25 June 2015
EMA/CHMP/282380/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pregabalin Accord

International non-proprietary name: pregabalin

Procedure No. EMEA/H/C/004024/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

An agency of the European Union

Table of contents

List of abbreviations

AE	Adverse Event(s)
Alu	Aluminium
AR	Assessment Report
ASMF	Active Substance Master File
AUC	Area under the plasma concentration versus time curve
BE	Bioequivalence
Ca^{2+}	Calcium ion
CEP	Certificate of Suitability
CoA	Certificate of Analysis
CL_{cr}	Creatinine clearance
C_{max}	Maximum measured concentration of drug in plasma
CNS	Central Nervous System
CHMP	Committee for Medicinal Products for Human Use
CTD	Common Technical Document
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GABA	Gamma-aminobutyric acid
GAD	Generalized Anxiety Disorder
GC	Gas Chromatography
HDPE	High Density Polyethylene
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonisation
IR	Infrared
KF	Karl Fisher (titration)
L	Liters
LLOQ	Lower Limit of Quantification
LoD	Limit of Detection
LoQ	Limit of Quantitation
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
µg	Microgram
mg	Milligram
NMT	Not More Than
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PL	Package Leaflet
ppm	Parts per million
PVC	Polyvinyl Chloride
PVdC	Polyvinylidene Chloride
PPCP	Polypropylene Copolymer
QC	Quality Control
QWP	Quality Working Party

RH	Relative Humidity
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
$t_{1/2}$	Elimination half life
TSE	Transmissible Spongiform Encephalopathy
UV	Ultraviolet
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Limited submitted on 31 July 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Pregabalin Accord, 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 22 May 2014.

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:

Treatment of
- adjunctive therapy in adults with partial seizures with or without secondary generalisation.
- the treatment of Generalised Anxiety Disorder (GAD) in adults.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

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

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:

Lyrica 25 mg hard capsules
Lyrica 50 mg hard capsules
Lyrica 75 mg hard capsules
Lyrica 100 mg hard capsules
Lyrica 150 mg hard capsules
Lyrica 200 mg hard capsules
Lyrica 225 mg hard capsules
Lyrica 300 mg hard capsules

Marketing authorisation holder: Pfizer Limited

- Date of authorisation: 06/07/2004
- Marketing authorisation granted by:
  - Community

  - Community Marketing authorisation numbers:
    For 25mg - EU/1/04/279/001-005, EU/1/04/279/026 & EU/1/04/279/036
    For 50mg - EU/1/04/279/006-010 & EU/1/04/279/037
    For 50mg - EU/1/04/279/011-013, EU/1/04/279/027, EU/1/04/279/030 & EU/1/04/279/038
    For 100mg - EU/1/04/279/014-016 & EU/1/04/279/039

For 150mg - EU/1/04/279/017-019, EU/1/04/279/028, EU/1/04/279/031 & EU/1/04/279/040
For 200mg - EU/1/04/279/020-021 & EU/1/04/279/041
For 225mg - EU/1/04/279/033-035 & EU/1/04/279/042
For 300mg - EU/1/04/279/023-025, EU/1/04/279/029, EU/1/04/279/032 & EU/1/04/279/043

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

Product name, strength, pharmaceutical form:
Lyrica 25 mg hard capsules
Lyrica 50 mg hard capsules
Lyrica 75 mg hard capsules
Lyrica 100 mg hard capsules
Lyrica 150 mg hard capsules
Lyrica 200 mg hard capsules
Lyrica 225 mg hard capsules
Lyrica 300 mg hard capsules

- Marketing authorisation holder: Pfizer Limited
- Date of authorisation: 06/07/2004
- Marketing authorisation granted by:
  - Community

- Community Marketing authorisation numbers:
For 25mg - EU/1/04/279/001-005, EU/1/04/279/026 & EU/1/04/279/036
For 50mg - EU/1/04/279/006-010 & EU/1/04/279/037
For 50mg - EU/1/04/279/011-013, EU/1/04/279/027, EU/1/04/279/030 & EU/1/04/279/038
For 100mg - EU/1/04/279/014-016 & EU/1/04/279/039
For 150mg - EU/1/04/279/017-019, EU/1/04/279/028, EU/1/04/279/031 & EU/1/04/279/040
For 200mg - EU/1/04/279/020-021 & EU/1/04/279/041
For 225mg - EU/1/04/279/033-035 & EU/1/04/279/042
For 300mg - EU/1/04/279/023-025, EU/1/04/279/029, EU/1/04/279/032 & EU/1/04/279/043

