EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 April 2015
EMA/368328/2015
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Duloxetine Sandoz

International non-proprietary name: duloxetine

Procedure No. EMEA/H/C/004009/0000

Note

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

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List of abbreviations

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
AUC_{0-inf}	Area Under the plasma Concentration-time curve from time zero to infinity
AUC_{0-t}	Area Under the plasma Concentration-time curve from time zero to t hours
BDL	Below the limit of detection
BE	Bioequivalence
BLQ	Below limit of quantification
BSE	Bovine spongiform encephalopathy
CEP	Certificate of Suitability of the Ph. Eur.
CL/F	Oral clearance
C_{max}	maximum plasma concentration
CoA	Certificate of Analysis
CP	Centralised procedure
CRF	Case report form
CRS	Chemical reference substance
DMF	Drug Master File = Active Substance Master File
EC	European Commission
EMA	European Madicines Agency
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HPLC	High Pressure Liquid Chromatography
CHMP	Committee for Human Medicine Products
ICH	International Conference of Hamrnization
INN	International Non-proprietary Name
IR	Infrared
IS	Internal standard
K_{el}	Elimination rate constant
LLOQ	Lower Limit of Quantification
LOD	Limit of Detection
LoQ	List of Questions
LOQ	Limit of Quantification
MA	Marketing Authorisation
MAA	Marketing Authorisation Aplication
MAH	Marketing Authorisation holder
MS	Mass Spectrometry
ND	Not detected
NMT	Not more than
NSAID	Non-Steroidal Anti-Inflammatory Drug
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PhV	Pharmacovigilance
PIL	Patient Information Leaflet
PK	pharmacokinetic
PP	Polypropylene
PVC	Poly vinyl chloride
QC	Quality Control (samples)
QP	Qualified Person
RRF	
RSD	Relative standard deviation
Rt	Retention time
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
STD	Standard Deviation
T/R	Test/Reference

T_{max}	time for maximum concentration (* median, range)
TSE	Transmissible spongiform encephalopathy

1. Recommendations

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the generic application for Duloxetine Sandoz in the treatment of major depressive disorder, diabetic peripheral neuropathic pain and generalised anxiety disorder in adults

is not approvable since "major objection" has been identified, which preclude a recommendation for marketing authorisation at the present time. Details of this major objection are provided in the List of Questions (see section 5).

The major objection precluding a recommendation of marketing authorisation, pertains to the following principal deficiencies:

Clinical/bioanalytical/PK/statistical study site Azidus has not been previously inspected in relation to a centralised MAA procedure and therefore, the inspection of the clinical studies AZ/BE/01/12/11 and AZ/BE/01/12/12 will be carried out in the year 2015.

During the assessment, numerous concerns were raised regarding the GCP compliance during both studies, especially regarding the In-study and Pre-study validation and adequate clarifications and justifications should be provided (questions are listed below).

Since clinical studies AZ/BE/01/12/11 and AZ/BE/01/12/12 are the pivotal studies provided for this application, their GCP compliance is a major concern.

In addition, satisfactory answers must be given to the "other concerns" on quality, non-clinical and clinical data as detailed in the *List of Questions*.

Questions to be posed to additional experts

Inspection issues

GMP inspection(s)

Valid manufacturing authorisations and certificates for GMP compliance for all sites of the manufacturing process are available.

However, the manufacturer's authorisation responsible for batch control does not cover microbiological testing. Therefore, a site for microbiological testing for the batch release in EU should be confirmed and an adequate GMP certificate for the microbiological testing site should be submitted.

GCP inspection(s)

Clinical/bioanalytical/PK/statistical study site Azidus has been inspected by several non-EU authorities (including Brazil, Turkey, Chile) for GCP and by member state Poland for GLP. Study site Azidus has not been previously inspected in relation to a centralised MAA procedure and therefore, the inspection of the clinical studies AZ/BE/01/12/11 and AZ/BE/01/12/12 will be carried out in the year 2015. During the assessment, numerous concerns were raised regarding the GCP compliance during both studies.

A request for GCP inspection has been adopted for the following clinical studies: AZ/BE/01/12/11 and AZ/BE/01/12/12. The outcome of this inspection and the satisfactory responses to its findings are part of the responses to the LoQ and will be needed by Day 121.

2. Executive summary

2.1. Problem statement

N/A (generic application)

2.2. About the product

Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor. It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors.

Duloxetine 30 mg and 60 mg is authorised in EU in adults for the treatment of major depressive episodes; the treatment of diabetic peripheral neuropathic pain; the treatment of generalised anxiety disorder. Duloxetine 20 mg and 40 mg is authorised in EU for women for the treatment of moderate to severe stress urinary incontinence.

The starting and recommended maintenance dose is 30 mg or 60 mg once daily (depending on the indication) with or without food with a maximum dose of 120 mg per day.

2.3. The development programme/compliance with CHMP guidance/scientific advice

To support the application, the Applicant has submitted two bioequivalence studies. Two bioequivalence studies were conducted on the 60 mg gastro-resistant capsules strength under fasting and fed conditions. In vivo bioequivalence studies for the other strength (30 mg) have been waived.

The Applicant did not receive CHMP Scientific Advice pertinent to the clinical investigation.

2.4. General comments on compliance with GMP, GLP, GCP

GMP: No issues that would trigger a GMP inspection have been identified by the CHMP during the assessment of the information in Module 3 of the dossier.

GCP: Issues that would trigger a GCP inspection have been identified by the CHMP during the assessment of the information in Module 5 of the dossier. However, a routine inspection of the clinical studies AZ/BE/01/12/11 and AZ/BE/01/12/12 will be carried out in the year 2015 since the clinical/bioanalytical/PK/statistical study site Azidus has not been previously inspected in relation to a centralised MAA procedure.

