



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

London, 21 July 2011
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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pramipexole Accord

International nonproprietary name: pramipexole

Procedure No.: EMEA/H/C/2291

Note

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



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List of Abbreviations

alu – aluminium

ASMF – Active Substance Master File

AUC_{0-t} - area under the plasma concentration versus time curve from time zero to the last measurable concentration

AUC_{0-∞} - area under the plasma concentration versus time curve

BE – Bioequivalence

BMI - Body Mass Index

CHMP - Committee for Medicinal Products for Human Use

C_{max} - Maximum measured plasma concentration

¹³C-NMR – Carbon-13 Nuclear Magnetic Resonance

DA – Dopamine

EDTA - Ethylenediaminetetraacetic acid

EMA – European Medicines Agency

ERA - Environmental Risk Assessment

FT-IR – Fourier Transform InfraRed

GC – Gas Chromatography

GCP – Good Clinical Practice

¹H-NMR – Proton (also Hydrogen-1) Nuclear Magnetic Resonance

HPLC – High Performance Liquid Chromatography

ICH – International Conference on Harmonisation

LOD - Limit of detection

LOQ - Limit of quantitation

MAH – Marketing Authorisation Holder

mg – milligram

MS – Mass Spectroscopy

Ph Eur - European Pharmacopoeia

PK - Pharmacokinetics

pKa – Acid dissociation constant (also acidity constant)

PD - Parkinson's disease

PSUR – Periodic Safety Update Report

RH – Relative Humidity

RLS – Restless Legs Syndrome

RMP – Risk Management Plan

SmPC – Summary of Product Characteristics

$t_{1/2}$ - elimination or terminal half-life

T_{max} - time of maximum measured plasma concentration

UV – Ultraviolet

Medicinal product no longer authorised

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Ltd submitted on 1 November 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Pramipexole Accord 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg and 1.1 mg tablets, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004 – 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 February 2010.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Pramipexole Accord 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).

Pramipexole Accord is indicated in adults for symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in doses up to 0.54 mg of base (0.75 mg of salt).

The legal basis for this application refers to the Article 10(1) of Directive 2001/83/EC.

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

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
 - Product name, strength, pharmaceutical form: **Mirapexin 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg, 1.1 mg tablets**
 - Marketing authorisation holder: **Boehringer Ingelheim International GmbH**
 - Date of authorisation: **23-02-1998**
 - Marketing authorisation granted by:
 - **Community**
 - Community Marketing authorisation number: **EU/1/97/051/001-012**
- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
 - Product name, strength, pharmaceutical form: **Mirapexin 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg, 1.1 mg tablets**
 - Marketing authorisation holder: **Boehringer Ingelheim International GmbH**
 - Date of authorisation: **23-02-1998**
 - Marketing authorisation granted by:

– **Community**

- Community Marketing authorisation number: **EU/1/97/051/001-012**

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: **Mirapexin 0.18 mg tablets**
- Marketing authorisation holder: **Boehringer Ingelheim International GmbH**
- Date of authorisation: **23-02-1998**
- Marketing authorisation granted by:
 - **Community**
 - Community Marketing authorisation numbers: **EU/1/97/051/003-004**
- Bioavailability study number: **245-07**

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. Manufacturers

Manufacturer responsible for batch release

Accord Healthcare Ltd.

Sage House

319 Pinner road

North Harrow, Middx HA1 4HF

United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Eva Skovlund

- The application was received by the EMA on 1 November 2010.
- The procedure started on 17 November 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 February 2011.
- During the meeting on 14-17 March 2011, 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 18 March 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 April 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 June 2011.
- During the CHMP meeting on 20-23 June 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 27 June 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the outstanding issues to all CHMP members on 7 July 2011.
- During the meeting on 18-21 July 2011, 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 Accord on 21 July 2011.

2. Scientific discussion

2.1. Introduction

Pramipexole Accord 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg, 1.1 mg tablets is a generic medicinal product containing pramipexole, in form of the dihydrochloride monohydrate salt, as the active substance. Pramipexole is administered orally.

