EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 April 2015
EMA/CHMP/102862/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pregabalin Sandoz

International non-proprietary name: pregabalin

Procedure No. EMEA/H/C/004010

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

Table of contents

List of abbreviations

AE	adverse event
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASMF	Active Substance Master File = Drug Master File
AUC	Area Under the plasma Concentration
AUC0-inf	Area Under the plasma Concentration-time curve from time zero to infinity
AUC0-t	Area Under the plasma Concentration-time curve from time zero to t hours
BE	Bioequivalence
Cmax	maximum plasma concentration
DMF	Drug Master File = Active Substance Master File
EMA	European Medicines Agency
EU	European Union
GABA	Gamma-aminobutyric acid
GAD	Generalised Anxiety Disorder
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HPLC	High Pressure Liquid Chromatography
CHMP	Committee for Human Medicine Products
ICH	International Conference of Hamrnization
INN	International Non-proprietary Name
IPC	In-process control test
ISR	Incurred Sample Reanalysis
LLOQ	Lower Limit of Quantification
LOD	Limit of Detection
LOQ	Limit of Quantification
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
ND	Not detected
NMT	Not more than
OOS	Out of Specifications
Ph.Eur.	European Pharmacopoeia
PhV	Pharmacovigilance
PK	pharmacokinetic
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PVC	Poly vinyl chloride
PVDC	Polyvinylidene chloride
QA	Quality Assurance
QC	Quality Control (samples)
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
STD	Standard Deviation
TSE	Transmissible Spongiform Encephalopathy
Tmax	time for maximum concentration (* median, range)

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sandoz GmbH submitted on 9 July 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Pregabalin Sandoz, 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 25 April 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 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:

Neuropathic pain

Pregabalin Sandoz is indicated for the treatment of peripheral and central neuropathic pain in adults.

Epilepsy

Pregabalin Sandoz is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised Anxiety Disorder

Pregabalin Sandoz is indicated for 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 studies with the reference medicinal product Lyrica® 50 mg and Lyrica® 300mg hard gelatin capsules instead of non-clinical and clinical unless justified otherwise

Information on paediatric requirements

Not applicable

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, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg, hard gelatin capsule
- Marketing authorisation holder: Pfizer GmbH
- Date of authorisation: 8 July 2004
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/04/279/001-043

■ 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, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg, hard gelatin capsule
- Marketing authorisation holder: Pfizer GmbH
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/04/279/001-043

■ 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 gelatin capsuleMarketing authorisation holder: Pfizer GmbHDate of authorisation: 8 July 2004
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number(s): EU/1/04/279/006-010, EU/1/04/279/037Bioavailability study number(s): 2011-16-HGC-2

■ 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® 300 mg, hard gelatin capsule
- Marketing authorisation holder: Pfizer GmbH
- Date of authorisation: 8 July 2004
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number(s): EU/1/04/279/023-025, EU/1/04/279/029, EU/1/04/279/032, EU/1/04/279/043

Bioavailability study number(s): **2011-17-HGC-4**

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

LEK Pharmaceuticals d.d.
Verovškova ulica 57
1526 Ljubljana
Slovenia

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Radka Montoniová

- The application was received by the EMA on 9 July 2014.
- The procedure started on 20 August 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 November 2014.
- The PRAC Rapporteur's Risk Management Plan Assessment report was endorsed by PRAC on 4 December 2014.
- During the meeting on 18 December 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 December 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 February 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 March 2015.
- The PRAC Rapporteur's Risk Management Plan Assessment report was endorsed by PRAC on 12 March 2015.
- During the CHMP meeting on 26 March 2015, 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 consolidated List of Outstanding Issues on 1 April 2015.
- The PRAC Rapporteur's Risk Management Plan Assessment report was endorsed by PRAC on 10 April 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 13 April 2015.
- During the meeting on 23 April 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 Sandoz.

2. Scientific discussion

2.1. Introduction

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

The active substance of Pregabalin Sandoz 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 Sandoz 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 Sandoz is the same as authorized for the Reference medicinal product. 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 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg or 300 mg of pregabalin as active substance.

Other ingredients are:

Capsule content: pregelatinised starch, maize starch and talc.