2.5. Type of application and other comments on the submitted dossier

The type of application for Duloxetine Sandoz, 30 mg and 60 mg, gastro-resistant capsules, hard is a generic application made according to Article 3(3) of Regulation EC 726/2004 “Generic of a Centrally Authorised Medicinal Product” and Article 10(1) of Directive 2001/83/EC. The Applicant is Sandoz GmbH. The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Cymbalta 30 mg and 60 mg, gastro-resistant capsule, hard, authorised in EU since 2004, with Eli Lilly Nederland B.V. as marketing authorisation holder.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

Active substance in the drug product, duloxetine hydrochloride, is supplied from two manufacturers. For both drug substance manufacturers the CEP procedure is applied.

The proposed drug product Duloxetine Sandoz gastro-resistant capsules, hard is available in two strengths, 30 mg and 60 mg of duloxetine (as hydrochloride) per capsule. Both capsule strengths are produced from the same gastro-resistant pellets filled in different capsule sizes. The manufacturer of gastro-resistant pellets and capsules was stated. The capsules are packed in three different container types (Alu-OPA/Alu/PVC blisters, Alu-PVC/Aclar blisters or HDPE bottles) in the different pack sizes.

The finished product quality control testing site in the EEA and the site responsible for batch release in the EEA have been stated.

Submitted Module 3 does not provide sufficient data on drug product quality and, thus, a number of concerns have been raised. Furthermore, Module 2.3.P of Quality Overall Summary includes additional dissolution profiles of the batches not included in the development section of Module 3.2.P. Thus, data in the Module 3 and Quality Overall Summary are not harmonized.

3.1.2. Active Substance

Manufacture, characterisation and process controls

Duloxetine hydrochloride is described in Ph.Eur. 7.5. (7/2012:2594). Two manufacturers have been selected as manufacturers of the drug substance. For both manufacturers Certificates of Suitability are issued, of which valid copies are provided in the dossier. For one manufacturer duloxetine hydrochloride stability data are covered by the CEP. For the other manufacturer duloxetine hydrochloride stability data are provided in the dossier and the proposed re-test period could be acceptable if adequate storage conditions will be defined. Since CEP procedure is applied, no further information is required from the drug substance manufacturers.

Specification

The drug product manufacturer's specification for duloxetine hydrochloride has been set according to the current Ph.Eur. monograph with additional tests for residual solvents, particle size and microbial limits. However, it is not fully in line with provided CEPs (residual solvents). Furthermore, determination of polymorphic form has not been included in the drug substance specification which is not justified. Accordingly, few questions have been raised.

Stability

Stability data for duloxetine from one source are not covered by the CEP, therefore the data have been provided in the dossier. The stability study has been conducted according to the Guideline on stability testing CPMP/QWP/122/02.

It has also been demonstrated that in-house HPLC methods for assay, related substances and chiral purity are stability indicating. During the validation of HPLC methods for determination of

related substances, assay and chiral purity (R-isomer), photo degradation study has been performed in line with ICH Q1B which has revealed that the drug substance is photostable.

Information (including validation data) on analytical procedures used in the stability studies should be provided. The defined limits for stability study parameters are same as the limits proposed in section 3.2.S.4.1 and the relevant analytical procedures are given in section 3.2.S.4.2.

The accelerated and long-term stability studies up to thirty-six months are performed as per in-house specification and methods of analysis.

There are no significant changes of tested parameters (appearance, loss of drying, related substances, assay and enantiomeric purity) up to 6 months under accelerated and up to 48 months under long-term conditions. The conclusion of the stability studies is should be clarified and particularly, the temperature conditions for storing the drug substance should be defined according to CPMP/QWP/609/96/Rev 2 Guideline on declaration of storage conditions.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The drug product is presented as gastro-resistant capsules, hard in the strengths of 30 mg and 60 mg of duloxetine (as hydrochloride). Both capsule strengths are manufactured from the same gastro-resistant pellets filled in different capsule size.

Formulation development was performed on 60 mg capsules (30 mg capsules are dose proportional). The choice of excipients in the drug product is based on the composition of the reference product Cymbalta. The function of each excipient in the formulation is briefly discussed without considering the potential interaction of duloxetine and the enteric coating agent and formation of a related impurity. Consequently, in the other sections, including control and stability sections, several objections are raised concerning potential formation of this impurity in the drug product.

Adequate dissolution data as a support to biowaiver for 30 mg capsules has not been provided in the development section as all presented dissolution profiles for both strengths are related to the small laboratory batches/5000 capsules. Since, in Module 2.3.P and Module 1.5.2 dissolution profiles on additional batches have been presented, it is presumed that dissolution data as a support to biowaiver for 30 mg capsules are available. Consequently, major objection has not been raised.

Manufacture of the product and process controls

Data on the manufacturing process development are also found incomplete since critical parameters which have direct impact on the quality of the drug product have not been concerned. Presented validation data for the 3 exhibited batches do not demonstrate that optimum efficiency and homogeneity of the manufacturing process have been ensured. A number of questions considering presented validation results and in-process controls have been raised.

Since the manufacturing process is considered as a non-standard process, full validation data and certificates of analysis should be presented for commercial batches of both capsule strengths.

Product specification

Provided drug product specifications are standard for the pharmaceutical form and include relevant physicochemical, identification, assay and impurities tests. Since few objections have been raised,

specifications are not acceptable at this moment. Also several issues have been raised on proposed analytical methods and validation data.

Stability of the product

Although all available results of the stability studies are within proposed specification limits, considering that several objections about the drug product specifications and analytical methods have been raised, proposed shelf-life cannot be accepted at this time point. Additionally, stability results for each container type are not provided at all conditions nor were all parameters tested which is not acceptable since reduced design has not been applied. During stability testing at all conditions, changes in dissolution profile in buffer stage and increase in loss on drying are observed which is not discussed.