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. Pramipexole is a non-ergot dopamine agonist with actions similar to those of bromocriptine. 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. Pramipexole is also indicated in adults for symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in doses up to 0.54 mg of base (0.75 mg of salt).

The efficacy and safety of pramipexole has been demonstrated in randomised, placebo-controlled and comparative trials. A summary of these studies may be found in the EPAR for Mirapexin.

The indication of Pramipexole Accord is the same as authorised for the reference medicinal product Mirapexin. Mirapexin 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). Mirapexin is also indicated in adults for symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in doses up to 0.54 mg of base (0.75 mg of salt).

Parkinson's disease (PD) is a neurodegenerative disorder characterised by bradykinesia, rigidity, postural imbalance and tremor. The incidence of PD increases with age and on average, 2 to 3 % of the population in the western world will develop PD. The cause of the disease is still unknown. PD develops due to loss of neuronal functions within the basal ganglia and the substantia nigra of the brain. More specifically, there is a marked deficiency in the nigrostriatal dopamine (DA) system due to degeneration of nigral DA neurons. Thus, restoration of the dopaminergic transmission forms the central strategy for the treatment of PD.

Restless Legs Syndrome (RLS) is a neurological sensory-motor disorder characterised by four essential diagnostic criteria defined by the International Restless Legs Syndrome Study Group (IRLSSG) in 1995 and updated in 2003, with an estimated prevalence in the general population of 2.5% to 15%. Dopamine agonists, including pramipexole, were regarded as first line treatment in 'Principles and Practice of Sleep Medicine'.

Mirapexin was authorised through the centralised procedure and therefore the qualitative and quantitative composition of the active substance [pramipexole in form of the dihydrochloride monohydrate salt] and the excipients [mannitol, maize starch, anhydrous colloidal silica, povidone, magnesium stearate] is identical in all Member States. The formulation of Pramipexole Accord tablets differs namely by the inclusion of microcrystalline cellulose which is not present in the reference medicinal product.

The bioequivalence has been studied only with the 0.18 mg strength and for other strengths a biowaiver was claimed.

2.2. Quality aspects

2.2.1. Introduction

Pramipexole Accord is presented as tablets containing pramipexole, in form of the dihydrochloride monohydrate salt, as the active substance. Tablets contain 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg or 1.1 mg of pramipexole which is an equivalent of respectively 0.125 mg, 0.25 mg, 0.5 mg, 1.0 mg and 1.5 mg of the salt.

The tablets are white to off-white, round, flat faced, bevel edged and differentiated by presence of a breakline and appropriate bossing:

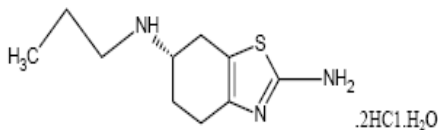
- 0.088 mg tablets: inscription 'I1' on one side and are plain on the other side
- 0.18 mg tablets: inscription 'I' and '2' on either side of the breakline on one side and breakline on the other side
- 0.35 mg tablets: inscription 'I' and '3' on either side of the breakline on one side and breakline on the other side
- 0.7 mg tablets: inscription 'I' and '4' on either side of the breakline on one side and breakline on the other side
- 1.1 mg tablets: inscription 'I' and '5' on either side of the breakline on one side and breakline on the other side

Excipients used in the preparation of Pramipexole Accord tablets are well known excipients such as mannitol, maize starch, anhydrous colloidal silica, povidone, magnesium stearate and microcrystalline cellulose.

Pramipexole Accord tablets are packed in aluminium (alu/alu) blisters.