■ 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: Lyrica 50 mg hard capsules & Lyrica 300 mg hard capsules
- Marketing authorisation holder: Pfizer Limited
- Date of authorisation: 06/07/2004
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation numbers:

    For 50mg: EU/1/04/279/006-010 & EU/1/04/279/037

    For 300mg: EU/1/04/279/023-025, EU/1/04/279/029, EU/1/04/279/032 & EU/1/04/279/043

- Bioavailability study numbers: 169-12 (For 50mg)
  170-12 (For 300mg)

Information on paediatric requirements

Not applicable

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

Manufacturers responsible for batch release

Accord Healthcare Ltd
Ground Floor
Sage House
319 Pinner Road
North Harrow, Middlesex
HA1 4HF
United Kingdom

WESSLING Hungary Kft.
Fóti út 56.
Budapest
H-1047
Hungary

1.3. Steps taken for the assessment of the product

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

Rapporteur: Outi Mäki-Ikola

- The application was received by the EMA on 31 July 2014.
- The procedure started on 20 August 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 November 2014.
- During the meeting on 18 December 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 10 March 2015.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 23 April 2015.
- During the CHMP meeting on 21 May 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 22 May

2015.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 16 June 2015.
- During the meeting on 25 June 2015, 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 Pregabalin Accord.

2. Scientific discussion

2.1. Introduction

Pregabalin Accord is a generic medicinal product of Lyrica, which has been authorised in the EU since 6 July 2004.

The active substance of Pregabalin Accord is pregabalin, an analogue of the neurotransmitter gamma-aminobutyric acid (GABA). Pregabalin decreases central neuronal excitability by binding to an auxiliary subunit (α2-δ protein) of a voltage-gated calcium channel on neurons in the central nervous system. Pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P.

The safety and efficacy profile of pregabalin has been demonstrated in several clinical trials, details of which can be found in the EPAR for Lyrica. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this product. Since this application is a generic application referring to the reference medicinal product Lyrica, summary of the clinical data of pregabalin is available and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted.

Pregabalin Accord hard capsules have the same qualitative and quantitative composition, in terms of active substance, and the same pharmaceutical form as the reference product Lyrica. Bioequivalence of the 50 mg dose with the reference 50 mg Lyrica capsule and 300mg dose with the reference 300mg Lyrica capsule was demonstrated clinically. For the remaining doses, CHMP has accepted a biowaiver.

The indication proposed for Pregabalin Accord is a subset of indication authorized for the reference medicinal product, namely treatment of

- adjunctive therapy in adults with partial seizures with or without secondary generalisation.

- the treatment of Generalised Anxiety Disorder (GAD) in adults.

The proposed pack sizes are consistent with the dosage regimen and duration of use.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg of pregabalin as active substance.

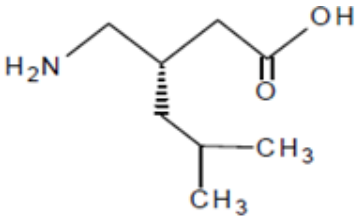
Other ingredients are: pregelatinized starch, talc (E553b), gelatin (capsule shell), titanium dioxide (E171) (capsule shell), red iron oxide (E172) (75, 100, 200, 225 and 300 mg strengths capsule shell), sodium laurilsulfate (capsule shell). The printing ink composition is shellac, iron oxide black (E172), propylene glycol and potassium hydroxide.

The product is available in PVC/alu blister, in PVC/alu perforated unit dose blisters and in HDPE bottles.

2.2.2. Active substance

General information

The chemical name of Pregabalin is (*S*)-3-(Aminomethyl)-5-methylhexanoic acid and has the following structure:



The structure has been confirmed by the following methods: element analysis, IR, UV, ^{1}H-NMR, ^{13}C-NMR, MS and X-ray diffraction.

The active substance is a white to off-white crystalline powder, not hygroscopic, sparingly soluble in water, and practically insoluble in acetone.

