25 June 2015
EMA/CHMP/373461/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Duloxetine Zentiva

International non-proprietary name: duloxetine

Procedure No. EMEA/H/C/003935/0000

Note

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

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List of abbreviations

5-HT Serotonin

ATC The Anatomical Therapeutic Chemical Classification System

CL/F Apparent clearance after oral administration

Cmax Maximum plasma drug concentration

GAD Generalised Anxiety Disorder

MAO Monoamine Oxidase Inhibitor

MDD Major Depressive Disorder

NE Norepinephrin

NET Norepinephrin Reuptake Transporters

NSAID Non-steroidal Anti Inflammatory Drug

PDN Painful diabetic neuropathy

SERT Serotonin Reuptake Transporters

SNRI Serotonin Norepinephrine Reuptake Inhibitor

SSRI Selective Serotonin Reuptake Inhibitor

t ½ Elimination half-life

TCA Tricyclic Antidepressant

tmax Time to reach Cmax

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Zentiva, k.s. submitted on 14 August 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Duloxetine Zentiva, 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 23-01-2014.

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

The applicant applied for the following indications:
- Treatment of major depressive disorder.
- Treatment of diabetic peripheral neuropathic pain.
- Treatment of generalised anxiety disorder.

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 Cymbalta 30 and 60 mg gastro-resistant capsules instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
  - Product name, strength, pharmaceutical form: Yentreve 20 mg hard gastro-resistant capsules
  - Marketing authorisation holder: Eli Lilly Nederland B.V.
  - Date of authorisation: 08-11-2004
  - Marketing authorisation granted by:
    - Community
  - Community Marketing authorisation number: EU/1/04/280/001, EU/1/04/280/007, EU/1/04/280/008.

- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
  - Product name, strength, pharmaceutical form: Cymbalta 30/60 mg hard gastro-resistant capsules
  - Marketing authorisation holder: Eli Lilly Nederland B.V.
  - Date of authorisation: 17-12-2004
  - Marketing authorisation granted by:
    - Community
      - Community Marketing authorisation number: EU/1/04/296/001-009

- 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: Cymbalta 60 mg hard gastro-resistant capsules

- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 17-12-2004
- Marketing authorisation granted by:
  - Community
  - (Community) Marketing authorisation number(s): EU/1/04/296/002
- Bioavailability study numbers:
  DLN-P1-453 (Sponsor Project No 12/11/DLX/PK1)
  DLN-P1-592 (Sponsor Project No 31/11/DLX/BSD)
  DLN-P1-593 (Sponsor Project No 32/11/DLX/BFE)

Information on paediatric requirements

Not applicable

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Duloxetine Zentiva has been given a Marketing Authorisation in Turkey on 14-02-2014.

1.2. Manufacturers

Manufacturer responsible for batch release

S.C. Zentiva S.A.
50 Theodor Pallady Blvd.
District 3, 032266
Bucuresti
Romania

1.3. Steps taken for the assessment of the product

The Rapporteur and appointed by the CHMP:

Rapporteur: Kristina Dunder

- The application was received by the EMA on 14 August 2014.
- The procedure started on 24 September 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 December 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 9 January 2015
- During the meeting on 22 January 2015, 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 22 January 2015

- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 February 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 March 2015
- PRAC RMP Advice and assessment overview, adopted by PRAC on 10 April 2015
- During the CHMP meeting on 23 April 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 13 May 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 3 June 2015
- PRAC RMP Advice and assessment overview, adopted by PRAC on 11 June 2015
- During the meeting on 25 June 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Duloxetine Zentiva.

2. Scientific discussion

2.1. Introduction

This application for a marketing authorisation for Duloxetine Zentiva concerns a generic medicinal product of the centrally authorised product Cymbalta.