2.2.2. Active Substance

Pramipexole dihydrochloride monohydrate, the active substance, is chemically designated as (6S)-6-N-propyl-4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine dihydrochloride monohydrate, and has the following structure:



Pramipexole dihydrochloride monohydrate is a white or almost white crystalline powder. It is freely soluble in water, soluble in methanol, slightly soluble in ethanol (96%) and practically insoluble in methylene chloride. Its pKa is 7.2 and pH is 2.8 to 3.4. The molecule has one chiral center and exhibits isomerism. In the manufacture of Pramipexole Accord tables, the same as for the reference medicinal product, the S-enantiomer is used.

Manufacture

Information about manufacturing process has been provided using the Active Substance Master File (ASMF) procedure. The active substance is synthesised in a two step synthesis followed by the salt formation and purification step. Detailed description of the manufacturing process was provided.

Critical parameters and accompanying in-process controls, to ensure quality of the final compound, have been defined and are controlled.

Confirmation of the chemical structure of pramipexole dihydrochloride monohydrate was provided by elemental analysis (confirmation of the determined elementary composition), spectroscopic methods as UV, FT-IR, ¹H-NMR, ¹³C-NMR and MS (mass spectra). Also the physicochemical characteristics such as polymorphism, solubility, pKa and pH have been investigated. Polymorphism was studied using the X-ray diffraction.

Pramipexole dihydrochloride monohydrate was analyzed using the Ph Eur HPLC method to identify all potential impurities. Impurities have been well characterised in relation to their origin and potential carry-over into the final drug substance. Chemical names, structure, limit of detection (LOD) and limit of quantitation (LOQ) along with their limits in the release specifications have been described. Other impurities which were observed at minor concentrations are also controlled at a level of 0.10% under Maximum Single Unknown Impurities and Total Impurities at a level of 0.50%. As the below mentioned impurities are specified in the Ph Eur monograph, the structural elucidation for the same has not been provided.

Specification

The active substance specification includes tests for appearance, solubility, appearance of solution, identification (IR), specific optical rotation, presence of chlorides, pH, related substances (HPLC), enantiomeric purity (HPLC), heavy metals, water content, sulphated ash, assay (potentiometric titration), bioburden, residual solvents (GC), HCl content and particle size distribution (laser diffraction). The specification generally complies with the Ph Eur monograph for pramipexole with additional in-house tests for which suitable validation data are provided.

A detailed description for all analytical methods was provided. Most of the methods are Ph Eur apart from particle size, HCl content and residual solvents. Full method validation data was provided for the non compendial (in-house) analytical methods.

In general analytical methods proposed are suitable to control the quality of the drug substance.

Data on four batches of the active substance, used in the manufacture of the product used for validation, bioequivalence (BE) and stability study have been presented. Results for all these batches were provided by both the active substance and the finished product manufacturers. In addition results for three recently manufactured batches were provided.

Certificates of analyses for the active substance were provided and all batch analysis results comply with the specifications and show a good uniformity from batch to batch.

Stability

Stability studies were performed for the first three validation batches in accordance with the ICH requirements under the following conditions: 40°C ± 2°C/75 ± 5% RH (accelerated), 30 ± 2°C/65% ± 5% RH (intermediate) and 25 ± 2°C/60% ± 5% RH (long term - real time). Data obtained cover period of 5 years at long-term conditions and 6 months at accelerated conditions.

Forced degradation studies showed that pramipexole dihydrochloride monohydrate is stable under exposure to elevated temperatures (heat), humidity (including in the dissolved state) and light. The results were also within specifications after exposure to acid or alkaline conditions. Under oxidative conditions an unknown impurity was observed.

Results obtained from the stability studies demonstrated adequate stability of the active substance and confirmed the proposed re-test period.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim of the pharmaceutical development was to obtain immediate release tablets, containing quantitatively and qualitatively the same active substance as the reference medicinal product, and to be bioequivalent.

Similarity with Mirapexin tablets was addressed by way of composition comparisons, dissolution studies, solubility studies and comparative impurity profiles.

Compositions of Pramipexole Accord tablets and the reference medicinal product are similar. The formulation of Pramipexole Accord tablets contain the same excipients as Mirapexin, and differ only by the presence of microcrystalline cellulose which is not used in the reference medicinal product.