Pregabalin exhibits stereoisomerism due to the presence of one chiral centre. Enantiomeric purity is controlled routinely by HPLC. Pregabalin shows polymorphism. According to the literature survey conducted by the applicant, pregabalin can exist in different polymorphic forms: amorphous, hemihydrate form, Form I, II, III & IV and alpha form. The polymorphic forms "amorphous", "hemihydrate", "Form I, II & III (formed by octanol & acetone)" are not possible to be formed under the manufacturing process conditions followed by the active substance manufacturer. The absence/non carryover of α-form in the active substance was demonstrated. DSC & XRD values cited in literature & actual experimental results for form IV are identical to the form manufactured by the active substance supplier (named Form-I by the active substance manufacturer). Batch analysis data provided confirmed that the active substance manufacturer consistently produces this form. In addition, polymorphism is controlled by a XRD identification test in the active substance specifications.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture, characterisation and process controls

The active substance is sourced from one supplier using three manufacturing sites including two sites involved in the manufacture of intermediates.

Pregabalin is synthesized in six main chemical reactions using commercially available well defined starting materials with acceptable specifications. Enantiomeric purity is controlled by the process and by chiral HPLC.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Specification

The active substance specification includes tests for: description, solubility (Ph. Eur.), identification (IR, HPLC, XRD), specific optical rotation (Ph. Eur.), assay (HPLC), related substances (HPLC), enantomeric purity (HPLC), residual solvents (GC), water content (KF), sulfated ash (Ph. Eur.), heavy metals (Ph. Eur.), appearance of solution (Ph. Eur.), particle size (laser diffraction), microbiological examination (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data of seven production scale active substance batches are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data were provided on five production scale batches of active substance from the proposed supplier, stored in the container closure system intended for the market, for up to 18 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines.

The following parameters were tested: description, identification by IR and XRD, specific optical rotation, water content, appearance of solution, related substances, enantiomeric purity, assay and microbial limit. The analytical methods used were the same as for release and were stability indicating.

No significant changes occurred in the parameters studied.

Photostability testing following the ICH guideline Q1B was performed on one batch. The substance was found to be photostable.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the retest period proposed by the ASMF holder.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

The aim was to formulate pregabalin capsules, which are robust, stable, bioequivalent and dose proportional to the reference product Lyrica. The applicant followed the reference product line: 25 mg and 50 mg capsules

are dose proportional with respect to each other, and the 75-225 mg strengths are dose proportional with respect to 300 mg capsules.

Formulation development was initiated by characterisation of the reference product (including disintegration time, assay, related substances content and dissolution).

Excipients similar to reference product Lyrica were chosen but maize starch was replaced by pre-gelatinised starch for easier capsule filling, and lactose monohydrate and anhydrous silica (colloidal) were not used. Active substance /excipients compatibility studies were performed and no incompatibility issues were identified. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The lubricant concentration was optimized based on the results from studies assessing impact of the quantity of lubricant (purified talc) on the dissolution profile.

Studies were performed to demonstrate that the polymorphic form of active substance remains unaffected during manufacturing process and upon storage in the proposed packaging.

The similarity of the developed product with the reference product was assessed by comparison of dissolution and impurity profiles and by bioequivalence (BE) studies.

Two bioequivalence studies were performed with the 50 mg and 300mg strengths showing bioequivalence between of the proposed finished product and the reference medicinal product Lyrica . A bio-waiver was requested for the 25 mg strength based on the result from BE-study with 50 mg capsules, and a biowaiver was also requested for the 75 mg, 100 mg, 150 mg, 200 mg and 225 mg strengths based on the results from BE-study with 300 mg capsules. All the conditions for biowaiver for additional product strengths as stated in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) fulfilled. Comparative dissolution profile of Pregabalin Accord 25 mg capsules with the 50 mg capsules and Pregabalin Accord 75 mg, 100 mg, 150 mg, 200 mg and 225 mg capsules with the 300 mg capsules was performed. Conditions and methods of the dissolution studies are in accordance with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98). Results of the BE study using the 50 mg capsules can be extrapolated to the 25 mg strength, and results of the BE study using the 300 mg capsules can be extrapolated to the 75 mg, 100 mg, 150 mg, 200 mg, and 225 mg strengths.

The development of the dissolution method is described and the discriminatory power has been demonstrated.

The impurity profiles of both generic and reference products in all strengths are similar.

