15 December 2016
EMA/14344/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pregabalin Zentiva k.s.

International non-proprietary name: pregabalin

Procedure No. EMEA/H/C/004277/0000

Note

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

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List of abbreviations

AE	adverse event
AP	Applicant's Part of ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
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
CoA	Certificate of Analysis
CRO	Certified Research Organisation
DMF	Drug Master File = Active Substance Master File
DSC	Differential Scanning Calorimetry
EC	European Commission
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union
FPM	Finish Product Manufacturer
GABA	Gamma-aminobutyric acid
GAD	Generalised Anxiety Disorder
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCP	Health Care Professional
HDPE	High Density Polyethylene
HPLC	High Pressure Liquid Chromatography
CHMP	Committee for Human Medicine Products
ICD	Informed Consent Document
ICSR	Individual Case Safety Report
IEC	Independent Ethics Committee
ICH	International Conference of Hamrnization
INN	International Non-proprietary Name
IPC	In-process control test
IR	Incidence Rate
IR	Infrared
ISR	Incurred Sample Reanalysis
LLOQ	Lower Limit of Quantification
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantification
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MHRA	British National Competent Authority
MR	Medical Representative
MRI	Magnetic resonance imaging
MS	Mass Spectrometry
ND	Not detected
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NSAID	Non-Steroidal Anti-Inflammatory Drug

OOS	Out of Specifications
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PhV	Pharmacovigilance
PIL	Patient Information Leaflet
PK	pharmacokinetic
PMS	Post Marketing Surveillance
PP	Polypropylene
PS	Photo-Sensitivity
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PT	Preferred Term
PVC	Poly vinyl chloride
PVDC	Polyvinylidene chloride
QA	Quality Assurance
QC	Quality Control (samples)
QOS	Quality Overall Summary
QP	Qualified Person
Rf	Retention factor
RH	Relative Humidity
RMM	Risk Minimization Measure
RMS	Reference Member State
RR	Reporting Rate
RRT	Relative retention time
RSD	Relative standard deviation
Rt	Retention time
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
STD	Standard Deviation
T/R	Test/Reference
Tmax	time for maximum concentration (* median, range)
TSE	Transmissible spongiform encephalopathy
UV	Ultraviolet
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Zentiva k.s. submitted on 29 April 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Pregabalin Zentiva k.s., 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 23 July 2015.

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 indications: Treatment of neuropathic pain, epilepsy and generalised anxiety disorder (GAD)

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.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form Lyrica, 25/50/75/100/150/200/225/300 mg, capsule, hard
- Marketing authorisation holder: Pfizer Limited
- Date of authorisation: 6 July 2004
- Marketing authorisation granted by:
  - Community
- Marketing authorisation numbers: EU/1/04/279/001-043; 045

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

- Product name, strength, pharmaceutical form: Lyrica, 25/50/75/100/150/200/225/300 mg, capsule, hard
- Marketing authorisation holder: Pfizer Limited
- Date of authorisation: 6 July 2004
- Marketing authorisation granted by:
  - Community
- Marketing authorisation numbers: EU/1/04/279/001-043; 045

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, capsule, hard
- Marketing authorisation holder: Pfizer Limited
- Date of authorisation: 6 July 2004
- Marketing authorisation granted by:
  - Community
- Marketing authorisation number: EU/1/04/279/024
- Bioavailability study number: 2011-003609-28

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Alar Irs

- The application was received by the EMA on 29 April 2016.
- The procedure started on 23 May 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 27 June 2016.
- During the meeting on 21 July 2016, 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 12 September 2016.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 3 October 2016.
- During the CHMP meeting on 13 October 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 11 November 2016.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 28 November 2016.
- During the meeting on 15 December 2016, 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 Zentiva k.s.

2. Scientific discussion

2.1. Introduction

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

The active substance of Pregabalin Zentiva k.s. 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 characterised 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 Zentiva k.s. 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 300mg dose with the reference 300mg Lyrica capsule was demonstrated clinically. For the remaining doses, CHMP has accepted a biowaiver.

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 and 300 mg of pregabalin as active substance.