Similarity between Pramipexole Accord and the reference product was also shown by dissolution testing. Comparative dissolution profiles of Pramipexole Accord 0.18 mg tablets and reference product Mirapexin 0.18 mg tablets, and Pramipexole Accord 0.18 mg tablets and other strengths of Pramipexole Accord tablets, in three different media: 0,1 M HCl, acetate buffer pH 4,5 and phosphate buffer pH 6,8 have been conducted. The dissolution profiles of the test product and the reference product were considered similar in all three media.

An impurity comparison of Pramipexole Accord and the reference product was undertaken. Results showed no degradation to occur as a result of the manufacturing process as the impurity profile for the generic product was similar to that of the product.

The application concerns five strengths however the bioequivalence was demonstrated between Pramipexole Accord 0.18 mg tablets and Mirapexin 0.18 mg tablets, and a biowaiver for the 0.088 mg, 0.35 mg, 0.7 mg and 1.1 mg strengths was claimed. The biowaiver could be applied since:

- other strengths are manufactured by the same manufacturer and process,
- the drug input has been shown to be linear over the therapeutic dose range,
- the qualitative composition of the strengths is the same; the amount of the active substance is less than 5 % of the tablet weight and amounts of different excipients are the same for all the concerned strengths and only the amount of active substance is changed.
- the ratio between amounts of active substance and excipients is the same,
- dissolution profiles of the additional strengths and the strength used in the bioequivalence study were similar under identical conditions

The reference product is presented as uncoated tablets therefore Pramipexole Accord was also developed as uncoated tablets.

Different formulations were prepared and studied during the development program. A formulation optimisation study was performed regarding the effects of the concentration of excipients. The selection of excipients was based not only on the reference product but also on the results from laboratory scale formulations. The final formulation was chosen based on the results from these studies.

Different technological processes such as direct tableting and wet granulation were tested during the development. Direct compression was selected as the final manufacturing process.

Adventitious agents

None of the excipients used in the drug product are of animal origin. Magnesium stearate used in the formulation is of vegetal origin.

Manufacture of the product

The proposed manufacturing process is dry, direct-compression. This standard manufacturing process has been sufficiently characterised and includes weighing, sieving, mixing by co-sifting procedure and compressing as steps during manufacture. A flow diagram and detailed description of the manufacturing process have been provided. The critical steps and in-process controls have been identified. Process validation has been carried out on three consecutive batches for all strengths of Pramipexole Accord. The batch analysis results show that the medicinal product can be manufactured reproducibly according to the agreed finished product specifications.

Product Specification

The product specification is standard for tablets and contains tests with suitable limits for appearance (description), average weight of tablets, identification (HPLC and UV), disintegration time, friability, resistance to crushing, water content by loss on drying, dissolution, uniformity of dosage units (by content uniformity), related substances (HPLC), assay (HPLC), subdivision of tablets and microbial limits.

Full details of all analytical methods have been provided. All non pharmacopoeial methods have been satisfactorily validated. The HPLC methods used for assay, dissolution, content uniformity and related substances have been validated in accordance with ICH requirements. As part of method validation, stress studies (UV light, heat, water/acid/base hydrolysis and oxidation) were performed to provide an indication of the stability-indicating properties and specificity of the HPLC method.

Batch analysis data was provided on three production scale batches of each strength. Batches met the proposed specification limits. Results showed that tablets can be manufactured reproducibly according to the finished product specifications.

Stability of the product

Stability studies were carried out under ICH conditions of 25°C/60% RH (long term), 30°C/65% RH (intermediate) and 40°C/75% RH (accelerated) on three production scale batches each of Pramipexole Accord tablets.

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

In summary the stability data provided support the proposed shelf-life and storage conditions.

2.2.4. Discussion on chemical and pharmaceutical aspects

Information about the active substance, pramipexole dihydrochloride monohydrate, has been provided using the Active Substance Master File Procedure. The chemical-pharmaceutical documentation was of acceptable quality.