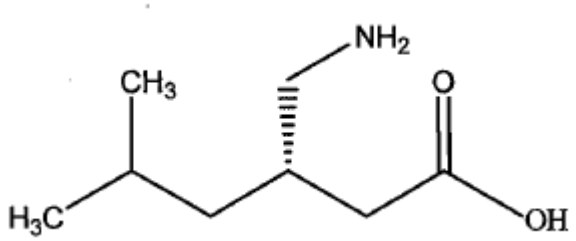
Capsule shell: gelatin, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172), and iron oxide black (E172)

The product is available in PVC/PVDC/Alu blisters and HDPE bottle with PP screw cap.

2.2.2. Active substance

General information

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



The structure has been confirmed by the following methods: elemental analysis, thermogravimetric analysis, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, FT-IR spectroscopy, UV spectroscopy and optical rotation.

The active substance is a white to off-white non-hygroscopic crystalline powder and is highly soluble in hydrophilic media.

Pregabalin exhibits stereoisomerism due to the presence of 1 chiral centre. Enantiomeric purity is controlled routinely by chiral HPLC. Polymorphism has been observed for pregabalin. The active substance suppliers produce polymorphic form I (anhydrous crystalline form) which is thermodynamically stable with respect to conversion to other polymorphs. This form is also present in the reference medicinal product.

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 two manufacturers and its production is supported by two active substance master files (ASMFs).

Pregabalin is synthesized in three (for one of the manufacturers) and four (for the other) main steps using commercially available well defined starting materials with acceptable specifications.

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 manufacture of the active substance has been provided in the restricted parts of the ASMFs and it was considered satisfactory.

Specification

The active substance specification includes tests for appearance, identification (IR), loss on drying (Ph Eur), sulphated ash (Ph Eur), heavy metals (Ph Eur), related substances (HPLC), enantiomeric purity (HPLC), assay (potentiometric titration), and residual solvents (GC). The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Analysis data on commercial scale batches of the active substance from both manufacturers (six from one, three from the other) were provided. The results are within the specifications and consistent from batch to batch and indicate that active substance from both sources is of suitable quality.

Stability

Stability data on ten commercial scale batches of active substance from one manufacturer and four on commercial scale from the other, stored in container closure systems representative of those intended for the market for up to 60 and 24 months respectively under long term conditions (25 ºC / 60% RH) was provided. Additional data on six commercial scale batches from one manufacturer and four on commercial scale from the other stored for up to 6 months under accelerated conditions (40 ºC / 75% RH) was also provided. The protocols and conditions are in line with the ICH guidelines. The following parameters were tested: appearance, identification (IR), water content (KF), related substances (HPLC), enantiomeric purity (HPLC), assay (HPLC) and polymorphic form (PXRD). Results were within acceptance criteria for all parameters tested for both manufacturers and no trends were observed.

One production batch of pregabalin from each manufacturer was tested under different stressed conditions: in solution in the presence of acid, base, oxidant or reductant; in the solid state at high temperature and high humidity, high temperature and low humidity, and exposed to daylight and UV

light following ICH guideline Q1B, in order to study its degradation. Results show that pregablin is not very stable under acidic, alkaline and oxidative conditions but stable under the other tested conditions

The stability results indicate that the drug substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest periods in the proposed containers.

2.2.3. Finished medicinal product

Pharmaceutical development

The objective was to develop a hard gelatine capsule containing pregabalin bioequivalent to the reference medicinal product Lyrica.

The solubility and permeability of the active substance was studied during development. Polymorphism and particle size are not critical parameters for the dissolution rate. Both active substance suppliers produce one polymorphic form (form I).

All excipients of the capsule filling (talc, starch pregelatinised and maize starch) are commonly used in the pharmaceutical industry and are described in Ph Eur. The hard gelatin capsules contain gelatin (Ph Eur) and colorants, titanium dioxide (Ph Eur) and ferric oxides (USP/NF and 231/2012/EC). 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.

Two bioequivalence studies were performed investigating Pregabalin 300 mg and 50 mg hard gelatin capsules versus the innovator products Lyrica 300 mg and 50 mg hard gelatin capsules. In both studies, the test products meet the bioequivalence criteria in terms of rate and extent of absorption after administration of single dose when compared to the reference products.