Duloxetine (ATC code: N06AX21), a combined serotonin (5-hydroxytryptamine) and norepinephrine reuptake inhibitor (SNRI). It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors. Duloxetine dose-dependently increases extracellular levels of serotonin and noradrenaline in various brain areas. It possesses central pain inhibitory actions, probably related to its potentiation of serotonergic and noradrenergic activity in the CNS.

Cymbalta is approved for treatment of major depressive disorder, treatment of diabetic peripheral neuropathic pain and in the treatment of generalised anxiety disorder.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as gastro-resistant hard capsules containing duloxetine hydrochloride equivalent to 30 mg and 60 mg of duloxetine as active substance.

Other ingredients are:

Capsule content: sucrose, maize starch, hypromellose, talc, hypromellose acetate succinate and triethyl citrate.

Capsule cap: indigo carmine (E132), titanium dioxide (E171) and gelatin.

Capsule body: titanium dioxide (E171), gelatin and yellow iron oxide (E172) (60 mg).

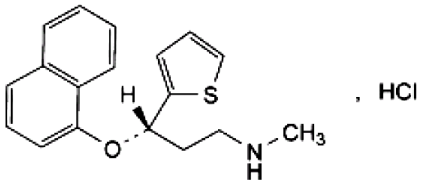
The product is available in opaque PVC/PCTFE/Alu blisters

2.2.2. Active substance

General information

The active substance is duloxetine hydrochloride, which is described in the Ph Eur.

The chemical name of duloxetine hydrochloride is (3S)-N-Methyl-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propan-1-amine hydrochloride and has the following structure:



The active substance is a white or almost white not hygroscopic powder, sparingly soluble in water, freely soluble in methanol, and practically insoluble in hexane.

Duloxetine hydrochloride exhibits stereoisomerism due to the presence of one chiral centre. Enantiomeric purity is controlled routinely by chiral HPLC/specific optical rotation. In addition, no changes are seen during manufacture or storage of the finished product. Absence of routine testing of polymorphic form in the finished product is considered justified.

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

As there is a monograph of duloxetine in the European Pharmacopoeia, the second manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for duloxetine which has been provided within the current Marketing Authorisation Application for the second manufacturer if the active substance.

Manufacture, characterisation and process controls

Two suppliers manufacture the active substance.

An Active Substance Master File has been submitted by one of the manufacturers. The active substance is synthesized in 4 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. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

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

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability for duloxetine hydrochloride supplied by the second manufacturer.

Specification

The finished product manufacturer applies the specifications set in the Ph Eur monograph for duloxetine hydrochloride. In addition, tests for microbiological purity (according to Ph Eur) and residual solvents are included.

The active substance specification applied by the finished product manufacturer includes tests for appearance, identity (specific optical rotation, IR, identity of chlorides (Ph Eur), enantiomeric purity (Ph Eur), related substances (Ph Eur), heavy metals (Ph Eur), loss on drying (Ph Eur), sulphated ash (Ph Eur),assay (HPLC), microbiological purity (Ph Eur), and residual solvents (GC).

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

Batch analysis data (3 commercial scale batches per manufacturer) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

For one manufacturer, stability data on two production scale batches of active substance stored in the intended commercial package for 6 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 were provided. Photostability testing following the ICH guideline Q1B was performed on 1 batch. Results on stress conditions at elevated temperature (100°C for 24 hours), light (daylight and UV radiation for 24 hours), oxidizing (H2O2), alkaline (NaOH) and acidic (acetic acid or HCl) medium were also provide on 1 batch.

The following parameters were tested: appearance, specific optical rotation, related substances (HPLC), enantiomer purity, loss on drying, assay (HPLC) and microbiological quality. All the results at all storage conditions were acceptable in accordance to the specifications. No changes or trends of the results were observed.