The active substance has been satisfactorily characterized and the synthesis is well controlled. Pramipexole dihydrochloride monohydrate is highly soluble and highly permeable, therefore was classified as BCS class 1 active substance. Known and potential impurities have been satisfactorily

addressed. The control tests and specifications for the active substance are in line with the ICH and Ph Eur and are considered satisfactory. A retest period was supported by satisfactory stability studies that show that the active substance is stable in solid form.

The finished product is an immediate release tablet containing 0.088 mg, 0.18 mg, 0.35 mg, 0.7 mg or 1.1 mg of pramipexole in form of the dihydrochloride monohydrate salt. The composition of the finished product has been described, and all excipients have been fully characterised.

The applicant has demonstrated that Pramipexole Accord is bioequivalent to the reference product Mirapexin. The development pharmaceuticals has been satisfactorily described and the formulation is considered satisfactorily justified. The method of manufacture is considered standard and has been satisfactorily described. Process validation has been carried out on three consecutive batches for all strengths of Pramipexole Accord. The batch analysis results show that the product can be manufactured reproducibly according to the agreed finished product specifications.

The scope of the finished product specification complies with ICH Q6A and the Ph Eur requirements for tablets, limits comply with regulatory requirements and are in line with batch data. The analytical methods and validation data are satisfactory.

The stability program is considered satisfactory. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The results of tests carried out indicate that physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

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.

2.3.2. Ecotoxicity/environmental risk assessment

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

2.3.3. Conclusion on the non-clinical aspects

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

2.4. Clinical Aspects

2.4.1. Introduction

This is an application for tablets containing pramipexole dihydrochloride monohydrate. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment *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

This application concerns 5 strengths of pramipexole dihydrochloride monohydrate; 0.125 mg (=0.088 mg pramipexole), 0.25 mg (=0.18 mg pramipexole), 0.5 mg (=0.35 mg pramipexole), 1.0 mg (=0.7 mg pramipexole) and 1.5 mg (=1.1 mg pramipexole) but bioequivalence has been studied with the 0.25 mg strength only. The applicant has applied for a biowaiver for the tablet strengths of 0.125 mg, 0.5 mg, 1.0 mg and 1.5 mg.

According to the *Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**)*, there are general biowaiver criteria that should be fulfilled. For the current application, all of the conditions of the requirements in the Bioequivalence guideline for a biowaiver are considered fulfilled for all strengths. In conclusion, the CHMP considered a biowaiver for the additional strengths acceptable.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study performed with the 0.25 mg (=0.18 mg pramipexole base) strength. Since this is a generic application, no further clinical studies are required and the applicant provides none.

2.4.2. Pharmacokinetics

Methods

Study design

Project no. 245-07 was an open-label, balanced, randomised, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study in healthy male subjects under fasting conditions.

Either a single dose of 0.25 mg (0.18 mg pramipexole base) of Pramipexole dihydrochloride tablets or Mirapexin 0.18 mg tablets was administered to each subject with 240 ml of water following an overnight fast of at least 10 hours. Dinner was served approximately 10 hours before dosing. Four hours after dosing snacks and meals were provided to the subjects at appropriate times.

Blood sampling was performed pre-dose and at 0.5, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.50, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 20, 24, 48 and 72 hours following the drug administration in each period. The wash out period was 7 days.

The study was performed at Lambda Therapeutic Research Ltd, Navi Mumbai, Maharashtra, India. The bioanalysis facility was located in India. A statement of GCP compliance from the study centre was submitted.

Test and reference products

Pramipexole dihydrochloride 0.25 mg tablets (0.18 mg pramipexole base) manufactured by Intas Pharmaceuticals Limited, India (Batch No. L01436, exp. date 01/2012) has been compared to Mirapexin 0.18 mg tablets manufactured by Boehringer Ingelheim Pharma GmbH & Co. KG, Germany (Batch No: 905343, exp. date 06/2012).