As part of manufacturing process development, the parameters blending time and lubrication time of common blend were optimized, effect of particle size on blend and content uniformity was studied and no significant impact was observed, holding time of intermediate was validated.

The primary packaging is PVC/alu blisters, PVC/alu perforated unit dose blisters and HDPE bottles. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: sifting/milling, blending, encapsulation and packing. The process is considered to be a standard manufacturing process.

In-process controls are: description, loss on drying, assay and blend uniformity of common blend; and for single strength capsules: description, average net content of capsule, average weight of 20 filled capsules, uniformity of weight, disintegration time , lock length. In-process control during packing is leak-test. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Major steps of the manufacturing process have been validated by a number of studies on three batches (smaller production batch size) of each strength.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

The manufacturing process will be validated according to the presented process validation scheme on three consecutive production batches of each strength.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form : description, average net content, identification of active substance (HPLC, chemical reaction), identification of colorants (chemical reaction), loss on drying (Ph. Eur.), dissolution test, uniformity of dosage units (Ph. Eur.), related substances (HPLC), assay (HPLC), microbial enumeration tests (Ph. Eur.), *Escherichia coli* (Ph. Eur.).

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

The in house analytical procedures are described and validated.

Batch analysis results are provided for three batches (smaller production batch size) of each strength. Batch analysis results confirmed the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data were provided on two smaller production scale batches of finished product of each strength stored for up to 18 months under long term conditions at 25 ºC / 60%, and for up to 6 months under accelerated conditions at 40 ºC / 75% RH, according to the ICH guidelines. The stability batches are identical to those proposed for marketing and were packed in PVC-alu blister, HDPE bottle proposed for marketing, and in a PPCP container intended for bulk storage and transportation. Bracketing is applied for the HDPE container size (30 and 500 capsules container studied).

Samples were tested according to release specifications except for the limits for total impurities and loss on drying (wider limit at shelf life). Matrixing is applied to microbiological quality control. The analytical procedures used are the same as for release and are stability indicating.

In addition, one batch of 25mg strength and one batch of 300mg strength were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Results showed that the finished product is not light sensitive.

A thermal cycling study has been carried out one batch of 25mg strength and one batch of 300mg strength to study the effect of transportation on stability of the finished product. Batches were subjected to three cycles of two days at accelerated conditions followed by refrigerated temperature (- 10 º C to -20 ºC). Although a significant increase was observed for loss on drying on the lower strength, all the results for both strengths were within the specification limits..

An in-use stability study was performed on one batch of 25mg strength and one batch of 300mg strength packaged in HDPE bottle (100's count). The product was maintained at 25 ± 2°C and 60 ± 5% RH throughout the study. In-use stability study results are found satisfactory for both strengths for the duration covered (50 days and 100 days).

Based on available stability data, the shelf-life is 2 years with no special storage condition. The in-use shelf-lives after first opening are 30 days (for HDPE 30's count) and 100 days (for HDPE 200's count). These shelf-lives are acceptable and included in the SmPC.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture are provided.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give assurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

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

considered acceptable.

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

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Pregabalin Accord manufactured by Accord Healthcare Ltd is considered unlikely to result in any significant increase in the combined sales volumes for all pregabalin containing products and the exposure of the environment to the active substance. Thus, the environmental risk is expected to be similar and not increased. The CHMP endorsed this view.

2.3.3. Discussion on non-clinical aspects

NA

2.3.4. Conclusion on the non-clinical aspects

The non-clinical overview presented by the applicant is largely based on published scientific literature which is acceptable since pregabalin is a well-known active substance.

There are no objections to the approval of Pregabalin Accord from a non-clinical point of view. The SmPC of Pregabalin Accord is in line with that of the reference product Lyrica and is therefore acceptable.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for hard capsules containing pregabalin. To support the marketing authorisation application the applicant conducted 2 bioequivalence studies with cross-over design under fasting conditions. These studies were pivotal for the assessment.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of pregabalin based on published literature. The SmPC is in line with the SmPC of the reference product.

No scientific advice by the CHMP was given for this medicinal product. For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/Corr**) 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

According to the Guideline on the Investigation of Bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), if the pharmacokinetic of the active substance is linear and that the bioequivalence is demonstrated for one strength, in vivo bioequivalence studies for the other strengths could be waived. An exemption from the requirement to perform bioequivalence studies would be justified when the following conditions are met: the pharmaceutical products have the same manufacturer, same qualitative composition, same ratio between active substance and excipients and in vitro dissolution profile comparable to the reference product.

