **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 applicant justified that for this generic product with well-known safety profile it is not necessary to establish a risk management plan containing other measures than routine pharmacovigilance.

- **User consultation**

The package leaflet of Pramipexole Teva has passed a user consultation test. The package leaflet with a few minor exceptions has been harmonised with the reference medicinal product PL.

2.6 Overall conclusions, risk/benefit assessment and recommendation

The application contains adequate quality, non clinical and 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

Pramipexole Teva 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 data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Pramipexole Teva in the above mentioned indication was favourable and therefore recommended the granting of the marketing authorisation.