Difference in content of active substances in both products is within 5 %. Due to the dissolution properties (> 85 % within 15 minutes) and the proportionality of 25 mg and 50 mg on the one side and 75 mg to 300 mg on the other side, a biowaiver is acceptable for the strengths 25 mg and for 75 mg, 100 mg, 150 mg, 200 mg and 225 mg.

The only qualitative differences in composition of the test product used in bioequivalence studies and the proposed commercial formulation are in the colouring agent in capsule shell and the imprinting of capsule. Comparative dissolution profile results of the clinical batches have been provided for both strengths (300 mg and 50 mg) of generic and reference products used in bioequivalence studies in three dissolution media (0.1N HCl; pH 4.5 phosphate buffer and pH 6.8 phosphate buffers). The dissolution profiles are similar in all three pHs for 50 mg strength. More than 85% of the product is released within 15 minutes, therefore the calculation of f2 is not necessary for 50 mg strength. The f2 factors were calculated for BE batches of 300 mg strength for reference and test product.

The manufacturing process is a standard process for hard gelatine capsules with well-known excipients. It consists of mixing steps and encapsulation. The validation results of the manufacturing process as well as final batch release and stability data prove that the manufacturing process gives products of consistently good quality.

Pregabalin capsules are packed in PVC/PVDC//Al blisters or HPDE bottles. The packaging materials were selected taking into account stability considerations and marketing aspects. The materials are in accordance with the Ph Eur and Directive 2002/72/EC. The suitability of the container closure systems have been demonstrated by means of stability studies.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: production of a pre-mix blend, production of a final mix (mother blend), filling of capsules and packaging. The process is considered to be a standard manufacturing process.

Based on the validation data, there are no particular critical steps in the standard capsules manufacturing process. Four process validation reports were provided. According to these reports, in-process parameters, quality parameters and process parameters were controlled, all three process validation batches fulfilled the requirements of the relevant control methods, and all three process validation batches of mother blend and six batches of capsules fulfilled the requirements of the relevant control methods. Therefore, the process is reproducible and capable of consistently yielding product of the required quality.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form and comprise of tests for appearance, uniformity of dosage units (Ph Eur), dissolution (Ph Eur), identification (HPLC, IR), assay (HPLC), related substances (HPLC), water content (Ph Eur), and microbial purity (Ph Eur).

The proposed limits for water content are quite high, so the CHMP recommends revising them once additional commercial manufacturing experience has been gained and additional stability data generated.

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

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

Stability of the product

Stability data of three pilot batches of all strengths batches of finished product stored under long term conditions for 24 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines was provided. The batches were identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, uniformity of dosage units (Ph Eur), water content (Ph Eur), dissolution, identification (HPLC, IR), assay (HPLC), related substances (HPLC) and microbiological purity. The analytical procedures used are stability indicating.

Additionally, a photostability study was performed on one batch according to the conditions given in ICH guideline Q1B. Samples were illuminated without packaging material for 22 hours with 250 W/m2 and samples packed in PVC/PVDC-Al blisters were also tested as a control. The temperature was controlled and did not exceed 30 °C.

A reduced stability testing design (bracketing) was used for the 100mg, 150mg, 200mg and 225mg strengths according to ICH guideline Note for guidance on bracketing and matrixing designs for stability testing of drug substances and drug products (CPMP/ICH/4104/00).

All results comply with the proposed specifications and no significant change in product quality was observed.

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

Adventitious agents

Gelatine obtained from bovine sources is used in the product. A valid TSE CEP from the suppliers of the gelatine used in the manufacture was 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 reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The proposed limits for water content are quite high, so the CHMP recommends revising them once additional commercial manufacturing experience has been gained and additional stability data generated.

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 Sandoz manufactured by Sandoz GmbH 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 Sandoz from a non-clinical point of view. The SmPC of Pregabalin Sandoz 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; 2011-17-HGC-4 (with the highest strength, 300 mg), and Study 2011-16-HGC-2 (with 50 mg). These studies were pivotal for the assessment.

The biowaivers for 25 mg (from the 50 mg strength), and for 75 mg, 100 mg, 150 mg, 200 mg and 225 mg strengths (from the 300 mg strength) are acceptable.