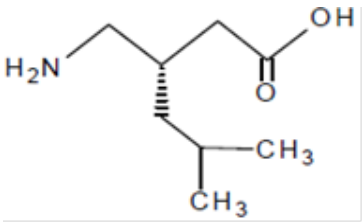
Other ingredients are: lactose monohydrate, pregelatinized maize starch, talc, gelatin (capsule body and capsule cap), titanium dioxide E171 (capsule body and capsule cap), black iron oxide E172 (25/50/75/150/225/300 mg strength capsule body and 25/50/150 mg strength capsule cap), red and yellow iron oxide E172 (100/200 mg strength capsule body and 75/100/200/225/300 mg strength capsule cap).

The product is available in OPA/alu/PVC/alu blisters for the 25 mg capsules and PVC/alu blisters for the 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg capsules.

2.2.2. Active substance

General information

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



The structure has been confirmed by the following methods: element analysis, IR, NMR, MS, X-ray diffraction and thermal analysis.

The active substance is a white to off-white powder, not hygroscopic, sparingly soluble in water, and very slightly soluble in acetonitrile and in methanol.

Pregabalin exhibits stereoisomerism due to the presence of one chiral centre. Enantiomeric purity is controlled routinely by chiral HPLC. Pregabalin shows polymorphism. The active substance's suppliers produce the same polymorphic form. During the polymorphic research on pregabalin, it was demonstrated that polymorphic form produced by active substance manufacturers is the most common and stable one. During the performed investigations the suppliers were unable to produce any other polymorph in spite of efforts made (testing of different solvents, drying options).

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

Manufacture, characterisation and process controls

The active substance is sourced from two suppliers corresponding to seven manufacturing sites including five sites involved in the manufacture of intermediates.

Pregabalin is synthesized in 2 main chemical reactions with additional steps of purification of the intermediate and final active substance by one supplier and in 3 main chemical steps with additional step of purification of the final active substance by another supplier using commercially available well defined starting materials with acceptable specifications. Enantiopurity 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: appearance, identity (IR, HPLC), assay (HPLC), related substances (HPLC), enantiomeric purity (HPLC), methyl carbamate content (HPLC), residual solvents (GC), water content (KF), sulphated ash (Ph. Eur.), heavy metals (Ph.Eur.), bromide content (Ph. Eur.), particle size (laser diffraction), microbiological quality (Ph. Eur.).

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

Following CHMP request, the active substance specifications were revised during the procedure to be in compliance with recent pregabalin EP monograph. The company has demonstrated the equivalence of in-house methods used for analysis of related substances with the compendial methods.

Data demonstrating that the same polymorphic form is obtained from all the applied suppliers were provided. As each API manufacturer has demonstrated the consistency of physical form produced as well as stability of polymorph I, the omission of a control of the polymorphic form in the active substance specifications is considered acceptable.

Batch analysis data of the active substance (at least 3 production scale batches for each manufacturing site) are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data were provided on at least 3 production scale batches of active substance from one of the proposed manufacturers, stored in a container closure system representative of that intended for the market, for up to 36 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.

Stability data were provided on at least 3 pilot scale batches of active substance from the other proposed manufacturer, stored in a container closure system representative of that intended for the market for up to 48 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: appearance, identification (IR, HPLC), loss on drying and/or water (KF), specific optical rotation (for one active substance supplier), enantiomeric purity (HPLC), assay (HPLC), related substances (HPLC), particle size (for two active substance suppliers) microbiologic quality (for one active substance supplier).

Additional investigations on the stability of the polymorphic form demonstrated sufficient physical stability of polymorph produced by active substance manufacturers.

Photostability testing following the ICH guideline Q1B was performed on one batch. The substance was found to be photostable. Results on stress conditions were also provided for one batch of each manufacturer. Stress conditions studies included: elevated temperature, light, oxidizing, alkaline and acidic medium, high humidity. Results showed that pregabalin in solid state very slightly degrades when exposed to heat, to high humidity or when exposed to oxidation combined with heating. Pregabalin degrades when exposed to heat in solution or when exposed to extreme basic condition or acidic conditions.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the retest period proposed by the ASMF holders. However the finished product manufacturing site has confirmed that no re-test period is used for the active substance and that the full analysis is performed on the active substance each time before it is included in the finished product manufacturing process.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

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

Comparison of the impurity profiles, water content and particle size distribution of API batches supplied from different suppliers used in the pilot productions of pregabalin 300 mg hard capsules were provided. Results showed no significant differences.

Due to high solubility of pregabalin, particle size distribution of the active substance was considered as a non-critical parameter.

Studies were provided to demonstrate the absence of polymorphic form change during finished product manufacture and stability.