Population studied

Healthy, non smoking, Indian, male, adult volunteers aged between 18-55 years (mean age 26 years), having a Body Mass Index (BMI) between 18.5-24.9 kg/m² (mean BMI 22 kg/m²) and having given their voluntary written informed consent, were enrolled in the study. They did not have any significant diseases or clinically significant abnormal findings in any of the screening procedures carried out. Volunteers who complied with all the inclusion and none of the exclusion criteria were enrolled into the study. No female subjects were included in the trial. According to the applicant, the subject population for the bioequivalence study was selected with the aim to minimize variability and permit detection of differences between pharmaceutical products, and therefore the study was performed with healthy males only.

The subjects were not allowed to take any medicine within 14 days prior to dosing. Subjects had to abstain from consumption of grapefruits or its products within a period of 48 hours prior to dosing. In addition the subjects had to abstain from any xanthine containing food or beverages (like chocolate, tea, coffee or cola drinks), tobacco and tobacco containing products for 24 hours prior to dosing and throughout the stay in the clinical facility. Alcohol and alcoholic products, cigarettes and recreational drugs were not allowed until the last PK sample was taken.

A total of 30 subjects were checked-in for the study. Of these, 28 subjects were randomised to treatment. Two subjects were extra subjects and they were not dosed.

A total of 28 subjects were dosed in period I and 25 subjects completed the study.

3 subjects did not report for period II check-in due to personal reasons. They were considered to be discontinued from the study on their own accord. These subjects were therefore not included in the efficacy analysis.

Protocol deviations:

Samples were not collected within ± 02 minutes of scheduled time for 4 subjects in period I and for 2 subjects in period II (these two were also two of the four in period I). The deviation varied from 7 to 260 minutes. The time points concerned were at 48 hours (2 subjects) and at 72 hours (4 subjects). The reason for the deviations was late arrival of the subjects. Actual time points were used for the pharmacokinetic and statistical evaluations.

Ambulatory samples were not collected for 3 subjects (at time point 72 hours) in period I (one of these subjects were later excluded from the study because he did not show up for period II) and for 1 subject (at time point 48 hours) in period II. The reason for these missing samples was that the subjects did not show up. Missing samples were denoted as "M" in the statistical analysis.

One subject in period I did not refrain from drinking water till 2 hours after dosing. He was given ice cubes to suck to treat his adverse event (nausea).

Two subjects in period I did not follow the posture restriction deviation (to be in sitting or ambulatory posture for 3 hours post dose). They were allowed to lie down due to adverse events (nausea and dizziness).

The CHMP considered that the choice of population was acceptable, and that the protocol deviations most probably did not affect the study results.

Analytical methods

Plasma samples (containing K_2EDTA as anticoagulant) obtained in the bioequivalence study were analysed for pramipexole by a validated LC/MS/MS analytical method as per in house procedures.

Sample analysis was conducted at Lambda Therapeutic Research Ltd., India to determine the plasma concentration of pramipexole in the study sample. The long-term freezer stability for pramipexole has been established for 589 days at $-65^{\circ}C + 10^{\circ}C$ and covers the study sample storage period of twenty six (26) days.

A total of 1147 plasma samples were analysed. In total 25 samples (2.2%) were reanalysed due to the following reasons: 11 were repeated due to unidentified processing error, 7 were repeated due to significant variation in response of internal standard, 6 were repeated due to low calibration curve standard was eliminated, 1 was repeated due to anomalous concentration.

Pharmacokinetic Variables

Primary Parameters:

- Maximum measured plasma concentration (C_{max})
- The area under the plasma concentration versus time curve from time zero to the last measurable concentration (AUC_{0-t})
- The area under the plasma concentration versus time curve from time zero to infinity ($AUC_{0-\infty}$)

Secondary Parameters:

- Time of maximum measured plasma concentration (T_{max})
- First order rate constant associated with the terminal (log -linear) portion of the curve (λ_z)

- The elimination or terminal half-life ($t_{1/2}$)
- % of residual area (AUC_% Extrap_obs)

The pharmacokinetic parameters were calculated by non-compartmental model using WinNonlin Professional Software Version-5.0.1 (Pharsight Corporation, USA).