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 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 (from the 50 mg strength), and for 75 mg, 100 mg, 150 mg, 200 mg and 225 mg strengths (from 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; Study 2011-17-HGC-4 (with the highest strength, 300 mg), and Study 2011-16-HGC-2 (with 50 mg). Neither pharmacodynamic nor therapeutic equivalence studies were submitted.

Table 1. Tabular overview of clinical studies

Type of Study	Study Identifier	Objective of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
BE	2011-17-HGC-4	To determine bioequivalence of Pregabalin hard gelatin capsule 300 mg in comparison to a reference	Open label, randomized, 2-way cross-over, single-dose	Pregabalin hard gelatin capsule 300 mg capsule, oral Lyrica® 300 mg, capsule, oral	Planned for completion: at least 30; Enrolled: 34; Drop-outs: 0; Withdrawals: 0; Completed: 34	Healthy male volunteers	Single dose per 24 hours period; Washout phase: 7 days	Complete
BE	2011-16-HGC-2	To determine bioequivalence of Pregabalin hard gelatin capsule 50 mg in comparison to a reference	Open label, randomized, 2-way cross-over, single-dose	Pregabalin hard gelatin capsule 50 mg, oral Lyrica® 50 mg, capsule, oral	Planned for completion: at least 52; Enrolled: 56; Drop-outs: 1; Withdrawals: 0; Completed: 55	Healthy male volunteers	Single dose per 24 hours period; Washout phase: 7 days	Complete

2.4.2. Pharmacokinetics

Methods

Studies design

Study 2011-17-HGC-4 and 2011-16-HGC-2

These were open-label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single dose, comparative oral bioavailability studies conducted in healthy, adult subjects

under fasting conditions. A washout period of 7 days was maintained between each treatment schedule.

Blood samples were collected prior to drug administration and at 0.167, 0.333, 0.500, 0.667, 0.833, 1.00, 1.17, 1.33, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 12.0, 16.0, and 24.0 hours post-dose, in each period.

Test and reference products

Study 2011-16-HGC-2

Pregabalin Sandoz 50 mg manufactured by Hexal AG (batch No. AS6609-A/1, manufacturing date Feb 2010; retest date Jan 2012) has been compared to Lyrica 50mg manufactured by Pfizer Limited (Batch No: 0463120D/1, exp. date Nov 2013.

Study 2011-17-HGC-4

Pregabalin Sandoz 300 mg manufactured by Hexal AG (batch No. AS3167-A/1, manufacturing date Feb 2010; retest date Jan 2012) has been compared to Lyrica 50mg manufactured by Pfizer Limited (Batch No: 04671 20D11, exp. date Nov 2013.

For both 50mg and 300mg formulations, the differences between the formulation of the tested product and the formulation intended for marketing were minor. The CHMP was of the opinion that these differences have no clinical impact.

Population studied

Study 2011-16-HGC-2

Assuming an intra-subject co-efficient of variation of approximately 20% for Cmax, the number of subjects required would be 52 subjects (with an expected ratio of 0.91 to 1.10, power: 95% and α=5%). To account for possible dropouts, 56 subjects were enrolled in this study in order to complete with a minimum of 52 subjects.

56 male, healthy, non-smoker subjects were enrolled. One subject (No.48) discontinued due to serious adverse event (convulsion) in the first period of the study, and his data were not included in the PK evaluation. In total, data from 55 subjects were used for the pharmacokinetic/PK and statistical analysis/evaluation.

Study 2011-17-HGC-4

Assuming an intra-subject co-efficient of variation of approximately 15% for Cmax, the number of subjects required would be 30 subjects (with an expected ratio of 0.91 to 1.10, power: 95% and α =5%). To account for possible dropouts, 34 subjects were enrolled in this study in order to complete with a minimum of 30 subjects.

34 male, healthy, non-smoker subjects were enrolled. There were no drop-outs or withdrawn subjects. Data from all subjects were used in the PK and statistical evaluation.

