23 April 2015
EMA/CHMP/238550/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Duloxetine Mylan

International non-proprietary name: duloxetine

Procedure No. EMEA/H/C/003981

Note

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

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

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List of abbreviations

AE	Adverse Events
ANOVA	Analysis of Variance
AUC 0-t	Area under the concentration versus time curve calculated using the trapezoidal rule up to the last measurable time point
AUC 0-inf	Area under the concentration versus time cure from time 0 to Infinity
BE	Bioequivalence
BLQ	Below the lower limit of quantification
Cmax	Maximum observed drug concentration in plasma
COA	Certificate of analysis
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
LSM	Least Square Mean
mg	Milligram
mL	Millilitre
mmol	Millimole
ng	Nanogram
PK	Pharmacokinetic
Tmax	Time to Observe Maximum Drug Concentration in Plasma

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Generics (UK) Limited submitted on 18 August 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Duloxetine Mylan, 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 20 March 2014

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

- "Treatment of major depressive disorder.
- Treatment of diabetic peripheral neuropathic pain.
- Treatment of generalised anxiety disorder.
- Duloxetine Mylan is indicated in adults."

The legal basis for this application refers to:

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

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

Information on paediatric requirements

Not applicable

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: YENTREVE 20 mg and 40 mg hard gastro resistant capsules Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 2004-08-13
- Marketing authorisation granted by:

Community

Community Marketing authorisation number: EU/1/04/280/001-8

■ 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 mg and 60 mg hard gastro-resistant capsules

- Marketing authorisation holder: Eli Lilly Nederland B.V.

- Date of authorisation: 2004-12-17 EU/1/04/296/001-4
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/04/296/001-9

■ 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: 2004-12-17
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation numbers: EU/1/04/296/002-005, 007-008
- Bioavailability study numbers: ARL/13/025 and ARL/13/026

Licensing status

Duloxetine Mylan has been given a Marketing Authorisation in Australia on 29 April 2013.

An application was filed in the following countries: USA, Australia and Canada.

1.2. Manufacturers

Manufacturers responsible for batch release

McDermott Laboratories Limited T/A Gerard Laboratories T/A Mylan Dublin
35 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

Mylan B.V.
Dieselweg 25
NL- 3752 Bunschoten
Netherlands

Mylan Hungary Kft.
Mylan utca. 1
H-2900 Komárom
Hungary

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: John Joseph Borg

- The application was received by the EMA on 18 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 Rapporteur's Risk Management Plan (RMP) Assessment Report was endorsed 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 23 January 2015.
- The summary report of the GMP inspection carried out at the following site: Unichem Laboratories Limited Plot 17 & 18 Pilerne Industrial Estate Pilerne Bardez 403 511 Goa INDIA between 9 -12 September 2014 was issued on 6 November 2014.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 February 2015.
- The PRAC RMP Advice and assessment overview was agreed on 12 March 2015 (Annex 6).
- During the CHMP meeting on 26 March 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 31 March 2015.
- The PRAC Rapporteur's Risk Management Plan Assessment Report was endorsed by PRAC on 10 April 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 9 April 2015.
- During the meeting on 23 April 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Duloxetine Mylan.

2. Scientific discussion

2.1. Introduction

This report concerns the generic application for Duloxetine Mylan for which the originator product was Cymbalta 30 mg and 60 mg hard gastro-resistant capsules marketed by Eli Lilly Netherland B.V.

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 dose-dependently increases extracellular levels of serotonin and noradrenaline in various brain areas of animals.

Duloxetine normalised pain thresholds in several preclinical models of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

To support this application Mylan applied for a marketing authorisation for 2 strengths of Duloxetine tablets 30mg and 60mg, conducting two way crossover comparative bioavailability studies under fasting and fed conditions against the reference product. The bio-equivalence studies were conducted with the highest strength 60 mg Duloxetine hard gastro-resistant capsules versus the Cymbalta (duloxetine HCl) 60 mg gastro-resistant capsules.

2.2. Quality aspects

2.2.1. Introduction

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

Other ingredients are:

Capsule content: sugar spheres (sucrose, maize starch), hypromellose, macrogol, crospovidone, talc, sucrose, hypromellose phthalate, diethyl phthalate.

Capsule shell: brilliant blue (E133), titanium dioxide (E171), gelatin, gold ink (30 mg) and white ink (60 mg), yellow iron oxide (E 172) (for 60mg only).