The composition of the strengths 25 and 50 mg of the test product is quantitatively proportional. Further, the composition of the strengths 75, 100, 150, 200, 225 and 300 mg of the test product is quantitatively proportional. Therefore, two single-dose bioequivalence studies have been conducted with the highest strength of both composition groups, i.e. with 50 and 300 mg hard gelatine capsules.

A biowaiver has been applied for the 25 mg strength based on the results of the BE study with the 50 mg strength and for 75 mg, 100 mg, 150 mg, 200 mg and 225 mg strengths based on the results of the BE study with the 300 mg strength. The applicant provided a tabular listing of the composition of the respective strengths and their dissolution curves at pH 1.2, 4.5 and 6.8. More than 85% of the drug was dissolved within 15 minutes at all pH values tested.

Based on these results, the CHMP concluded that the general biowaiver criteria were met. Therefore, two bioequivalence studies with the 50 mg and the 300mg doses and a biowaiver for the additional strengths were considered adequate.

Clinical studies

To support the application, the applicant has submitted 2 bioequivalence studies, one with the 50 mg strength (Study 169-12) and one with the highest 300 mg strength (Study 170-12).

Table 1. Tabular overview of clinical studies

Study Number	Study Title	Number of subjects
169-12	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of two products of Pregabalin Capsules 50 mg in normal, healthy, adult, human male subjects under fasting condition	28
170-12	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of two products of Pregabalin Capsules 300 mg in normal, healthy, adult, human male subjects under fasting condition	28

2.4.2. Pharmacokinetics

Methods

Study design

Study 169-12

Study 169-12 was an open-label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single dose, bioequivalence study conducted in healthy, adult subjects under fasting conditions. A washout period of 5 days was maintained between each treatment schedule.

Blood samples were collected pre-dose (time 0.000) and at 0.167, 0.333, 0.500, 0.667, 0.833, 1.000, 1.250, 1.500, 1.750, 2.000, 2.500, 3.000, 4.000, 5.000, 6.000, 8.000, 12.000, 16.000, 24.000, 36.000 and 48.000 hours post dose in each period.

Study 170-12

Study 170-12 was an open-label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single dose, bioequivalence study conducted in healthy, adult subjects under fasting conditions. A washout period of 4 days was maintained between each treatment schedule.

Blood samples were collected in accordance with the same schedule as in study 169-12. .

Test and reference products

Study 169-12

Pregabalin Accord 50 mg manufactured by Intas Pharmaceuticals Ltd (batch No. P06474; exp. date 03/2015) has been compared to Lyrica 50 mg, manufactured by Pfizer Manufacturing Deutschland GmbH (Batch No: 0790012 U; exp. date 12/2014).

Study 170-12

Pregabalin Accord 300 mg manufactured by Intas Pharmaceuticals Ltd (batch No. P06481; exp. date 03/2015) has been compared to Lyrica 300 mg manufactured by Pfizer Manufacturing Deutschland GmbH (Batch No: 0488032 U; exp. date 02/2015).

Population studied

Study 169-12 and Study 170-12

The maximum within-subject variability in primary PK parameters was estimated to be ~17 % for C_{max}. Using assumptions test/reference ratio 91.00-109.00 %, significance level 5 %, power ≥ 80 % and BE limits 80.00-125.00 %, a crossover study with minimum 28 dosed subjects was considered to be sufficient, allowing for potential dropouts and withdrawals.

The study subjects were healthy volunteers. Demographic data, medical history, general physical examination including vital signs measurements, ECG, chest X-ray, haematology, biochemistry, serology as well as urine analysis were collected in the screening phase. Standard inclusion and exclusion criteria were used.

Study 169-12

28 subjects were dosed and all of them completed the study.

Study 170-12

28 subjects were dosed in Period I of the trial. Three subjects were withdrawn from the study on medical grounds in Period I. In addition, one subject discontinued from the study on his own accord in Period II.

A total of 24 subjects completed the study and these data were used for PK and statistical analyses. The collected samples of the four withdrawn/discontinued subjects were also analysed as per protocol.