Statistical comparison of the pharmacokinetic parameters of the two formulations was carried out using PROC MIXED of SAS® Release 9.1.3 (SAS Institute Inc., USA) to assess the bioequivalence of both the formulations.

The CHMP considered that the choice of the primary pharmacokinetic variables and non-compartmental method was acceptable.

Statistical methods

Dataset for the estimation of pharmacokinetic parameters was prepared using WinNonlin Professional Software (Version 5.0.1) for pramipexole. Estimation of pharmacokinetic parameters was also carried out using the same software. Descriptive statistics of the pharmacokinetic parameters were calculated and reported for pramipexole.

Statistical analysis was performed on the data obtained by assaying the pramipexole content in plasma samples using SAS® Release 9.1.3 (SAS Institute Inc., USA). The comparison of the pharmacokinetic parameters was carried out using PROC MIXED of SAS® Release 9.1.3 (SAS Institute Inc., USA).

Analysis of variance was carried out by employing PROC MIXED of SAS® Release 9.1.3 (SAS Institute Inc., USA) for un-transformed and In-transformed pharmacokinetic parameters C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for pramipexole.

ANOVA model included Sequence, Formulation and Period as fixed effects and Subject (Sequence) as a random effect. Sequence effect was tested using Subject (Sequence) as error term. An F-test was performed to determine the statistical significance of the effects involved in the model at a significance level of 5% ($\alpha=0.05$). Two one-sided tests for bioequivalence and 90% confidence intervals for the ratio of the least squares means between the test and reference formulations were calculated for untransformed and In-transformed data of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for pramipexole. The power of test to detect 20% difference between test and reference formulations was computed and reported for un-transformed and In-transformed pharmacokinetic parameters C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for pramipexole. Ratio of least squares means of test and reference formulation was computed for untransformed and In-transformed pharmacokinetic parameters C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ of pramipexole.

Ratio analysis was reported for un-transformed and In-transformed pharmacokinetic parameters C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for pramipexole.

To be considered bioequivalent, the 90% confidence intervals of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ had to fall within an acceptance range of 80-125%.

The CHMP considered that the statistics had been adequately described and the methods were considered acceptable.

Results

The pharmacokinetic parameters for the test and reference products are shown in Table 1.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} median, range)

Treatment	AUC _{0-t} xg/ml/h	AUC _{0-∞} xg/ml/h	C _{max} xg/ml	t _{max} h	T _{1/2} h
Test	5590.67 \pm 97 6.88	6257.81 \pm 11 63.60	519.00 \pm 84.43	2.50 (1.00- 5.00)	7.072 \pm 1.20
Reference	5627.68 \pm 91 5.05	6283.40 \pm 10 57.73	525.88 \pm 94.41	2.25 (1.50- 6.00)	7.031 \pm 0.84
*Ratio (90% CI)	99.4 (97.16- 101.74)	99.5 (97.32- 101.77)	98.9 (95.19- 102.86)	-	-
CV (%)	4.7 %	4.6 %	7.9 %	-	-
AUC _{0-∞} 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 C _{max} maximum plasma concentration T _{max} time for maximum concentration T _{1/2} half-life					

*In-transformed values

The CHMP concluded that bioequivalence between the test and reference product has been appropriately shown. The 90% confidence intervals for the ln-transformed C_{max}, AUC_{0-t} and AUC_{0-∞} were within the acceptance range of 80-125%. The randomization scheme was considered appropriate.

AUC_{0-t} derived from the measurements was covering 80% or more of the AUC_{0-∞} for all the subjects included, demonstrating that the 72 hours sampling time was sufficient to estimate the bioavailability of pramipexole.