The qualitative composition of the generic product is identical to the reference product except for the excipient pregelatinised starch that is used instead of maize starch due to better flow properties and except for the capsule shell composition (absence of sodium laurilsulphate/silica colloidal anhydrous, different colorants used compared to the reference product) and except for the printing inks composition.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards or with EC regulation for the colorants Black/Red/Yellow iron oxides. 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 compatibility of the active substance with lactose was described based on literature data and stability studies results. Pregabalin active substance as a primary amine can form conjugates with lactose by undergoing a Maillard reaction. Forming of conjugates was confirmed for Pregabalin Zentiva k.s pilot batches during the stability studies and it is also comparable to original product Lyrica.

Strengths of 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg of pregabalin hard capsules were developed like Lyrica capsules to be dose proportional to each other and to contain 75 % of pregabalin.

Unlike the reference product, pregabalin 50 mg hard capsules were developed to be manufactured like higher strengths of pregabalin capsules, to be dose proportional to higher strengths of pregabalin hard capsules and contains 75 % of pregabalin.

The lowest strength, 25 mg of pregabalin hard capsules, was intended to be developed like higher strengths of pregabalin hard capsules, but since the amount was too small for encapsulation into available sizes of capsules, it was not possible. A different composition was prepared. The ratios of lactose and pregelatinized starch in the formulation were increased compare to the composition of Lyrica 25 mg capsules and the same percentage amount of glidant talc was used compare to formulations of pregabalin hard capsules strengths from 50 mg to 300 mg.

The similarity of developed product with reference product was assessed by comparison of dissolution and impurity profiles and by bioequivalence study.

The dissolution profiles of all strengths of pregabalin hard capsules, manufactured with API from all proposed suppliers, were compared with the ones of Lyrica. The profiles were determined for 0.1 N HCl, 0.067 M HCl and buffers of pH 4.5 and 6.8. Bioequivalence between the investigational pregabalin 300 mg capsules and the reference product Lyrica 300 mg capsules has been demonstrated. For the 50 mg, 75 mg, 100 mg, 150 mg, 200

mg and 225 mg strengths, the applicant applies for biowaiver based on the general requirements for biowaiver of an additional strength, while for the strength 25 mg Biopharmaceutics Classification System (BCS)-based biowaiver was requested. Pregabalin is a BCS class I active substance and a BCS-based biowaiver is acceptable for all strengths. Based on the results from dissolution tests (> 85 % within 15 minutes at three pH levels), pregabalin hard capsules are an immediate release formulations meeting criteria for a BCS-based biowaiver according to the Bioequivalence Guideline (see also clinical section).

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.

The manufacturing process development was started with the strength 300 mg. Two different way of production were tested - wet granulation and direct mixing. Batch produced by wet granulation showed deterioration of impurity profile due to water, which contributes to the Maillard reaction. After that the flowability and compressibility of the batches obtained by direct mixing but containing different excipient composition were evaluated. The batch formulation containing lactose monohydrate, pregelatinised starch showed the best results and was used for preparation of pilot batches.

The primary packaging is OPA/alu/PVC/alu blisters for the 25 mg capsules and PVC/alu blisters for the 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg capsules. 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 three main steps: blend preparation, encapsulation, and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies on three consecutive pilot batches of pregabalin 25 mg hard capsules, on pregabalin common granule and one batch of each strength. All proposed active substance suppliers were used in the validation batches.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

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

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form : appearance, average mass of one capsule, identification (UPLC, IR), identification of colorants (Ph. Eur.), assay (UPLC), uniformity of dosage units (Ph. Eur.), dissolution test (UPLC), related substances (HPLC), microbial count (Ph. Eur.), Escherichia coli, water content (KF), disintegration (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 one pilot scale batch for the 100 mg strength, two pilot scale batches of the 200/225 mg strengths, three pilot scale batches of the 25/50/150 mg strengths, 4 pilot scale batches of the 75/300 mg strengths manufactured with active substance batches from two suppliers. 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 for eight pilot scale batches of 25/50/150/300 mg strengths, four pilot scale batches of 75 mg strength, one pilot scale batch of 100/200/225 mg strength of finished product stored under long term conditions for 24 months at 25 ºC / 60% RH, 12 month at 30 ºC / 65% RH 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 the primary packaging proposed for marketing. 10 of the stability batches were manufactured using active substance batches from the two proposed suppliers.