Further, it is stated that this medicinal product does not require any special storage conditions but at the same time storage in the original package in order to protect from moisture is proposed (type of container has not been specified). The need for protection of the drug product from moisture has not been evident from presented stability results, and, thus, it is not possible to assess whether there is a need for any special storage conditions without additional information.

Stability data after first opening of the bottle should be provided and shelf-life after first opening should be proposed accordingly.

3.1.4. Conclusions on the chemical, pharmaceutical and biological aspects

A number of concerns have been raised with respect to the quality of the drug product. Before Duloxetine Sandoz 30 mg and 60 mg gastro-resistant capsules, hard could be recommended for approval, the Applicant should provide satisfactory responses to the other concerns, as outlined in the List of Questions.

3.2. Non clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided. No further non-clinical studies are required. However, references cited in the non-clinical literature review are not provided in Module 4.

3.2.1. Ecotoxicity / environmental risk assessment

Since the introduction of Duloxetine Sandoz manufactured by Sandoz GmbH 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, no ERA was submitted. This is considered acceptable.

3.2.2. Conclusion on non-clinical aspects

There are no major objections to approval of Duloxetine Sandoz from a non-clinical point of view although there are some minor issues that need to be clarified. The non-clinical overview is up-to-date and seems to be based on adequate scientific literature. However, full-text papers should be submitted for all the references.

3.3. Clinical aspects

An adequate Clinical Overview containing a sufficient outline of the published literature regarding the clinical pharmacology, efficacy and safety of duloxetine has been submitted. It refers to 50 publications dating from 2000 up to the year 2014 that are not included in the Module 5 Literature references. Full-text papers should be submitted for all references cited in the section 2.5.7 Literature references.

Different pack sizes, not identical to the reference product's pack sizes, are proposed by the Applicant. Considering the fact that the proposed pack sizes enable additional flexibility in the therapy introduction, dose titration as well as therapy discontinuation, proposed pack sizes are considered acceptable.

According to EMA reference INS/GCP/2014/024, clinical/analytical/PK/statistical facility used in the trials supporting this application has not been previously inspected in relation to a centralised MAA procedure. The inspection of the clinical studies AZ/BE/01/12/11 and AZ/BE/01/12/12 will be carried out in year 2015 in accordance with Article 57 of Council Regulation (EC) No. 726/2004 and Article 15 of Directive 2001/20/EC.

During the assessment, numerous concerns were raised regarding the GCP compliance during both studies, especially regarding the In-study and Pre-study validation. All observations are presented in the Rapporteur's clinical report in detail and will be taken into account during the planned GCP inspection.

Exemption

In accordance with the *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1*, bioequivalence has been demonstrated at the 60 mg strength which is the most sensitive to detect a potential difference between the products. Two bioequivalence studies were conducted on the 60 mg strength under fasting and fed conditions. The Applicant requests for waiver of a BE study on the 30 mg strength based on the results of the BE study with the 60 mg strength. Since both strengths are dose proportional and general biowaiver criteria of *Guideline on the investigation of bioequivalence* are met, a waiver for additional strength (30 mg) is possible. The dissolution profiles between two strengths of the test product show similarity in 0.1N HCl followed by pH 6.8 as well as at pH 4.5 followed by pH 6.8. Additionally, dissolution tests with 2 hours in 0.1 N HCl and at pH 4.5 show a release of less than 10%. Final decision on the acceptability of the waiver for additional strength (30 mg) will be made after the Applicant provides additional information on the size of the batches in question.

In vitro comparative dissolution profiles between the biobatches of the test and reference product were investigated in 0.1N HCl followed by pH 6.8 phosphate buffer only. Additional dissolution profiles between the test and reference product (60 mg) performed at pH 4.5 followed by pH 6.8 should be provided.

Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective of Study	Study Design and Type of Control	Investigational Products; Dosage Regimen; Route of Administration	Number of Subjects	Subject Type	Duration of Treatment	Study Status; Type of Report
Bioequivalence (BE)	Azidus Laboratories Limited Study No. AZ/BE/01/12/12	Section 5.3.1.2 (Module 5)	Primary objective of the study is to investigate the bioequivalence of Duloxetine Hydrochloride Gastro resistant Capsules 60mg of [redacted] and Cymbalta® (Duloxetine Hydrochloride) Gastro Resistant capsules 60 mg of Lilly S.A., Spain, Market Authorization by Eli Lilly Nederland BV, Netherland in 56 healthy adult, human subjects under fed conditions.	Open label, balanced, randomized, two treatment, two sequence, two period, single dose, crossover, oral bioequivalence study under fed conditions	**Reference:** Cymbalta® (Duloxetine hydrochloride) Gastro-Resistant Capsules Capsules, 60 mg Single dose, Oral route of administration. **Test:** Duloxetine hydrochloride) Gastro-Resistant Capsules, Capsules, 60 mg Single dose, Oral route of administration.	56 (56 males) 49 completing (49M)	Healthy subjects	Single dose	Complete As per ICH E3 Guideline