Analytical methods

Study 2011-16-HGC-2 and Study 2011-17-HGC-4

Plasma pregabalin concentrations were measured using a validated solid phase extraction with UPLC-ESI-MS/MS bioanalytical method on Waters Acquity and Quattro Premier XE mass spectrometer using deuterium labelled pregabalin (pregabalin D4) as internal standard. K3-EDTA was used as an anticoagulant. A calibration curve was extending from 0.0300 to 15.00 µg/mL with a LLOQ of 0.0300 µg/mL. Additional precision and accuracy was conducted for calibration curve parameters in range of 0.03 µg/ml to 3.00 µg/ml and for back calculated concentration for calibration curve standards in range of 0.03 µg/ml to 2.40 µg/ml.

In-study validation

Study 2011-16-HGC-2

Plasma concentrations of pregabalin were determined by the above mentioned validated method. In total 4416 samples were collected and 2208 samples were run in 31 batches including 3 batches of incurred samples for reanalysis. Calibration range was validated to be between 0.03 and 3.0 µg/ml. QC concentration samples were 0.09 µg/ml (LQC), 1.20 µg/ml (MQC) and 2.40 µg/ml (HQC). Inter-run precision was ≤3.09% and the mean accuracy ranged from 98.67 to 100.0%. LLOQ was below 1/20 of average Cmax (i.e.1.744 µg/ml). Incurred sample reanalysis (ISR) was performed on 222 samples. Results of ISR were within the acceptance criteria i.e. at least 2/3rd of reanalysed samples had difference within ±20% compared to initial analysis (only two samples for subject No. 26 have not passed).

Study 2011-17-HGC-4

2270 samples were collected and 1360 samples were run in 20 batches including 2 batches for incurred samples for reanalysis and 1 batch for repeat analysis. Reanalysis was performed due to 1 sample (out of acceptance criteria for accuracy) in calibration standard concentration STD 7 (0.150 µg/ml) in run No. 3. Calibration range was validated to be between 0.03 and 15.0 µg/ml. QC concentration samples were 0.09 µg/ml (LQC), 6.0 µg/ml (MQC) and 12.0 µg/ml (HQC). Inter-run precision was ⩽3.0% and the mean accuracy ranged from 98.33 to 99.0%. LLOQ was below 1/20 of average Cmax (i.e. 8.478 µg/ml). ISR was performed on 136 samples, of which none of them deviated more than 20% from the original value.

Pharmacokinetic variables

Study 2011-16-HGC-2 and Study 2011-17-HGC-4

Pharmacokinetic parameters were evaluated using a standard non-compartmental model. The primary and secondary pharmacokinetic parameters (AUCo-t, AUCo-inf, Cmax, Tmax, Kel and T1/2) were evaluated by using WinNonlin® Enterprise Software (Version 5.3).

Statistical methods

Study 2011-16-HGC-2 and Study 2011-17-HGC-4

The statistical comparison of the pharmacokinetic parameters was carried out using procedure PROC GLM of SAS® Version 9.2 (SAS Institute Inc., USA). Analysis of variance was carried out using SAS® Version 9.2 (SAS Institute Inc., USA) for ln-transformed Cmax, AUC0-t and AUC0-inf and untransformed Tmax, Kel and t½. ANOVA model included sequence, subject nested into sequence, period and formulation effects.

Criteria for conclusion of bioequivalence were based on the statistical results of 90% confidence intervals (80.00-125.00%) for the geometric least square mean ratio (A/B) of the pharmacokinetic parameters Cmax and AUC0-t.

The sequence effect has been tested at the 0.10 level of significance using the subjects nested within sequence mean square from the ANOVA as the error term. All other effects such as formulation and period were tested at 0.05 level of significance.

Two one-sided 90% confidence intervals for geometric least square means ratio obtained from the analysis of ln-transformed Cmax, AUC0-t and AUC0-inf of Test (A) and Reference (B) formulations were constructed using root mean square error computed by PROC GLM.

Intra-subject variability and power were calculated for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-inf using root mean square error computed by PROC GLM.

No interim analysis was performed in either of the studies

Results

Study 2011-16-HGC-2

The results of this study are summarised in Tables 2-3 below.