For the second manufacturer, three validations batches stored in the intended for commercial package for 60 months at 25°C/60% RH and for 6 months at 40°C/75% RH. The following parameters were tested: appearance, identification (IR), P-XRD, loss on drying, related compounds (HPLC), enatiomeric purity (HPLC) and assay (HPLC). All the results in all batches at both accelerated and long-term storage conditions complied with the specification limits. There were no specific trends observed.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period with no special temperature storage conditions in sealed duplicate polyethylene bags placed into a PE drum.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The objective of the development was to prepare a formulation containing duloxetine hydrochloride which would be bioequivalent to the reference product. Cymbalta gastro–resistant hard capsules was the chosen reference medicinal product.

Duloxetine is an active substance described in the Ph. Eur. The characteristics of the active substance were taken into account during the finished product development. 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. Commonly used excipients in pharmaceutical area for the production of enteric coated pellets was chosen. A enteric coated layer containing a water suspension of hypromellose acetate succinate, talc and triethyl citrate is added on the pellets. Triethyl citrate is a plasticiser which prohibits cracking of enterosolvent layer of pellets. Quantities of these excipients were determined on the basis of results of acid-resistance and stability of the pellets. Sugar spheres are mainly used as inert cores in capsule and tablet formulations, particularly multi-particulate sustained–release formulations. Sugar spheres contain sucrose, Maize starch and may also contain starch hydrolysates and colour additives. Hypromellose acetate succinate is mainly used as component of controlled or sustained-release dosage forms, enteric coating agent, film-forming agent and solid dispersion vehicle. It is also used in the manufacture of capsules as an adhesive. Talc is used as lubricant and sucrose is used as capsule diluent. Opadry clear complete film coating system contains hypromellose and talc. No incompatibility between excipients has been observed and no incompatibility between excipients has been described in literature.

For the formulation development, layering technology and enteric coating were taken into consideration. Layering technology was used for the pellets manufacture. Sugar spheres of different sizes were used as starting material upon which layers of active ingredient, separation and enteric polymer were applied. The functions of the separating layer are to provide a smooth base for the application of the enteric layer, to prolong the pellets resistance to acid conditions, to improve stability by inhibiting any interaction between the active substance and the enteric polymer in the enteric layer and improve stability by protecting the active substance from light exposure. For the protection of the active substance against decomposition in stomach, enteric polymer hypromellose acetate succinate (aqueous suspension of the dispersion of HPMC AS in water) was used as the base of enteric coating.

A single dose dissolution study in 0.1 M hydrochloric acid for 120 minutes followed by pH 6.8 phosphate buffer for 120 minutes (official/release media) and pH 4.5 acetate buffer for 120 minutes followed by pH 6.8 Phosphate buffer for 120 minutes (to simulate fed condition) on the 60 mg strength was carried out on the reference product Duloxetin 60 mg gastro-resistant hard capsules, and slightly different formulations of the generic medicinal product (differences in quantity of enteric coating layer and separating layer and technology process of enteric coating layering). Based on the f2 results, one of the formulations was chosen for marketing. The choice of in-vitro dissolution method was described and acceptable discriminatory ability of the method was demonstrated.

A bioequivalence study was performed for the 60 mg strength showing bioequivalence between the reference product and the proposed commercial formulation. The formulation used during bioequivalence studies is the same that the used for marketing except the colorants used.

In order to support the biowaiver of the 30 mg strength and the similarity of dissolution profiles of the 30 mg strength and the 60 mg strength, comparative dissolution profiles of the two strengths were measured in two dissolution media. It was confirmed that the 30 mg capsules fulfil the general biowaiver conditions, presented in the Guideline on the investigation of bioequivalence. The comparison of dissolution profiles of the two strengths in pH 6.8 (after 2 hours in acidic media pH 1.2) and in pH 6.8 (after 2 hours in acetate buffer pH 4.5) demonstrated that the biowaiver for the 30 mg strength can be granted.

The development of the manufacturing process was based on the reference medicinal product parameters.