Type of Study	Study Identifier	Location of Study Report	Objective of Study	Study Design and Type of Control	Investigational Products; Dosage Regimen; Route of Administration	Number of Subjects	Subject Type	Duration of Treatment	Study Status; Type of Report
Bioequivalence (BE)	Azidus Laboratories Limited Study No. AZ/BE/01/12/11	Section 5.3.1.2 (Module 5)	Primary objective of the study is to investigate the bioequivalence of Duloxetine Hydrochloride Gastro resistant Capsules 60mg of [redacted] and Cymbalta® (Duloxetine Hydrochloride) Gastro Resistant capsules 60 mg of Lilly S.A., Spain, Market Authorization by Eli Lilly Nederland BV, Netherland in 56 healthy adult, human subjects under fasting conditions.	Open label, balanced, randomized, two treatment, two sequence, two period, single dose, cross over, oral bioequivalence study under fasting conditions	**Reference:** Cymbalta® (Duloxetine hydrochloride) Gastro-Resistant Capsules Capsules, 60 mg Single dose, Oral route of administration. **Test:** Duloxetine hydrochloride) Gastro-Resistant Capsules, Capsules, 60 mg Single dose, Oral route of administration.	56 (56 males) 49 completing (49M)	Healthy subjects	Single dose	Complete As per ICH E3 Guideline

3.3.1. Pharmacokinetics

Study AZ/BE/01/12/11

Methods

Study design

This study was an open label, balanced, randomized, two treatment, two sequence, two period, single dose, cross-over, oral bioequivalence study comparing test and reference products containing duloxetine hydrochloride 60 mg, gastro resistant capsules in 56 healthy, adult, human subjects under fasting conditions.

The clinical phase of the study was conducted at Azidus Laboratories Ltd., 23, School Road, Rathnamangalam, Vandalur, Chennai – 600048, India from 28-JAN-2012 (date of check-in of period I) to 08-FEB-2012 (date of collection of ambulatory sample in period II). Clinical study report was signed on 29-MAR-2012.

Fasting conditions were applied considering that the subjects arrived at the clinical site at least 12 hours before dosing. All subjects were maintained in a fasting state for at least 8 hours prior to dosing and for at least 4 hours after dosing in each period.

The sampling time schedule/duration and wash-out period (7 days) were adequate taking into account the time of maximum concentration (t_{max}) and elimination half-life ($t_{1/2}$) of duloxetine.

According to the Study protocol, post-dose samples will be collected within 2 minutes of the scheduled time where the end time of collection to the nearest minute would be recorded. According to the Study report, there were no protocol deviations during the study. In order to verify that for all 56 subjects, at all time points (even at 72 hours time point), there were no time deviations, it is necessary to provide the data on the exact sample collection time for all subjects.

The documentation does not provide the information on the exact storage conditions of the study samples during the clinical phase as well as during the transport to the bioanalytical facility.

Test and reference products

Table 2. Properties of the reference and test products

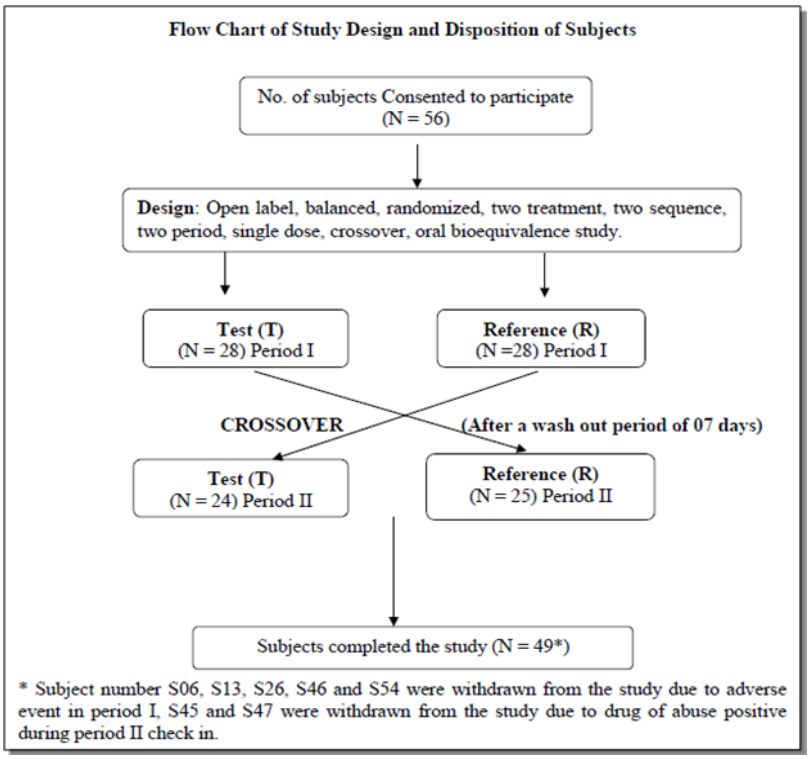
	Test product	Reference product
Product name	Duloxetine Hydrochloride Gastro-resistant capsules 60 mg	Cymbalta® (Duloxetine hydrochloride) Gastro-resistantcapsules 60 mg
MAH / Manufacturer		Eli Lilly Nederland BV, Netherland / Lilly S.A., Spain
Active substance	duloxetine hydrochloride	duloxetine hydrochloride
Strength	60 mg	60 mg
Dosage form	gastro-resistant capsules, hard	gastro-resistant capsules, hard
Batch No.		A740768
Manufacturing date / Expiry date		- / DEC-2012
Assay		98.7%
Route of administration	Oral	Oral

Choice of the reference product (Cymbalta 60 mg gastro-resistant capsules) is acceptable. Difference in the assay between test and the reference product did not reach 5%.

Composition and the formulation of the test product used in the bioequivalence study and the formulation proposed for commercial purpose are identical.

Population(s) studied

Figure 1. Flow chart of Study design and disposition of subjects in the Study AZ/BE/01/12/11



Fifty-six (56) healthy, adult, male human subjects (age 18 or older; Body Mass Index (BMI) 18.50 – 30.00 Kg/m2; body weight ≥ 50 kg) of Asian origin, non-smokers, having no significant disease or clinically significant abnormal findings during screening, were enrolled in the study. BE study was conducted on male volunteers only. This is acceptable, since the reference drug SmPC document (Cymbalta) does not indicate any clinically significant, gender associated influences on the plasma concentrations of duloxetine.