Samples were tested according to release specifications except for uniformity of dosage units (not performed) and except for the limits for total impurities and water content (wider limit at shelf life). The analytical procedures used are stability indicating. The limit for dissolution specification has been tightened during the procedure, however in the stability study old wider specification was used. The CHMP recommended that the applicant investigate the dissolution after 15 min in stability studies and provide relevant results whenever the data obtained at the next testing point is available.

In addition, one batch of 25/75 mg strength was 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.

Stress degradation tests also showed that the proposed finished product is acid sensitive, unstable at 10N NaOH, not stable at oxidizing condition (30 % H_2O_2), at 40 °C and not stable at 90 °C.

Based on available stability data, the shelf-life is 2 years and the storage condition is “Do not store above 30 °C”. They are acceptable and included in the SmPC.

Adventitious agents

Excipients lactose monohydrate and gelatin are of animal origin.

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Gelatine obtained from bovine sources is used in the product. A valid TSE CEP from the suppliers of the gelatine used in the manufacture is 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.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

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 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:

Dissolution after 15 minutes should be investigated in stability studies and relevant results should be provided whenever the data obtained at next testing point is available.

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 Zentiva k.s. 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 ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

Not applicable

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 Zentiva k.s. from a non-clinical point of view. The SmPC of Pregabalin Zentiva k.s. 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 one bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09) are of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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 50, 75, 100, 150, 200, 225 and 300 mg of the test product is quantitatively proportional. A tabular listing of the composition of the respective strengths and their dissolution curves at pH 1.2, 4.5 and 6.8 showed that more than 85% of the drug was dissolved within 15 minutes at all pH values tested. Therefore, one single-dose bioequivalence study has been conducted with the highest 300 mg strength only. The results of this study can be extrapolated to other strengths.

The 25-mg strength formulation of pregabalin capsules does not have a quantitatively proportional composition to the other strengths. Therefore, the applicant applied for BCS-based biowaiver for the 25-mg, meeting the criteria described in the Appendix III of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1). Pregabalin is a BCS-class I drug as it is highly soluble and permeable compound. Pharmacokinetic studies have shown that pregabalin is rapidly absorbed with bioavailability >90%, with mean tmax values ranging from 0.7 to 1.3 hours, the pharmacokinetics is linear in the therapeutic dose range

Based on these results and considerations, the CHMP concluded that the general biowaiver criteria were met. Therefore, a bioequivalence study with the 300mg dose and a biowaiver for the additional strengths and BSC-based biowaiver for 25 mg were considered adequate.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study.

2.4.2. Pharmacokinetics

Study 18/10/PRG/BSD: A Two-Way, Randomized, Single-Dose, Cross-Over, Balanced, Fasted Study of Pregabalin Zentiva 300 mg Capsules in Healthy Volunteers.

Methods

Study design

This was a single dose bioequivalence study under fasting conditions to demonstrate essential similarity between the test and reference product.

After an overnight fast, subjects were given the test or the reference product with 250 ml of water. Water was not permitted 1 hour before dosing and until 1 hour post-dosing. The subjects were served meals at 4 h post dose in both periods. Subjects were housed in clinical facilities until 36 hours post dose. There was a washout period of 7 days between the study periods. Following each drug administration, blood samples were taken at 0 (pre-drug), 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2, 3, 5, 9, 14, 24, 30 and 36 hours.

Test and reference products

Pregabalin Zentiva 300 mg manufactured by Zentiva, a.s. (batch No. Pilot 01, manufacturing date 08/2010; exp. date October 15, 2011) has been compared to Lyrica 300mg manufactured by Pfizer (Batch No: 0517031F, exp. date February 28, 2014).

Population studied

The number of subjects enrolled to the study was calculated using the following intrasubject variances (based on literature data): ≤ 10% and ≤ 15% for AUC and Cmax, respectively. The minimal number of subjects based on the criterion to achieve 90% probability of concluding bioequivalence if the difference between test and reference treatment is ≤ 8% was 22. To account for subject withdrawal and dropouts due to adverse events, non-compliance or personal reasons, 24 subjects were planned to be randomized and dosed.

Healthy male subjects (19 to 41 years of age) with a normal weight, liver and kidney function and no prior drug use were admitted. Subjects were allocated to study treatments according to the randomization schedule. 24 subjects were enrolled and completed both study periods.

Analytical methods

LC-MS/MS method was used for the determination of pregabalin plasma concentrations. The method was based on protein precipitation as a sample preparation technique, HPLC separation on a pentafluorophenylpropyl column and tandem mass spectrometric detection.