Inert sugar spheres were selected to prepare pellets coated with the active substance. The selected pellet size met the relevant requirements in a manufacture process. Pellets of different size were tested during the development, but were not considered suitable. Sugar was added to the separating layer to increase the pellets resistance in acid conditions. For the processing of separation coating some additional excipients were studied. In relation to the enteric coating, the experimental process indicated that the crucial points are quantity of applied enteric coating, the coating integrity and uniformity of the coating application over the pellet surface. The type of enteric polymer and thickness of enteric layer was determined to be critical for similarity of dissolution rate with the reference medicinal product.

The capsules are packed in blisters of opaque PVC/ PCTFE film-Aluminium foil. The PVC film complies with Ph Eur requirements and the EU regulations for materials intended for contact with food. Aluminium complies with the same EU Directive.

Acceptable specifications and certificate of analysis for the PVC/ PCTFE film and aluminium foil has been provided.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: active coating, protective coating, enteric coating, encapsulation and packaging. The process is considered to be a non-standard manufacturing process.

The process has been validated for three production scale batches of each strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, uniformity dosage units (Content uniformity (HPLC)), identity of duloxetine (HPLC, UV), identity of chlorides (Ph Eur), identity (titanium dioxide, indigo carmine, Ph Eur), disintegration (HPLC), related substances (HPLC), assay (HPLC), , dissolution (HPLC) and microbiological purity (Ph Eur) .

Batch analysis results are provided for 3 production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

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

Stability of the product

Stability data of 7 batches (production and pilot scale) of each strength of the finished product stored under long term conditions for up to 36 months at 25 ºC / 60% RH, for up 12 moths at 30 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, average mass of 1 capsule's filling, identity of duloxetine (HPLC, UV), identity of chlorides (Ph Eur), identity (titan dioxide, indigo carmine and ferric oxide), disintegration (Ph Eur), content of duloxetine (HPLC), content uniformity (HPLC), dissolution, microbiological purity (Ph Eur) and water (K.F). The analytical procedures used are stability indicating.

Supportive stability studies on one batch of capsules and on two batches of pellets stored at 25 ºC / 60% RH for up 12 months in bulk was as well studied. The tests parameters studies were appearance, identity of duloxetine (HPLC, UV), identity of chlorides, related substances (HPLC), content of duloxetine in 1 g of pellets (HPLC), dissolution (HPLC), microbiological purity (Ph Eur) and water (K.F.).

In addition, 1 batch of the lowest strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Test parameters were appearance (capsule and filling of capsule), average mass, related substance 3-isomer, other known impurities individually, unknown impurities individually and sum of impurities.

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

Based on available stability data, the shelf-life of two years with no special storage conditions as stated in the SmPC are acceptable.

Adventitious agents

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

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

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. 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 Duloxetine Zentiva is considered unlikely to result in any significant increase in the combined sales volumes for all duloxetine containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Conclusion on the non-clinical aspects

For a generic of a reference medicinal product no toxicological and pharmacological tests are required. The CHMP concluded that no additional non-clinical data were required.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for 2 different strengths (30mg and 60mg) of duloxetine gastro-resistant capsules. To support the marketing authorisation application the applicant conducted 2 bioequivalence studies with cross-over design, one under fasting conditions and one under fed conditions. These studies were pivotal 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 Rev. 1 / Corr) as well as the guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr 2), Note for guidance on modified release oral and transdermal dosage forms: section II (pharmacokinetic and clinical evaluation) (CPMP/EWP/280/96 Corr) and Question number 3 of the Questions & Answers: Positions on specific questions addressed to the Pharmacokinetics Working Party (EMA/618604/2008) in their current versions, are of particular relevance.

GCP

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

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

According to the current GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), a bioequivalence study investigating only one strength for each pharmaceutical form may be acceptable if all of the following 5 conditions are fulfilled:

- the pharmaceutical products are manufactured by the same manufacturing process;
- the drug pharmacokinetics is linear;
- the qualitative composition of the different strengths is the same;
- the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule);
- the dissolution profiles are similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

The applied product as well as the reference product is multiple-unit dosage forms, containing gastro-resistant pellets filled in capsules. For a multiple unit delayed-release formulation establishing bioequivalence at one strength only is sufficient provided that the formulations contain identical beads or pellets and that the dissolution profiles are similar.