Gold ink (30 mg) contains: shellac**,** propylene glycol**,** strong ammonia solution and yellow iron oxide.

White ink (60 mg) contains: shellac**,** propylene glycol**,** sodium hydroxide, povidone and titanium dioxide (E171

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

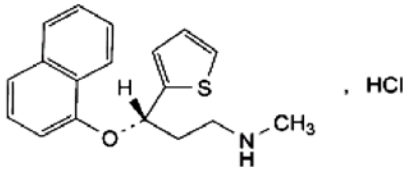
2.2.2. Active substance

General information

Duloxetine hydrochloride is an active substance described in the European Pharmacopoeia

The chemical name of duloxetine is (3 S)-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 powder, no hygroscopic, sparingly soluble in water, freely soluble in methanol, practically insoluble in hexane.

Duloxetine exhibits stereoisomerism due to the presence of 1 chiral centre. Enantiomeric purity is controlled routinely. Polymorphism has been observed for active substance and it is controlled during manufacturing.

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

Manufacture

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance specifications adopted by both active substance and finished product manufacturers have been provided and the specifications include tests as per current Ph. Eur. monograph together with the additional testing specified in the CEP for residual solvents by gas chromatography and test for residual catalyst (rhodium) by ICP-MS as mentioned in the CEP and based on the analytical procedures annexed with the CEP. The specifications adopted by the finished product manufacturer additionally include testing for particle size, and identification of polymorph (PXRD). In-house analytical methods have been satisfactorily validated.

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

Stability

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The purpose of the pharmaceutical development studies was to develop a bioequivalent generic version of the reference medicinal product Cymbalta. The developed product should be suitable for production scale batches and exhibit reproducible results. The product should also demonstrate acceptable stability performance in the proposed marketing packaging.

The following active substance attributes were considered during the development of Duloxetine hard gastro-resistant capsules: bulk density, tapped density, particle size, solubility, particle size distribution, hygroscopicity and potential isomerism.

The results indicated very poor to very-very poor flow properties of duloxetine hydrochloride. However, since the manufacturing processes of the finished product involves the preparation of drug coated pellets / beads by Wurster coating on inert sugar spheres, wherein the active substance is suspended in the coating solvent along with other excipients and is sprayed on to the core pellets, the flow properties of the active substance does not have any impact on manufacturing process. Solubility studies of the active substance demonstrated that duloxetine hydrochloride has pH dependent solubility with maximum solubility at pH 5.5 acetate buffer and is highly soluble as per the BCS solubility criteria. According to the particle distribution results, a satisfactory particle size limit was proposed. The active substance is slightly hygroscopic and the potential isomerism is controlled in line with the Ph Eur monograph.

The excipients selected for the formulation development are based on literature search, compatibility study, past experience of developing delayed release capsules dosage form and the qualitative formula of reference medicinal product, so as to have an essentially similar generic version of the branded product.

In order to select suitable excipients for the formulation, an active substance-excipient compatibility study was performed. The results of the excipients compatibility studies suggested that there was no significant change in physical appearance and related substances. Therefore it was concluded that all the excipients were compatible with duloxetine hydrochloride. Hence, these excipients were proposed for the prototype formulation development.

All of the excipients are conventional pharmaceutical ingredients that comply with the requirements of Ph Eur with the exception of Opadry clear YS-1R-7006 and empty hard gelatin capsule shells. They are included in the formulation at suitable levels and for recognised purposes. Opadry clear YS-1R-7006 and empty hard gelatin capsule shells are non-pharmacopoeial proprietary materials supplied to the agreed specifications. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Two bioequivalence studies were performed using the 60 mg strength in fed and fasting conditions; bio-waiver for the 30 mg strength was applied.

Comparative dissolution profile data in 0.1N 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 both strengths of the generic medicinal product and the reference product were provided. The amount of duloxetine released in acid resistance stage after 120 minutes from all the formulations is not more than 10 % and therefore complies with requirements of dissolution test for delayed release formulation as per *"Ph. Eur. General chapter –Dissolution test for Solid dosage forms (2.9.3)"*. For buffer stage (i.e. pH 6.8 Phosphate buffer), the similarity factor (f2 value) was calculated between the test product (Duloxetine 60 mg hard gastro-resistant capsules) and the reference product (Cymbalta 60 mg gastro resistant capsules) used in the bio-equivalence study.