Analytical methods

Study 169-12 and Study 170-12

Plasma concentrations of pregabalin were analysed by validated LC-MS/MS technique using solid phase extraction method. Pregabalin-d4 was used as an internal standard and human blank plasma containing K2EDTA was used as an anticoagulant.

Pre-study validation

The calibration range for pregabalin concentrations was from 20.195 ng/ml to 2503.690 ng/ml in study 169-12 and 50.477 ng/ml to 15059.121 ng/ml in study 170-12. The limit of detection for pregabalin was 5.293 ng/ml in study 169-12 and 15.310 ng/ml in study 170-12.

The method was validated for selectivity, selectivity in presence of co-administered drugs, verification of interfering potential by co-administered drugs, ion suppression through infusion, linearity and goodness of fit, sensitivity, limit of detection, precision and accuracy, haemolysis effect, robustness, recovery, dilution integrity, partial volume verification, matrix effect, matrix factor, re-injection reproducibility, stability (short term, long term, auto sampler, freeze and thaw, bench top, wet and dry extract bench top, evaporation, dry extract, verification of drug stability in blood, reagent stability, mobile phase stability, long term stability in matrix), system performance and carry-over/ contamination check.

169-12

Bioanalysis of samples

The total number of plasma samples collected for determination of pregabalin concentrations was 1232 (28 subjects, 22 samples/subject, two periods). 10 % of the samples (124 samples) were reanalysed to assess the reproducibility. A total of 123 incurred sample reproducibility experiments were found to be within the acceptance criteria.

170-12

Bioanalysis of samples: A complete set of samples were received from 24 subjects. Total number of 1130 samples (602 from period I and 528 from period II) were analysed. 10 % of the samples (124 samples) were reanalysed to assess the reproducibility. The incurred sample reproducibility experiments were found to be within the acceptance criteria.

Pharmacokinetic variables

Study 169-12 and study 170-12

C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were the primary PK parameters used for assessment of bioequivalence.

All PK parameters were derived individually for each subject from the concentration vs. time profiles of plasma pregabalin using non-compartmental model of WinNonlin Professional Software Version 5.3 (Pharsight Corporation, USA). Actual time-points of the sample collection were used for PK and statistical analysis.

Statistical methods

Study 169-12 and study 170-12

The comparison of the PK parameters was carried out using PROC GLM of SAS® Version 9.3 (SAS Institute Inc., USA). Analysis of variance was carried out by employing PROC GLM for ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for pregabalin.

ANOVA model included Sequence, Formulation, Subject (Sequence) and Period as fixed effects. Each analysis of variance included calculation of least squares means, the difference between adjusted formulation means and the standard error associated with this difference. 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). The power of the study to detect 20 % difference between the test and reference formulations was calculated and reported.

Ratio of geometric least squares means of test and reference formulation was calculated and reported for ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Inter and Intra-subject variability was calculated for ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

Using two one-sided tests for bioequivalence, 90 % confidence intervals for the ratio of geometric least squares means between drug formulations were calculated for ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Pregabalin. Bioequivalence of Test Product vs. Reference Product was concluded, if the 90 % confidence interval fell within the acceptance range 80.00 to 125.00 % for ln-transformed PK parameters.

Results

Study 169-12

The results are summarised in Table 2 and Table 3. Based on the PK parameters of pregabalin, the test and reference products were considered bioequivalent with respect to the rate and extent of absorption. The 90 % confidence intervals for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within the predefined acceptance ranges.

Table 2. PK parameters for pregabalin (non-transformed values)

PK parameter	Test		Reference	
	arithmetic mean	**SD**	**arithmetic mean**	**SD**
AUC_{0-t} (ng*h/ml)	11750.499	2051.7324	11735.610	1940.6386
$AUC_{0-\infty}$ (ng*h/ml)	12172.898	1988.8171	12126.917	1892.9860
C_{max} (ng/ml)	1823.251	472.4493	1912.807	492.5844
T_{max}* (h)	1.000	0.500 - 3.000	0.759	0.500 - 2.000
AUC_{0-t}	area under the plasma concentration-time curve from time zero to last sample at 48 hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, min-max)			

Table 3. Statistical analysis for pregabalin (ln-transformed values)

PK parameter	Geometric Mean Ratio Test / Reference	90 % Confidence Interval	CV %*
AUC_{0-t}	100.0	97.87 - 102.08	4.6
$AUC_{0-\infty}$	100.2	98.48 - 102.03	3.9
C_{max}	95.1	86.39 - 104.76	21.4
* Estimated from the Residual Mean Squares			

Study 170-12

The results are summarised in Table 4 and Table 5. Based on the PK parameters of pregabalin, the test and reference products were considered bioequivalent with respect to the rate and extent of absorption. The 90% confidence intervals for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within the predefined acceptance ranges.