The BE-studies were carried out on Duloxetin 60 mg gastro-resistant hard capsules. Studying the highest strength is adequate considering that the pharmacokinetics is linear (or possibly slightly non-linear with a more-than-proportional increase in plasma concentration with increasing doses). The dissolution properties have been compared with the reference product and found acceptable. From a pharmacokinetic perspective, a biowaiver for the lower 30 mg strength is thus acceptable. Requirements of biowaiver for the lower strength (30 mg) have thus been fulfilled.

Clinical studies

To support the application, the applicant has submitted two pivotal single-dose bioequivalence studies, using the 60 mg strength, one under fasting conditions and one under fed conditions:

Study DLN-P1-592 (fasted state)

Study DLN-P1-593 (fed state)

In addition, the applicant has submitted the synopsis of a pilot study in which 4 different test formulations were compared in the fed state. Conventional bioequivalence criteria were fulfilled for two of the formulations (test-1 and test-2). Based on the results from the pilot study, test-1 was selected as the to-be-marketed formulation and was used in the pivotal studies.

The application concerns a delayed-release formulation for which single-dose bioequivalence studies under fasting and fed conditions are adequate.

2.4.2. Pharmacokinetics

Duloxetine is administered as a single enantiomer. Duloxetine is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of duloxetine demonstrate large inter-subject variability (generally 50–60%), partly due to gender, age, smoking status and CYP2D6 metaboliser status.

Absorption: Duloxetine is well absorbed after oral administration with a C_{max} occurring 6 hours post dose. The absolute oral bioavailability of duloxetine ranged from 32% to 80% (mean of 50%). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11%). These changes do not have any clinical significance and therefore there are no restrictions with respect to food in the SmPC of the originator.

Distribution: Duloxetine is approximately 96% bound to human plasma proteins.

Biotransformation: Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both cytochromes P450-2D6 and 1A2 catalyse the formation of the two major inactive metabolites.

Elimination: The elimination half-life of duloxetine ranges from 8 to 17 hours (mean of 12 hours).

Linearity: According to the EPAR of Cymbalta there is an apparent slight non-linear behaviour and more-than-proportional increase in plasma concentration across the duloxetine dosage range of 40 mg/day to 120 mg/day. Nevertheless, the magnitude of the deviation from strictly linear pharmacokinetic behaviour is small. In a study by Zhao and colleagues, linear pharmacokinetics was observed within the range 30-90 mg (Zhao et al., 2009).

Study DLN-P1-592 and Study DLN-P1-593

Methods

Study design

Both studies were single-dose, two-way crossover studies conducted in 34 healthy volunteers at Algorithme Pharma Inc., Mount-Royal, Quebec, Canada in 2011. Blood samples were collected pre-dose and up to 48 hours post-dose and the study periods were separated by a wash-out period of 7 days. The meal provided in the fed study was consistent with the guideline recommendations for a high-fat high-calorie meal that is recommended for a study in the fed state The study design is considered acceptable by the rapporteur.

Test and reference products

Test product: Duloxetine, 60 mg, gastro-resistant capsules, manufactured by Zentiva, k.s., Czech Republic, batch No. 49310311 AA, expiry date: 12/2011, assayed content 101.0 %.

Reference product: Cymbalta, 60 mg, gastro-resistant capsules, by Eli Lilly from the Czech Republic market, batch No. A786483, expiry date: 03/2013, assayed content 101.3 %.

The assayed content of the batch used as test product did not differ more than 5% from that of the batch used as reference product.