Forty-nine (49) subjects completed the study. Sufficient details regarding the exact reasons for withdrawn subjects (drop-outs) have not been provided. Therefore, further information about drop-outs should be provided in details.

Analytical methods

Pre-study validation

Specific LC-MS/MS method for the determination of duloxetine in human plasma using Liquid-Liquid Extraction procedure was validated by Azidus Laboratories Ltd., Chennai, India according to the requirements from EMA *Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009*, validation study plans and Method SOP. No. AZ-BA-M-005 Version No.01. "*Determination of Duloxetine in Human Plasma by high performance liquid chromatography mass spectrometry/mass spectrometrometry*". The *Bioanalytical method validation report number AZ-BA-MV-R-005/2012 version 01*, dated 04-MAR-2012 is not signed.

During validation, reference standard duloxetine (analyte) and the internal standard duloxetine-naphthyl-d7-maleate were used. Validated calibration range of the method was 1.0202 ng/mL - 204.3652 ng/mL. The method was validated and met acceptance criteria with respect to: specificity/selectivity, sensitivity (LLOQ), detection limit, linearity/calibration curve, reinjection reproducibility, recovery, intra-day accuracy and precision, inter-day accuracy and precision, matrix effect/factor, stability (freeze and thaw stability, short term stability, in-injector stability, dry extract stability, wet extract stability, analyte stability in blood matrix, solution stability),

dilution integrity and reinjection reproducibility. Even though the method for determination of duloxetine was validated, the method was not entirely conducted according to the *Guideline on bioanalytical method validation* (missing data on selectivity, carry over effect, IS normalized matrix factor and long term stability of analyte in matrix). Additionally, inconsistencies in certain data throughout the report have been noticed.

In-study validation

In-study validation was performed by Azidus Laboratories Ltd., Chennai, India. Signed bioanalytical report including statement on GLP, protocol and SOP compliance, dated 29-MAR-2012, has been provided. Plasma concentrations of duloxetine were determined using the validated analytical LC-MS/MS method for determination of duloxetine in human plasma with K_3EDTA as anticoagulant as per the protocol No. AZ/P/10/11/04.
The first samples were collected on 29-JAN-2012 and the experimental phases, i.e. analysis of the samples were completed on 07-MAR-2012 indicating that the maximum storage time of the samples was 39 days.

The calibration curve standard for duloxetine for analysis of the study samples was between 1.0202 ng/mL – 204.3652 ng/mL. The nominal values of the quality control samples were 3.0587 ng/mL (LQC), 33.9855 ng/mL (MMQC), 84.9636 ng/mL (MQC) and 163.3916 ng/mL (HQC). A total of 55 analytical runs were used.

In global statistics, the CV for MMQC samples (including failed QC's) was 16.06%. According to the EMA *Guideline on bioanalytical method validation*, when the overall mean accuracy and precision exceeds 15%, it should lead to additional investigations justifying this deviation and in case of bioequivalence trials it may result in the rejection of the data.

Chromatograms for more than 20% of subjects are provided.

Incurred sample reanalysis has been investigated satisfactorily. The suitability of method validation has been confirmed.

Eight (8) of totally sixteen (16) reassayed samples were reanalysed due to "*Anomalous concentration value*". Reanalyses due to PK reasons are generally not acceptable (EMEA/CHMP/EWP/192217/2009). The Applicant should address this issue.

Additionally, due to some deviations from the Guideline, timeline inconsistencies and incomplete data of certain parts of the documentation further explanations and information should be provided.

Pharmacotinetic Variables

The pharmacokinetic evaluation was carried out by Azidus Laboratories Limited. Pharmacokinetic parameters were calculated for each formulation. The Mean, Standard Deviation (SD), Geometric mean, Coefficient of Variation (CV%) and Range (Minimum and Maximum) were calculated for primary (C_{max}, AUC_{0-t}) and the secondary (t_{max}, $t_{1/2}$, $K_{el,}$ $AUC_{0-\infty}$ and $AUC_{0-t}/AUC_{0-\infty}$) pharmacokinetic parameters.

The pharmacokinetic variables are adequate and in line with the EMA *Guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr **.*

Statistical methods

For duloxetine, analysis of variance was performed on the Ln-transformed data of C_{max} and AUC_{0-t}. The analysis of variance (ANOVA) of untransformed data as well as natural log-transformed data was carried out by Azidus Laboratories Limited by using the statistical software package SAS® for Windows, version 9.2 (Statistical Analysis System, SAS Institute, Cary NC, USA) General Linear Model (GLM) with sequence, subject nested within sequence, treatment and period as factors of the model.

The intra-subject coefficients of variation (based on Ln-ANOVA) for C_{max} and AUC_{0-t} were also displayed.

Statistics were adequately described and the methods are acceptable. The calculation of 90%-confidence intervals is in line with applicable EMA *Guideline CPMP/EWP/QWP/1401/98/ Rev. 1/Corr*** and is supported. Assessment of this 90%-confidence interval for the T/R ratio for AUC_{0-t} and C_{max} is appropriate for the assessment of the bioequivalence.

Results

The results are summarised in Table 3 and 4. The test to reference ratio of geometric LSmeans and corresponding 90% confidence interval for the C_{max} and AUC_{0-t} were all within the acceptance range of 80.00 to 125.00%.