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

Pharmacokinetic parameter	**Test**		**Reference**	
	arithmetic mean	**±SD**	**arithmetic mean**	**±SD**
$AUC_{(0-t)}$ (µg.hr/mL)	**11.054**	**1.446**	**11.035**	**1.556**
$AUC_{(0-\infty)}$ (µg.hr/mL)	**11.894**	**1.7625**	**11.859**	**1.837**
C_{max} (µg/mL)	**1.744**	**0.372**	**1.760**	**0.350**
T_{max} *	**0.833**	**0.50-3.00**	**0.833**	**0.50-2.50**
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t 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, range)			

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

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Reference**	**Confidence Intervals**	**CV%***
$AUC_{(0-t)}$	100.28%	99.18-101.39	3.45
C_{max}	98.68%	94.35-103.20	14.12
* estimated from the Residual Mean Squares			

The 90% confidence intervals for test/reference ratios observed for C_{max} and AUCs are within the pre-specified acceptance limits for bioequivalence, 80.00-125.00%. Therefore, the bioequivalence between test and reference products can be considered as demonstrated.

Study 2011-17-HGC-4

The results of this study are summarised in Tables 4-5 below.

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

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	±SD	arithmetic mean	±SD
$AUC_{(0-t)}$ (µg.hr/mL)	63.624	7.097	63.517	7.970
$AUC_{(0-\infty)}$ (µg.hr/mL)	68.406	8.405	68.213	9.126
C_{max} (µg/mL)	8.478	1.404	8.489	1.797
T_{max} *	1.330	0.50-3.00	1.330	0.67 - 3.00
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t 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, range)			

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

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	100.32%	99.00-101.66	3.22
C_{max}	100.71%	95.37-106.35	13.33
* estimated from the Residual Mean Squares			

The 90% confidence intervals for test/reference ratios observed for C_{max} and AUCs are within the pre-specified acceptance limits for bioequivalence, 80.00-125.00%. Therefore, the bioequivalence between test and reference products can be considered as demonstrated.

Safety data

Study 2011-16-HGC-2

One serious adverse event was observed during the course of the study. Subject No. 48 reported the SAE (convulsion) during period 1 of the study after the administration of the test product. The SAE was not life threatening, but severe in intensity and had a suspected relationship to the study drug. No other adverse events were observed.

Study 2011-17-HGC-4

Pregabalin test and reference formulation were generally well tolerated. Three subjects (subject No. 06, 07 and 25) reported adverse events during the conduct of the study (two cases of vomiting and one case of clinically significant increase in triglycerides levels) after treatment with the reference medication. In one case of vomiting (subject No. 25), causal relation with the reference product was suspected. There were no deaths, SAEs or significant AEs during the course of the study.

Conclusions

Based on the presented bioequivalence study 2011-16-HGC-2 Pregabalin Sandoz 50 mg is considered bioequivalent with Lyrica 50 mg. The results can be extrapolated to other strength 25 mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98.

Based on the presented bioequivalence study 2011-17-HGC-4 Pregabalin Sandoz 300 mg is considered bioequivalent with Lyrica 300 mg. The results can be extrapolated to other strengths 75 mg, 100 mg, 150 mg, 200mg 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

To support the application, two bioequivalence studies have been conducted with the highest strength of both composition groups, i.e. with 50 and 300 mg hard gelatine capsules.

Taking into account that the pharmacokinetics over the therapeutic dose range are linear and the requirements for in vitro dissolution testing, as set in Guideline on the Investigation of Bioequivalence for biowaiver of additional strengths, have been met, the applied bracketing approach for bioequivalence testing with two strengths is adequate.

The BE studies were performed as per protocol and all other pertinent requirements of the ICMR guidelines, ICH (Step 5) Guidance on Good Clinical Practice, Declaration of Helsinki (1996), EMA Guideline on the Investigation of Bioequivalence and in accordance with Good Laboratory Practice.

The methodological aspects of the design of the studies 2011-16-HGC-2 and 2011-17-HGC-4 are appropriate, i.e. open label, single-dose, randomized, 2-way crossover study design, where subjects are randomized into one of two sequences, each consisting of four periods is fully in line with the European requirements.

Both studies were conducted under standardised conditions. The sampling time points as well as the wash-out period of 7 days were adequate. Pregabalin was measured in human plasma using a validated UPLC-ESI-MS/MS method. The analytical method for the determination of pregabalin in human plasma and respective validations were adequate; the validation was performed according to the requirements of the EMA “Guideline on bioanalytical method validation” (EMEA/CHMP/EWP/192217/2009). Acceptance criteria were in a plausible range and were fulfilled.