Total number of 768 samples was received for the determination of pregabalin in plasma, they were stored at -18 ºC. Calibration standards (range 144.3-14 960 ng/ml, 7 levels) and quality control samples (concentrations 428.3, 3046 and 12 680 ng/ml) were prepared on September 21, 2011. Plasma samples were analysed in 9 analytical runs, including incurred sample analysis, all meeting the acceptance criteria.

Accuracy and precision was calculated based on the back calculated concentrations of calibration curve samples and QC samples (concentrations 428.3, 3046 and 12 680 ng/ml). The pregabalin levels in samples with measured concentration < 144.3 ng/ml (LLOQ) were reported as 0. Across sample analysis accuracy and

precision was within ±10%. Incurred sample reanalysis included 80 samples, for 8% of incurred samples reanalysed, original result differed more than 20%, whereas median difference was 6.95%.

Pharmacokinetic variables

The following parameters were calculated: Cmax and tmax were determined directly from the observed values; AUC(0-t) was calculated by linear trapezoidal rule and AUC(0-∞) determined by extrapolation to infinity; terminal rate constant β was obtained by linear regression analysis of the terminal phase of the ln C - time curve. The terminal halftime t1/2 was calculated as 0.6931/β. The estimated Clast* instead of observed value Clast was used in the calculation of AUC(0-∞).

Statistical methods

Two-way analysis of variance (ANOVA) was carried out on logarithmically transformed AUCs and Cmax values. The terms used in the ANOVA model were sequence, subject within sequence, period and formulation. To test for bioequivalence based on AUC(0-t) and Cmax (primary parameters) the geometric means and the 90% confidence intervals were estimated. The statistical analyses were performed using Phoenix WinNonlin 6.1 (Pharsight).

Results

The results of this study are summarised in the Tables 1 and 2 below.

Table 1 Pharmacokinetic parameters for pregabalin.

Pharmacokinetic parameter	Test		Reference	
	geometric mean	Geometric SD	geometric mean	Geometric SD
$AUC_{(0-t)}$ mg*h/mL	45.5	(38.8 ; 53.4)	44.8	(38.6 ; 52.0)
$AUC_{(0-\infty)}$ mg*h/mL	47.5	(40.8 ; 55.4)	46.7	(40.4 ; 54.0)
C_{max} µg/mL	6.42	(5.26 ; 7.84)	6.55	(5.50 ; 7.80)
T_{max}*h	1.09 (±0.3)		1.04 (±0.47)	
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 (* mean±SD)			

Table 2. Statistical analysis for pregabalin (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-inf)}$	101.84	98.51 ; 105.28	6.7%
$AUC_{(0-last)}$	101.73	98.23 ; 105.36	7.1%
C_{max}	98.00	91.94 ; 104.46	12.9%
* estimated from the Residual Mean Squares			

Safety data

There were no adverse events reported by any of the subjects throughout the duration of this study.

Conclusions

Based on the presented bioequivalence study Pregabalin Zentiva 300 mg capsules are considered bioequivalent with Lyrica 300 mg capsules.

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

A single dose bioequivalence study was considered sufficient since the application concerns an immediate release formulation. Steady state studies are not required as no accumulation of pregabalin is expected, and bioavailability is not affected by repeated doses. A single dose study under fasting conditions is an acceptable study design since the reference product can be taken with or without food. Considering that pregabalin is a BCS class I drug, a BCS-based biowaiver for all strengths would have been acceptable.

Analytical and validation reports were included in the final report. Analytical methods were validated and met the criteria in the EMA Guideline on Bioanalytical Method Validation. Pregabalin stability under various storage conditions had been demonstrated. Long term stability covered the real sample storage time. None of the determined concentrations exceeded the upper calibration limit and the maximum concentration determined was 9.6 µg/mL. None of the predose samples contained detectable amount of pregabalin, indicating that the length of washout period was sufficient. None of the first post-dose samples was a Cmax-sample indicating that blood collection times were appropriately placed.

There were no deaths or serious adverse events reported during the conduct of the study. The safety of pregabalin is well documented and both test and reference products are expected to have a comparable safety profile.