The extrapolated AUC (residual area) was below 20% in all but one subject with residual AUC 21.7% (S34; period II), but taking into account that sampling time was 72 hours, it was not found critical. Concentrations of both reference and test drug at pre-dose time point were BLQ. The LLOQ of 1.0202 ng/ml was not sensitive enough to detect levels of 5% of the minimum C_{max} to exclude the possibility of a relevant carry-over effect. For 5 subjects in period I (S34, S53, S08, S52 and S55) and for 1 subject in period II (S34) 5% of the C_{max} was below of the LLOQ value. However, considering the results at 48 h and/or 72 h time points in Period I (BLQ) as well as the wash-out period (7 days), carry-over effect can be excluded.

Table 3 Pharmacokinetic parameters for duloxetine (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-72h)}$ (µg.hr/mL)	1104.119	691.896	1183.544	905.541
$AUC_{(0-\infty)}$ (µg.hr/mL)	1179.503	773.521	1263.580	995.354
C_{max} (µg/mL)	62.631	30.252	62.750	36.651
T_{max} * (hr)	5.50	(3.00-10.00)	5.00	(2.00-8.00)
AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 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 (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-72h)}$ (µg.hr/mL)	101.50%	94.04% - 109.55%	22.81
C_{max} (µg/mL)	105.53%	96.46% - 115.44%	26.96
* estimated from the Residual Mean Squares			

Safety data

Tolerability of the test product is not significantly different from reference product and thus acceptable. There were no death or serious adverse events reported in this study.

The percentage of adverse events reported with test product is 46.16% and with reference product is 47.17%. All adverse events are drug related.

Study AZ/BE/01/12/12

Methods

Study design

This study was an open label, balanced, randomized, two treatment, two sequence, two period, single dose, crossover, oral bioequivalence study comparing test and reference products containing duloxetine hydrochloride 60 mg, gastro resistant capsules in 56 healthy, adult, human subjects under fed conditions.

The clinical phase of the study was conducted at Azidus Laboratories Ltd., 23, School Road, Rathnamangalam, Vandalur, Chennai – 600048, India from 31-JAN-2012 (date of check-in of period I) to 11-FEB-2012 (date of collection of the last ambulatory sample in period II). Clinical study report was signed on 29-MAR-2012.

Fed conditions were applied. High fat, high calorie breakfast was served to all subjects 30 minutes before dosing and consumed within 30 minutes. The exact specification of all meals is provided only in the study protocol.

The sampling time schedule/duration and wash-out period (7 days) were adequate taking into account the time of maximum concentration (t_{max}) and elimination half-life ($t_{1/2}$) of duloxetine.

According to the Study protocol, post-dose samples will be collected within 2 minutes of the scheduled time where the end time of collection to the nearest minute would be recorded. According to the Study report, there were no protocol deviations during the study. In order to verify that for all 56 subjects, at all time points (even at 72 hours time point), there were no time deviations, it is necessary to provide the data on the exact sample collection time for all subjects.

The documentation does not provide the information on the exact storage conditions of the study samples during the clinical phase as well as during the transport to the bioanalytical facility.

Test and reference products

Table 5. Properties of the reference and test products

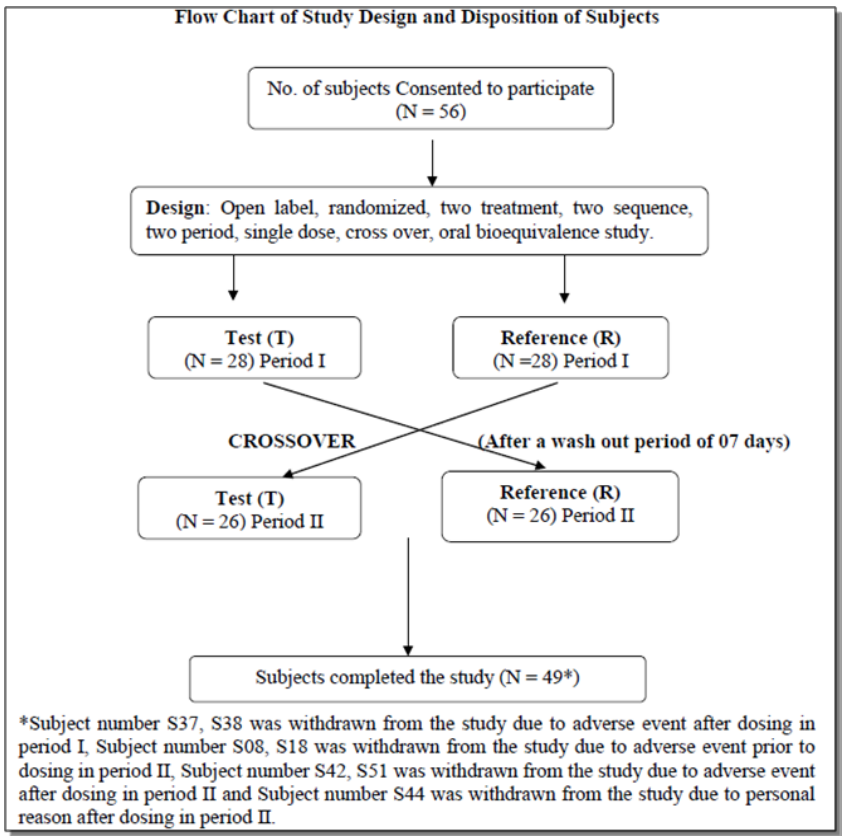
	Test product	Reference product
Product name	Duloxetine Hydrochloride Gastro-resistant capsules 60 mg	Cymbalta® (Duloxetine hydrochloride) Gastro-resistant capsules 60 mg
MAH / Manufacturer		Eli Lilly Nederland BV, Netherland / Lilly S.A., Spain
Active substance	duloxetine hydrochloride	duloxetine hydrochloride
Strength	60 mg	60 mg
Dosage form	gastro-resistant capsules, hard	gastro-resistant capsules, hard
Batch No.		A740768
Manufacturing date / Expiry date		NA / DEC-2012
Assay		98.7%
Route of administration	oral	oral

Choice of the reference product (Cymbalta 60 mg gastro-resistant capsules) is acceptable. Difference in the assay between test and the reference product did not reach 5%.