The pharmacokinetic and statistical methods applied were adequate. The test to reference ratio of geometric LSmeans and the corresponding 90% confidence interval for the Cmax and AUC0-t were all within the standard acceptance range of 80.00 to 125.00%.

The CHMP has asked the Applicant to provide more information concerning the GCP inspection reports. The additional details were assessed by CHMP to provide sufficient reassurance of the compliance of dosing in conducted bioequivalence studies.

The safety of the formulations was also assessed on the basis of clinical and laboratory examinations at the beginning, during and at the end of the study and by the registration of adverse events. As expected, the test and reference products had a comparable safety profile.

2.4.6. Conclusions on clinical aspects

Based on the results of the pivotal bioequivalence studies submitted, Pregabalin Sandoz 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 1.2 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 1.2 with the following content:

Safety concerns

Important identified risks	Weight gain
	Peripheral oedema and oedema-related events
	Dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury
	Discontinuation events
	Drug interactions (lorazepam, ethanol and CNS depressants)
	Euphoria
	Hypersensitivity and allergic reactions
	Congestive heart failure
	Vision-related events
	Abuse, misuse and dependence
Important potential risks	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 minimization measures	Additional risk minimization measures
Weight gain	Guidance is provided in sections 4.4 "Special warnings and precautions for use" and 4.8 "Undesirable effects" of the SmPC.	None
Peripheral oedema and oedema-related events	Guidance is provided in sections 4.4 "Special warnings and precautions for use" and 4.8 "Undesirable effects" of the SmPC.	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury	Guidance is provided in sections 4.4 "Special warnings and precautions for use", 4.7 "Effects on ability to drive and use machines", 4.8 "Undesirable effects" and 4.9 "Overdose" of the SmPC.	None
Discontinuation events	Guidance is provided in sections 4.2 "Posology and method of administration", 4.4 "Special warnings and precautions for use" and 4.8 "Undesirable effects" of the SmPC..	None
Drug interactions (lorazepam, ethanol and CNS depressants)	Guidance is provided in section 4.5 "Interaction with other medicinal products and other forms of interaction" of the SmPC.	None
Euphoria	Guidance is provided in sections 4.8 "Undesirable effects" of the SmPC.	None
Hypersensitivity and allergic reactions	Guidance is provided in sections 4.3 "Contraindications" 4.8 "Undesirable effects" of the SmPC.	None
Congestive heart failure	Guidance is provided in section 4.4 "Special warnings and precautions for use" of the SmPC And 4.8 "Undesirable effects" of the SmPC.	None
Vision-related events	Guidance is provided in sections 4.4 "Special warnings and precautions for use" 4.8 "Undesirable effects" and 5.1 "Pharmacodynamic properties" of the SmPC.	None
Abuse, misuse and dependence	Guidance is provided in sections 4.4 "Special warnings and precautions for use" of the SmPC.	None
Suicidality	Guidance is provided in section 4.4 "Special warnings and precautions for use" of the SmPC.	None
Haemangiosarcoma	Guidance is provided in section 5.3 "Preclinical safety data" of the SmPC.	None
Off-label use in paediatric patients	Reference is given in section 4.2 "Posology and method of administration" of the SmPC (Summary of Product Characteristics).	None
Pregnant and lactating women	Guidance is provided in section 4.6 "Fertility, pregnancy and lactation" of the SmPC.	

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 bridging report making reference to Lyrica (for content) and Sandoz generic clozapine, memantine and ziprasidone (for style and format). 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. 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 on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence studies form the pivotal basis with an open label, single-dose, randomized, 2-way crossover study 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.

The test formulation of Pregabalin Sandoz met the protocol-defined criteria for bioequivalence when compared with Lyrica. 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.

The results of study 2011-17-HGC-4 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 2011-16-HGC-2 with 50 mg formulation can be extrapolated to the 25 mg strength, 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 Sandoz in the treatment of:

Neuropathic pain

Pregabalin Sandoz is indicated for the treatment of peripheral and central neuropathic pain in adults.

Epilepsy

Pregabalin Sandoz is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised Anxiety Disorder

Pregabalin Sandoz is indicated for 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.