Bioequivalence between the investigational drug Pregabalin Zentiva 300 mg capsules and the reference drug Lyrica 300 mg capsules has been demonstrated. The 90%CIs are within the standard bioequivalence limit 90.00%-125.00%. Design of the bioequivalence study was acceptable. None of the predose samples contained detectable amount of pregabalin, indicating the washout period was sufficient. None of the first post-dose samples was observed as a Cmax-sample, indicating that blood collection times were appropriately placed. Area extrapolated to infinity for AUC(0-∞) calculation was less than 6%, indicating sufficient blood collection time.

2.4.6. Conclusions on clinical aspects

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

2.5. Risk management plan

The CHMP received the following PRAC advice on the submitted risk management plan (RMP).

The PRAC considered that the RMP for Pregabalin Zentiva k.s. version 1.0 (dated 07 April 2016) could be acceptable if the applicant addresses the outstanding query as described in the PRAC endorsed PRAC and CHMP rapporteurs' Joint assessment report dated 27 June 2016.

The CHMP endorsed this advice without changes.

The applicant addressed the outstanding query as requested by the PRAC and the CHMP.

The CHMP endorsed the RMP version 1. 1 (dated 09 September 2016) with the following content:

Safety concerns

Table 3 – Summary Table of the safety concerns

Important identified risks	• Hypersensitivity and allergic reactions • Peripheral oedema and oedema-related events • Dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury • Vision related events • Discontinuation events • Congestive heart failure • Weight gain • Drug interactions (lorazepam, ethanol and CNS depressants) • Euphoria • Abuse, misuse and drug 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

Table 4 – Summary Table of the risk minimisation measures

Safety concern	Routine risk minimisation measure	Additional risk minimisation measure
Important identified risks		
Hypersensitivity and allergic reactions	Wording in SmPC section 4.3, 4.4, 4.8 Prescription only medicine	None
Peripheral oedema and oedema-related events	Wording in SmPC section 4.8 Prescription only medicine	None
Dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury	Wording in SmPC section 4.4, 4.7, 4.8, 4.9 Prescription only medicine	None
Vision related events	Wording in SmPC section 4.4, 4.8, 5.1 Prescription only medicine	None
Discontinuation events	Wording in SmPC section 4.2, 4.4, 4.8, Prescription only medicine	None
Congestive heart failure	Wording in SmPC section 4.4, 4.8 Prescription only medicine	None
Weight gain	Wording in SmPC section 4.4, 4.8 Prescription only medicine	None
Drug interactions (lorazepam, ethanol and CNS depressants)	Wording in SmPC section 4.4, 4.5 Prescription only medicine	None
Euphoria	Wording in SmPC section 4.8 Prescription only medicine	None
Abuse, misuse and drug dependence	Wording in SmPC section 4.4 Prescription only medicine	None
Important potential risks		

Suicidality	Wording in SmPC section 4.4 Prescription only medicine	None
Haemangiosarcoma	Wording in SmPC section 5.3 Prescription only medicine	None
Off-label use in paediatric patients	Wording in SmPC section 4.2 Prescription only medicine	None
Missing information		
Pregnant and lactating women	Wording in SmPC section 4.6, 5.2 Prescription only medicine	None

2.6. PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

After the successful readability user testing, the applicant changed the font of the package leaflet. For the revised version of the leaflet, the applicant has made a bridging to the Zentiva house style. The house style has been successfully user tested in several procedures and therefore additional separate user testing is not needed. The CHMP accepted the bridging to design and layout.

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 non-clinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a two-way, randomized, single-dose, cross-over design. The study 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 Zentiva k.s. met the protocol-defined criteria for bioequivalence when compared with the reference product. 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. Bioequivalence of the two formulations was demonstrated.

Based on the presented bioequivalence study, pregabalin capsules 300 mg are considered bioequivalent with Lyrica hard capsules 300 mg with respect to rate and extent of absorption of pregabalin. The results of this study can be extrapolated to other strengths: 50 mg, 75 mg, 100 mg, 150 mg, 200 mg and 225 mg, according to conditions in the relevant Guideline. For 25 mg strength, BCS-based biowaiver was granted.

A benefit/risk ratio comparable to that of 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 Zentiva k.s. is favourable in the following indications:

Neuropathic pain

Pregabalin Zentiva k.s. is indicated for the treatment of peripheral and central neuropathic pain in adults.

Epilepsy

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

Generalised anxiety disorder

Pregabalin Zentiva k.s. is indicated for the treatment of generalised anxiety disorder (GAD) in adults.

The CHMP 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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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.

Additional risk minimisation measures

Not applicable

Obligation to conduct post-authorisation measures

Not applicable

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

Not applicable