Composition and the formulation of the test product used in the bioequivalence study and the formulation proposed for commercial purpose are identical.

Population(s) studied

Figure 2. Flow chart of Study design and disposition of subjects in the Study AZ/BE/01/12/12



Fifty-six (56) healthy, adult, male human subjects (age 18 or older; Body Mass Index (BMI) 18.50 – 30.00 Kg/m2; body weight ≥ 50 kg) of Asian origin, non-smokers, having no significant disease or clinically significant abnormal findings during screening, were enrolled in the study. BE study was conducted on male volunteers only. This is acceptable since the reference drug SmPC document (Cymbalta) does not indicate any clinically significant, gender associated influences on the plasma concentrations of duloxetine.

Forty-nine (49) subjects completed the study. Sufficient details regarding the exact reasons for withdrawn subjects (drop-outs) have not been provided. Therefore, further information about drop-outs should be provided in details.

Analytical methods

Pre-study validation

Same as for *Study AZ/BE/01/12/11; Analytical methods, Pre-study validation* (*see above*).

In-study validation

In-study validation was performed by Azidus Laboratories Ltd., Chennai, India. Signed bioanalytical report including statement on GLP, protocol and SOP compliance dated 29-MAR-2012 has been provided. Plasma concentrations of duloxetine were determined using the validated analytical LC-MS/MS method for determination of duloxetine in human plasma with K_3EDTA as anticoagulant as per the protocol No. AZ/P/10/11/05.

The first samples were collected on 01-FEB-2012 and the experimental phase, i.e. analysis of the samples were completed on 05-MAR-2012 indicating that the maximum storage time of the samples was 34 days.

The calibration curve standard for duloxetine for analysis of the study samples was between 1.0622 ng/mL – 202.6482 ng/mL. The nominal values of the quality control samples were 3.2323 ng/mL (LQC), 34.0239 ng/mL (MMQC), 85.0598 ng/mL (MQC) and 163.5766 ng/mL (HQC). A total of 54 analytical runs were used.

Chromatograms for more than 20% of subjects are provided.

Incurred sample reanalysis has been investigated satisfactorily. The suitability of method validation has been confirmed. However, it has been noticed that initial values for samples *S15_PII_36.00Hr* and *S43_PII_12.00Hr* in incurred sample reanalysis are not the same as values reported as individual duloxetine concentration (ng/mL) of subject samples in human plasma.

Eight (8) of totally twenty-six (26) reassayed samples were reanalysed due to "*Anomalous concentration value"*. Reanalyses due to PK reasons are generally not acceptable (*EMEA/CHMP/EWP/192217/2009*). The Applicant should address this issue.

Additionally, incomplete data of certain parts of the documentation further explanations and information should be provided.

Pharmacokinetic Variables

The pharmacokinetic evaluation was carried out by Azidus Laboratories Limited. Pharmacokinetic parameters were calculated for each formulation. The Mean, Standard Deviation (SD), Geometric mean, Coefficient of Variation (CV%) and Range (Minimum and Maximum) were calculated for primary (C_{max}, AUC_{0-t}) and the secondary (t_{max}, $t_{1/2}$, $K_{el,}$ $AUC_{0-\infty}$ and $AUC_{0-t}/AUC_{0-\infty}$) pharmacokinetic parameters.
The pharmacokinetic variables are adequate and in line with the EMA *Guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr **.*

Statistical methods

For duloxetine, analysis of variance was performed on the Ln-transformed data of C_{max} and AUC_{0-t}.

The analysis of variance (ANOVA) of untransformed data as well as natural log-transformed data was carried out by Azidus Laboratories Limited by using the statistical software package SAS® for Windows, version 9.2 (Statistical Analysis System, SAS Institute, Cary NC, USA) General Linear Model (GLM) with sequence, subject nested within sequence, treatment and period as factors of the model.

The intra-subject coefficients of variation (based on Ln-ANOVA) for C_{max} and AUC_{0-t} were also displayed.

Statistics were adequately described and the methods are acceptable. The calculation of 90%-confidence intervals is in line with applicable EMA *Guideline CPMP/EWP/QWP/1401/98/ Rev.*

*1/Corr*** and is supported. Assessment of this 90%-confidence interval for the T/R ratio for AUC_{0-t} and C_{max} is appropriate for the assessment of the bioequivalence.

Results

The results are summarised in Table 6 and 7. The test to reference ratio of geometric LSmeans and corresponding 90% confidence interval for the C_{max} and AUC_{0-t} were all within the acceptance range of 80.00 to 125.00%.

The extrapolated AUC (residual area) was below 20% in all but one subject with residual AUC 25.25% (S20, period I), but taking into account that sampling time was 72 hours, it was not found critical. Concentrations of both reference and test drug at pre-dose time point were BLQ. The LLOQ of 1.0622 ng/ml was not sensitive enough to detect levels of 5% of the minimum C_{max} to exclude the possibility of a relevant carry-over effect. For 3 subjects in period I (S29, S32 and S56) was below of the LLOQ value. However, considering the results at 72 h time points in Period I (BLQ), C_{max} values in period II (5% of C_{max}>LLOQ) as well as the wash-out period (7 days), carry-over effect can be excluded.