No pre-dose levels of pramipexole were detected in any subjects, showing that the wash-out period was long enough to avoid any carry-over effects.

According to the applicant, formulation, sequence and period effects for ln-transformed data for C_{max} and AUC_{0-∞} were found to be statistically insignificant. For AUC_{0-t} the formulation and sequence effects for the ln-transformed data were also statistically insignificant, however the period effect was statistically significant (p=0.0247). The MAH provided an acceptable explanation for this finding and the issue was considered to be resolved.

For the sampling points 48 and 72 hours, all plasma samples for all subjects were below limit of quantification. For one subject the plasma sample was below limit of quantification for the sample point 24 hours. No samples were above the limit of quantification.

Safety data

There were no deaths, serious or significant adverse events. Two subjects reported a total of two adverse events during the course of the study. Both adverse events (nausea and dizziness) were reported after receiving the reference product. They were considered possibly related to the administered medicinal product, mild in nature and both resolved. No adverse events were reported for the test product.

Upon conclusion of the clinical portion of the study, the results from all subjects, who completed post-study procedures including laboratory tests and vital signs measurements confirmed the absence of significant changes in the subjects' state of health.

Conclusions

Based on the presented bioequivalence study Pramipexole Accord is considered bioequivalent with Mirapexin.

The results of Study Project no. 245-07 with the 0.18 mg formulation can be extrapolated to the other applied strengths (0.088 mg, 0.35 mg, 0.7 mg and 1.1 mg), according to conditions in Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**).

2.4.3. Pharmacodynamics

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

2.4.4. Additional data

Not applicable.

2.4.5. Post marketing experience

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

2.4.6. Discussion on Clinical aspects

The CHMP assessment addressed pharmacokinetic data for a single bioequivalence study (Project no. 245-07). One single dose bioequivalence study is considered acceptable as the product is an immediate release formulation. The CHMP considered the design of the study to be acceptable. The sampling period of 72 hours is considered sufficient, and the wash-out period of 7 days is long enough to avoid any carry-over effect to the second period. The CHMP considered the analytical method used in the bioequivalence study to be acceptable. The study was conducted in line with GCP. The CHMP considered that bioequivalence between the test and reference product has been appropriately shown. The 90% confidence intervals for the ln-transformed C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were within the acceptance range of 80-125%.

2.4.7. Conclusions on clinical aspects

Based on the presented bioequivalence study, Pramipexole Accord 0.18 mg tablet is considered bioequivalent with Mirapexin 0.18 mg tablet.

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 did not require the applicant to submit a Risk Management Plan (RMP) because in general, it is accepted that RMPs are not required for generic products unless a safety concern requiring additional risk minimisation activities has been identified for the reference medicinal product. There is an RMP in place for Mirapexin, but there are no additional risk minimisation activities implemented except routine

activities in the form of information in the SmPC/PIL and labelling. The applicant has included in the proposed SmPC the information specified in the RMP of the reference product. At the request of the CHMP, the applicant has included also the changes resulting from variation application EMEA/H/C/xxxx/WS/0041/G which concerned an update of section 4.8 and other sections of the SmPC for the reference product. The CHMP considered the updated SmPC to be acceptable.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

2.6. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Mirapexin. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

This application concerns a generic version of pramipexole dihydrochloride monohydrate tablets. The reference product Mirapexin is indicated for the treatment of idiopathic Parkinson's disease and for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome. No nonclinical studies have been provided for this generic application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. 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; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with an open-label, randomised, two-treatment, two-period, two-sequence, single oral dose, crossover design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective EU requirements. The choice of dose, sampling points, overall sampling times as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Pramipexole Accord met the protocol-defined criteria for bioequivalence when compared with Mirapexin tablets. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

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.

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 Pramipexole Accord in the treatment of Parkinson's disease and moderate to severe idiopathic Restless Legs Syndrome is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management System

Not applicable

PSUR cycle

The PSUR cycle for the product will follow PSURs submission schedule for the reference medicinal product.

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

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.