The dissolution profiles of 60 mg strength Test biobatch vs. Reference biobatch, were not similar with the proposed QC dissolution method. The applicant justified the discrepancy for the *in vitro* dissolution data on the basis that although, the f2 value between the test and reference product was found to be below 50, these two products have been proven to be bioequivalent under both fasting and fed conditions. Therefore, it can be concluded that the difference in drug release profile of both strengths does not have any impact on the *in vivo* performance of the product

The manufacturing process development strategy objective was to design and develop stable and bioequivalent generic product of Duloxetine hard gastro-resistant capsules using commonly used excipients and similar to reference medicinal product. It was confirmed that there was no difference between the manufacturing process used to produce clinical batches and the process of the finished product. During optimisation of the manufacturing process, the drying temperature for drug coated pellets and for enteric coated pellets was evaluated. The enteric coating solvent composition was also optimised. The impact of the capsule filling machine speed was also evaluated during development.

The primary packaging is is PVC/PCTFE /Al blisters and HDPE bottle pack. The material complies with Ph Eur and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product

The manufacturing process consists of 6 main steps: preparation of drug coated pellets / beads, preparation of sub coated pellets/beads, preparation of lubricated enteric coated pellets / beads, encapsulation, and packaging. The process is considered to be a non-standard manufacturing process.

The manufacturing process is considered adequately validated for the proposed batch sizes for which full process validation results have been presented. 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.

However, as the manufacturing process is considered a non-standard process, process validation on the proposed additional larger commercial batch sizes should be successfully completed before product from these proposed larger scale batches can be marketed. The applicant committed to validate the commercial batches manufactured with the proposed additional batch sizes, as per the proposed validation protocol and the batches shall be released in the market only after successful completion of the process validation. The applicant has also documented the manufacturer's experience of similar gastro-resistant formulations and confirmed that the same manufacturing equipment used for the validated batches sizes will be used for the larger scale batches. This was considered acceptable.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form description, identification (HPLC, thin layer chromatography), dissolution (HPLC), uniformity of dosage units (content uniformity), related substances (HPLC), assay (HPLC), water content (KF), residual solvents (GC), microbiological test (Ph Eur), and color identification for capsule shell.

Batch analysis results are provided for 3 commercial 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 3 production scale batches of each strength of finished product stored under long term conditions for 36 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packagings proposed for marketing.

Samples were tested for description, dissolution (HPLC), related substances (HPLC), assay (HPLC), water content (KF) and microbiological test (Ph Eur). The analytical procedures used are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

An in-use stability study has been provided for the finished product in HDPE bottles in compliance with the CPMP guidance "Note for Guidance on in-use stability testing of human medicinal products". 3 months data from a 6

month study show that results are within the proposed specifications. A 3 months in-use shelf-life can be granted for the finished product stored in HDPE bottles at the moment.

In all the stability studies no significant changes and no trends were observed for all the investigated parameters. No formation or increase in levels of any degradation product was observed.

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

Adventitious agents

The gelatin in the capsule shell used in the finished product is of animal (bovine) origin. Current EDQM Certificates of Suitability are provided.

2.2.4. Discussion on chemical, and pharmaceutical aspects

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

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give 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. 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. Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Pharmacology

Reference is made to the SmPC of the reference product Cymbalta.

Duloxetine is a combined serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI), which weakly inhibits dopamine reuptake and has no significant affinity for histaminergic, dopaminergic, cholinergic or adrenergic receptors. Duloxetine dose-dependently increases extracellular levels of serotonin and noradrenaline in various brain areas of animals.

Pharmacodynamic effects

Duloxetine normalised pain thresholds in several preclinical models of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

The effectiveness of duloxetine in the treatment of MDD is linked to its inhibition of presynaptic neuron reuptake of serotonin and norepinephrine in the central nervous system, resulting in elevated levels of serotonin and norepinephrine in the synaptic cleft, enhancing monoaminergic neurotransmission. Although no specific animal models for MDD are available, the in vivo pharmacodynamic studies provide indirect evidence for the potential clinical efficacy of duloxetine. At therapeutic range, duloxetine is not expected to pose a risk on CNS, smooth muscle, renal, immune, or gastrointestinal functions. Substance abuse is unlikely.