Table 6 Pharmacokinetic parameters for duloxetine (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-72h)}$ (µg.hr/mL)	1188.30	603.707	1117.51	579.982
$AUC_{(0-\infty)}$ (µg.hr/mL)	1266.10	653.780	1180.60	616.307
C_{max} (ng/ml)	57.430	25.095	61.559	25.772
T_{max}* hr	8.00	(4.00-16.00)	7.00	(4.00-12.00)
<AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours>			
<AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 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 7 Statistical analysis for duloxetine (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-72h)}$ (µg.hr/mL)	106.42%	100.95% - 112.19%	15.66%
C_{max} (ng/ml)	92.11%	85.85% - 98.81%	20.96%
* estimated from the Residual Mean Squares			

Safety data

Tolerability of the test product is not significantly different from reference product and thus acceptable. There were no death or serious adverse events reported in this study.

The percentage of adverse events reported with test product is 11.11% and with reference product is 12.96% All adverse events are related to the drug.

Pharmacokinetic Conclusion

Based on the results of the presented bioequivalence studies, Duloxetine Sandoz 60 mg gastro-resistant capsules can be considered bioequivalent with Cymbalta 60 mg hard gastro-resistant capsules under fasting and fed conditions. However, major objection is raised due to a lack of GCP compliance mostly related with Pre-study and In-study validation. Therefore, final decision considering bioequivalence cannot be concluded at this time point. The results of studies AZ/BE/01/12/11 and AZ/BE/01/12/12 with 60 mg formulation can be extrapolated to other strength 30 mg, according to conditions in the relevant Guidelines. However, additional information on the size of the batches on which the dissolution tests have been performed should be provided.

3.3.2. Pharmacodynamics

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

3.3.3. Post marketing experience

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

3.3.4. Discussion on clinical aspects

The Applicant provided an adequate Clinical Overview on the clinical pharmacology, efficacy and safety based on the published literature. It refers to 50 publications dating from 2000 up to the year 2014 that are not included in the Module 5 Literature references.

Two (2) bioequivalence studies were conducted on the 60 mg gastro-resistant capsules strength under fasting and fed conditions during 2012. The bioequivalence has been performed at the strength that is the most sensitive to detect a potential difference between the products. Therefore, the selection of the drug product strength as well as the conditions under which the two studies were conducted are in line with the *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr *** and *the Note for guidance on modified release oral and transdermal dosage forms: section II (pharmacokinetic and clinical evaluation) (CPMP/EWP/280/96)*.

Design of both studies was an open label, balanced, randomized, two treatment, two sequence, two periods, single dose, crossover, oral bioequivalence study of Duloxetine Hydrochloride gastro resistant capsules 60 mg and Cymbalta (Duloxetine hydrochloride) gastro resistant capsules 60 mg of Lilly S.A., Spain, Market Authorization by Eli Lilly Nederland BV, The Netherlands in 56 healthy, adult, human subjects. The sampling time schedule and wash-out period (7 days) were adequate taking into account time of maximum concentration (t_{max}) and elimination half-life ($t_{1/2}$) of duloxetine. Although the design of both studies was adequate, concerns have been raised that need clarification, justification and/or additional information.

The results of these two studies concluded that they are both bioequivalent to the chosen reference product. The statistics is adequately described and the methods are acceptable. The calculation of 90%-confidence intervals is in line with applicable EMA *Guideline CPMP/EWP/QWP/1401/98 Rev. 1/*

Corr ** and is supported. Assessment of this 90%-confidence interval for the T/R ratio for AUC_{0-t} and C_{max} is appropriate for the assessment of the bioequivalence.

Clinical/bioanalytical/PK/statistical study site Azidus has been inspected by several non-EU authorities (including Brazil, Turkey, Chile) for GCP and by member state Poland for GLP. According to EMA reference INS/GCP/2014/024, Azidus has not been previously inspected in relation to a centralised MAA procedure therefore, the inspection of the clinical studies AZ/BE/01/12/11 and AZ/BE/01/12/12 will be carried out in the year 2015.

During the assessment, numerous concerns were raised regarding the GCP compliance during both studies, especially regarding the In-study and Pre-study validation. All observations are presented in this report in detail and will be taken into account by the Inspectors during the planned GCP inspection.

According to the *Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr* ** general biowaiver criteria (conditions a) to d)) are fulfilled for Duloxetine Sandoz 60 mg gastro-resistant capsules and Duloxetine Sandoz 30 mg gastro-resistant capsules. Therefore, a waiver for additional strength (30 mg) is acceptable. However, additional information should be provided.

3.3.5. Conclusions on clinical aspects

Duloxetine Sandoz is not approvable since “major objection” has been identified and thus the bioequivalence between Duloxetine Hydrochloride gastro-resistant capsules 60 mg and Cymbalta by Eli Lilly Nederland BV, The Netherlands cannot be concluded.

During the assessment, concerns were raised regarding the GCP compliance during both studies, especially regarding the In-study and Pre-study validation. All observations are presented in this report in detail and will be taken into account by the Inspectors during the planned GCP inspection.

Since clinical studies AZ/BE/01/12/11 and AZ/BE/01/12/12 are the only pivotal studies provided for this application, medicinal product Duloxetine Sandoz is not approvable as long as their GCP compliance is questionable.

3.4. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system as described by the applicant fulfils the 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.

3.5. Risk management plan

Issues and/or concerns for consideration by the PRAC when assessing the RMP.

Summary of safety concerns proposed by the applicant differs from the innovator’s RMP (Cymbalta). The applicant should update RMP “Summary of safety concerns” to be in line with the innovator’s RMP. Consequently, changes should be made throughout the RMP to reflect the changes to the list of safety concerns.

4. Benefit risk assessment

4.1. Conclusions

The application contains inadequate quality, non-clinical and clinical data. The bioequivalence has not been adequately shown.

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.