Table 4. PK parameters for pregabalin (non-transformed values)

PK parameter	Test		Reference	
	arithmetic mean	**SD**	**arithmetic mean**	**SD**
AUC_{0-t} (ng*h/ml)	66747.842	12088.6297	67515.975	12839.5417
$AUC_{0-\infty}$ (ng*h/ml)	67591.645	12128.5322	68508.126	12859.4797
C_{max} (ng/ml)	7606.884	1404.9078	8058.685	2031.3691
T_{max}* (h)	1.375	0.533 - 3.000	1.000	0.667 - 3.000
AUC_{0-t}	area under the plasma concentration-time curve from time zero to last sample at 48 hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (*median, min-max)			

Table 5. Statistical analysis for pregabalin (ln-transformed PK parameters)

PK parameter	Geometric Mean Ratio Test / Reference	90 % Confidence Interval	CV %*
AUC_{0-t}	99.1	97.20 - 100.96	3.8
$AUC_{0-\infty}$	98.9	97.06 - 100.68	3.7
C_{max}	95.7	89.88 - 101.97	12.7
* Estimated from the Residual Mean Squares			

Safety data

Study 169-12

Three adverse events (AEs) were reported by one subject after dosing of the reference product. All AEs resolved without sequelae. There were no deaths or serious or significant adverse event reported in the study.

Study 170-12

Three AEs were reported by three subjects, each in Period I of the study. One AE (*P. vivax* malaria) was serious (SAE) and two were significant (repeated vomiting; the subjects were withdrawn on medical grounds). The decisions to withdraw these subjects were justified and in accordance with GCP.

Conclusions

Based on the presented bioequivalence study 169-12 Pregabalin Accord 50 mg is considered bioequivalent with Lyrica 50 mg. The results can be extrapolated to 25 mg strength, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98.

Based on the presented bioequivalence study 170-12 Pregabalin Accord 300 mg is considered bioequivalent with Lyrica 300mg. The results can be extrapolated to other strengths: 75 mg, 100 mg, 150 mg, 200 mg and 225 mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98.

2.4.3. Pharmacodynamics

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

2.4.4. Post marketing experience

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

2.4.5. Discussion on clinical aspects

Standard study design elements and methods were utilized and pre-specified acceptance criteria were applied for assessment of BE. PK endpoints and BE criteria of both studies were in line with the recommendations of Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The inclusion and exclusion criteria were clearly stated in the protocol as well as the criteria for subject withdrawal. The pre-set BE criteria between the test and reference product were met.

The analytical methods and validations have been performed according to the relevant guideline (EMEA/CHMP/EWP/192217/2009) and were found approvable. The LLOQ of pregabalin was less than 5 % of Cmax, which was acceptable to the CHMP.

A single dose bioequivalence studies were considered sufficient since the application concerns an immediate release formulation. Steady state studies are not indicated as no accumulation of pregabalin is expected, and bioavailability is not affected by repeated doses.

The results confirm that blood sample collection schedule was appropriate as all pre-dose pregabalin concentrations were zero (or <LLOQ), C_{max} was not observed in the first post-dose sample for any of the subjects and the extrapolated area was less than 20 % for each subject indicating that the duration of sampling was sufficient.

The protocol deviations in study 169-12 included late check-in, late post-dose sampling due to problems in obtaining the sample, and one case of concomitant medication (paracetamol). The protocol deviations in study 170-12 included only late post-dose sampling (maximum deviation 4 minutes). Such deviations are anticipated to be seen in BE studies and are not expected to invalidate study results.

A routine GCP inspection of Study 170-12 (analytical and clinical laboratories) was performed. The study was found to be GCP compliant.

2.4.6. Conclusions on clinical aspects

Based on the results of the pivotal bioequivalence studies submitted, Pregabalin Accord hard capsules are considered bioequivalent to Lyrica hard capsules.

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.