Analytical methods

Plasma concentrations of duloxetine were determined with an adequately validated LC/MS/MS method using duloxetine-D3 as internal standard. K_2EDTA was used as anticoagulant. The calibration range was 0.500-100.00 ng/ml. Long-term stability of analyte in matrix for a period covering the time from first sample collection until last sample analysis was demonstrated. The performance of the analytical method was satisfactory. The use of an achiral analytical method is acceptable since duloxetine is given as pure enantiomer.

Pharmacokinetic Variables

Pharmacokinetic variables were calculated using conventional non-compartmental methods. The pharmacokinetic variables included C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, t_{max}, t½ and extrapolated AUC.

Statistical methods

The statistical analysis was performed on log-transformed AUC_{0-t} and C_{max} using ANOVA. Bioequivalence was to be concluded if the 90% confidence intervals for the test/reference ratio of the population geometric means fell within 80.00-125.00% for AUC_{0-t} and C_{max}.

Results

Study DLN-P1-592 in the fasted state

Table 1 Pharmacokinetic parameters for duloxetine (non-transformed values) in study DLN-P1-592 in the fasted state, n=28

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	CV%	arithmetic mean	CV%
$AUC_{(0-t)}$ (ng*h/ml)	640.46	51.5	658.28	45.7
$AUC_{(0-\infty)}$ (ng*h/ml)	699.10	56.5	706.29	50.3
C_{max} (ng/ml)	39.50	38.5	42.93	37.0
T_{max}*(h)	5.75 (4.50-9.00)		6.00 (3.00-8.00)	
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 2 Statistical analysis for duloxetine (ln-transformed values) in study DLN-P1-592 in the fasted state

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	94.92	86.20-104.52	21.3
C_{max}	92.30	82.60-103.14	24.7
* estimated from the Residual Mean Squares			

The extrapolated AUC was less than 20% in all subjects except in one subject given test product where it was just above 20 % (20.76%). No pre-dose concentrations were detected and no subjects reached t_{max} at the first sampling point.

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study DLN-P1-593 in the fed state

Table 3 Pharmacokinetic parameters for duloxetine (non-transformed values) in study DLN-P1-593 in the fed state, n=28

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	CV%	Arithmetic mean	CV%
$AUC_{(0-t)}$ (ng*h/ml)	737.47	52.6	694.61	60.4
$AUC_{(0-\infty)}$ (ng*h/ml)	794.95	58.0	750.97	66.7
C_{max} (ng/ml)	50.59	48.8	47.44	51.4
T_{max}*(h)	8.50 (6.50-11.00)		8.50 (5.00-12.00)	
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 4 Statistical analysis for duloxetine (non-transformed values) in study DLN-P1-593 in the fed state

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	107.55	101.31-114.18	13.1
C_{max}	106.69	99.14-114.82	16.1
* estimated from the Residual Mean Squares			

The extrapolated AUC was less than 20% in all subjects. Subject 27 had a period 2 (reference) pre-dose concentration of 0.569 ng/ml (result from repeated assay). Since the pre-dose concentration was less than 5% of the C_{max} value for this subject in period 2, the subject's data was included in the pharmacokinetic and statistical analysis. This was in accordance with the protocol and in line with guideline recommendations and is acceptable. No subjects reached t_{max} at the first sampling point.

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Conclusions

Based on the presented bioequivalence studies Duloxetine Zentiva 60 mg gastro-resistant capsules are considered bioequivalent with Cymbalta 60 mg gastro-resistant capsules.

The results of study DLN-P1-592 and DLN-P1-593 with the 60 mg capsules can be extrapolated to the other 30mg strength, according to conditions provided for in the Guideline on the Investigation of Bioequivalence.

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

In support of this application, results from two bioequivalence (BE) studies were provided, both using the 60 mg strength formulation.

No new efficacy or safety data has been submitted. The clinical overview, dated May 2014, consists of a review of published literature (58 references) on clinical, pharmacological and toxicological profile of duloxetine.