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 2 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 2 with the following content:

Safety concerns

Important identified risk (s)	• Discontinuation events • Weight gain • Dizziness, somnolence, loss of consciousness, Syncope and potential for accidental injury • Vision-related events • Congestive heart failure • Peripheral oedema and oedema-related events • Drug interactions (lorazepam, ethanol and CNS depressants) • Euphoria • Hypersensitivity and allergic reactions • Abuse, Misuse and Drug Dependence
Important potential risk (s)	• Suicidality • Haemangiosarcoma • Off-label use in paediatric patients
Missing information	• Pregnant and lactating women

Pharmacovigilance plan

Not applicable

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risk: Discontinuation	Section 4.2, 4.4 and 4.8 of Pregabalin Accord SPC has information on this safety concern	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
events		
Important identified risk: Weight gain	Section 4.4 and 4.8 of Pregabalin Accord SPC has information on this safety concern	None
Important identified risk: Dizziness, somnolence, loss of consciousness, Syncope and potential for accidental injury	Section 4.4, 4.7, 4.8, 4.9 and 5.1 of Pregabalin Accord SPC has information on this safety concern.	None.
Important identified risk: Vision-related events	Section 4.4, 4.8 and 5.1 of Pregabalin Accord SPC has information on this safety concern	None
Important identified risk: Congestive heart failure	Section 4.4 and 4.8 of Pregabalin Accord SPC has information on this safety concern	None
Important identified risk: Peripheral oedema and oedema-related events	Section 4.8 of Pregabalin Accord SPC has information on this safety concern	None
Important identified risk: Drug interactions (lorazepam, ethanol and CNS depressants)	Section 4.5 of Pregabalin Accord SPC has information on this safety concern	None
Important identified risk: Euphoria	Section 4.8 of Pregabalin Accord SPC has information on this safety concern	None
Important identified risk: Hypersensitivity	Section 4.3, 4.4 and 4.8 of Pregabalin Accord SPC has information on this safety concern	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
and allergic reactions		
Important identified risk: Abuse, Misuse and Drug Dependence	Section 4.4 and 4.8 of Pregabalin Accord SPC has information on this safety concern	None
Important potential risk: Suicidality	Section 4.4 of Pregabalin Accord SPC has information on this safety concern	None.
Important potential risk: Haemangiosarcoma	Section 5.3 of Pregabalin Accord SPC has information on this safety concern.	None.
Important potential risk: Off-label use in paediatric patients	Section 4.2, [redacted] of Pregabalin Accord SPC has information on this safety concern	None
Missing information: Pregnant and lactating women	Section 4.6 and 5.2 of Pregabalin Accord SPC has information on this safety concern.	None

2.7. PSUR submission

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a double bridging report making reference to Lyrica (for content) and Solifenacin succinate 5/10mg film-coated tablets (for design and layout). The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of pregabalin hard capsules. The reference product Lyrica is indicated for the treatment of peripheral and central neuropathic pain in adults, adjunctive therapy in adults with partial seizures with or without secondary generalisation and treatment of Generalised Anxiety Disorder (GAD) in adults. Pregabalin Accord indication is limited to adjunctive therapy in adults with partial seizures with or without secondary generalisation and treatment of Generalised Anxiety Disorder (GAD) in adults, which is acceptable. No nonclinical studies have been provided for this 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 based on information from published literature was considered sufficient.

The bioequivalence studies form the pivotal basis with an open-label, balanced, randomized, two-sequence, two-period, cross-over, single dose design. The design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

Based on the presented bioequivalence studies, Pregabalin capsules 300 mg are considered bioequivalent with Lyrica hard capsules 300 mg with respect to rate and extent of absorption of Pregabalin; and Pregabalin capsules 50 mg are considered bioequivalent with Lyrica hard capsules 50 mg with respect to rate and extent of absorption of Pregabalin.

The results of study 170-12 with 300 mg formulation can be extrapolated to other strengths: 75 mg, 100 mg, 150 mg, 200 mg and 225 mg, and the results of study 169-12 with 50 mg formulation can be extrapolated to the other strength 25 mg, according to conditions in the relevant Guideline.

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 Pregabalin Accord in the treatment of

- adjunctive therapy in adults with partial seizures with or without secondary generalisation.
- the treatment of Generalised Anxiety Disorder (GAD) in adults

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

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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