Bioequivalence has been adequately demonstrated between test (60 mg strength) and reference product. Bioequivalence of the 30 mg strength has also been accepted since all conditions for biowaiver of additional strength according to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP /1401/98 Rev. 1/ Corr) have been considered as fulfilled.

2.4.6. Conclusions on clinical aspects

Bioequivalence has been adequately demonstrated between test and reference product.

A summary of the literature with regard to clinical data of Duloxetine Zentiva and justifications that Duloxetine Zentiva does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

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 and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

2.6. Risk management plan

The PRAC considered that the risk management plan version 1.3 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• Suicidality • Hepatic risks • Stevens-Johnson Syndrome • Hyperglycaemia • Gastrointestinal tract bleeding
Important potential risks	• Renal failure • Cardiovascular events including those with concomitant use of NSAIDs (including myocardial infarction, heart failure, and stroke)
Missing information	• Prospective data about potential risks of exposure to duloxetine during pregnancy • Use of duloxetine 120 mg in elderly patients

Pharmacovigilance plan

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Suicidality	Warning in section 4.4 with description of these conditions, precautions, preventive measures and proper management. Especially in subjects with a predisposition to suicidal behaviour and in paediatric population (under 18 years of age). Listed in section 4.8 Pharmacodynamic properties are described in section 5.1	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Prescription only medicine.	
Hepatic risks	Proper method of administration described in section 4.2. Contraindication in conditions in section 4.3. Warning in section 4.4 with description of these conditions, precautions, risk factors, preventive measures and proper management. Listed in section 4.8 Preclinical safety data are detailed in section 5.3 Prescription only medicine.	None proposed.
Stevens-Johnson Syndrome	Listed in section 4.8. Prescription only medicine.	None proposed.
Hyperglycaemia	Listed in section 4.8. Prescription only medicine.	None proposed.
Gastrointestinal tract bleeding	Warning in section 4.4 with description of these conditions, precautions, risk factors, preventive measures and proper management. Listed in section 4.8. Prescription only medicine.	None proposed.
Renal failure	Proper method of administration described in section 4.2. Contraindication in conditions in section 4.3. Warning in section 4.4. Listed in section 4.8. Prescription only medicine.	None proposed.
Cardiovascular events including those with concomitant use of NSAIDs (including myocardial infarction, heart failure and	Contraindication in conditions in section 4.3. Warning in section 4.4 with description of these conditions, precautions, risk factors, preventive measures and proper management. Listed in sections 4.8. Prescription only medicine.	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
stroke)		
Prospective data about potential risks of exposure to duloxetine during pregnancy	Warning in section 4.6 with description of these conditions, precautions, risk factors, preventive measures and proper management. Preclinical safety data are detailed in section 5.3 Prescription only medicine.	None proposed.
Use of duloxetine 120 mg in elderly patients	Proper method of administration described in section 4.2. Warning in section 4.4 with description of these conditions, precautions, risk factors, preventive measures and proper management. Pharmacodynamic properties are described in section 5.1 Pharmacokinetic properties are detailed in section 5.2 Prescription only medicine.	None proposed.

2.7. PSUR submission

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

The applicant has submitted the report from user consultation of the package leaflet. The results 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.

3. Benefit-risk balance

This application concerns a generic version of Duloxetine gastro-resistant capsules.

The reference product Cymbalta is indicated for the treatment of major depressive disorder, treatment of diabetic peripheral neuropathic pain and the treatment of generalised anxiety disorder. 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.

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 two bioequivalence studies formed the pivotal basis of the application. The study designs were considered adequate to evaluate the bioequivalence of this formulation and were in line with the respective European requirements.

The test formulation of Duloxetine Zentiva 60mg gastro-resistant capsules met the protocol-defined criteria for bioequivalence when compared with Cymbalta 60mg capsules. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

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 Duloxetine Zentiva in the *treatment of major depressive disorder, treatment of diabetic peripheral neuropathic pain and in the treatment of generalised anxiety disorder* 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**

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 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 dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

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

Not applicable.