2.3.3. 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 Cmax 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.

Distribution

Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha-l acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

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 metabolites glucuronide conjugate of 4-hydroxy duloxetine and sulphate conjugate of 5-hydroxy 6-methoxy duloxetine. Based upon in vitro studies, the circulating metabolites of duloxetine are considered pharmacologically inactive. The pharmacokinetics of duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of duloxetine are higher in these patients.

Elimination

The elimination half-life of duloxetine ranges from 8 to 17 hours (mean of 12 hours). After an intravenous dose the plasma clearance of duloxetine ranges from 22 l/hr to 46 l/hr (mean of 36 l/hr). After an oral dose the apparent plasma clearance of duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

2.3.4. Toxicology

Duloxetine hydrochloride has been evaluated in a variety of toxicology studies in laboratory animals and in vitro test systems (refer to Cymbalta EPAR). Studies included single-dose toxicity in mice, rats, and dogs; repeated-dosetoxicity in mice, rats, and dogs; in vitro and in vivo genotoxicity; carcinogenic potential in mice and rats; and reproductive and developmental toxicity in rats and rabbits. All issues of concern are adequately dealt with within the summary of product characteristics of the Reference product Cymbalta.

2.3.5. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted by the applicant. The applicant justified the lack of an ERA on the following grounds: “given that Duloxetine 30 mg and 60 mg hard gastro-resistant capsules are aimed at

replacing rather than increasing prescriptions of Cymbalta 30 mg and 60mg hard gastro-resistant capsules, no increased environmental burden is envisaged from the licensing of this product." The CHMP agreed with the applicant since the legal basis for registration of Duloxetine Mylan gastro resistant capsules are according to article 10.1 (generic) of Directive 2001/83/EC. Thus an Environmental Risk Assessment does not need to be submitted in accordance with the guideline EMEA/CHMP/SWP/4447/00 corr I.

2.3.6. Discussion and conclusion on non-clinical aspects

There are no objections to approval of Duloxetine Mylan from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

The applicant has conducted two way crossover comparative bioavailability studies under fasting and fed conditions against the reference product. The studies were conducted with the highest strength 60 mg Duloxetine hard gastro-resistant capsules versus the innovator's Cymbalta (duloxetine HCl) 60 mg gelule gastro-resistant.

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

The applicant performed two bioequivalence studies using the 60mg strength fed and fasting, and applied for a biowaiver for the 30mg strength. The applicant argued that according to the CHMP Guideline on the Investigation of Bio-equivalence (CPMP/EWP/QWP/1401/98-Rev 01 – August 2010), Duloxetine 30 mg hard gastro resistant capsules satisfy the conditions for waiver of bioequivalence studies with Duloxetine 60 mg hard gastro-resistant capsules as discussed below:

- Both the strengths of Duloxetine hard gastro-resistant capsules are manufactured by the same manufacturer at the same manufacturing site using similar manufacturing process.
- The qualitative composition of both the strengths i.e. Duloxetine 30 mg and 60 mg hard gastro-resistant capsules is the same.
- Duloxetine pharmacokinetics is linear "Duloxetine plasma exposure increases in proportion to dose for doses up to 60 mg twice a day (Cymbalta TGA PI, 2012)". The bioequivalence study performed on Duloxetine 60mg hard gastro-resistant capsules can therefore be extended to Duloxetine 30mg hard gastro-resistant capsules.
- The excipients included in the composition of the formulation are well established and no interaction with the pharmacokinetics of the active substance is expected. The Duloxetine 60 mg hard gastro-resistant capsules are "scale up" of the Duloxetine 30 mg hard gastro-resistant capsules (the ratio of active ingredient to excipients is the same in the two strengths).
- The in vitro test of dissolution characteristics demonstrates that dissolution profiles of Mylan Laboratories Limited's Duloxetine 30 mg and 60 mg hard gastro-resistant capsules are similar.

Comparative dissolution studies had been provided as required and were properly discussed by the applicant.

The comparative dissolution studies between the test 60mg strength and the test 30mg strength were considered to be acceptable since the f2 similarity factor is over 50.

The claimed biowaiver to the 30mg strength was considered acceptable by CHMP.

2.4.2. Pharmacokinetics

Study ARL/13/025 Fasting

Methods

This was a randomized, balanced, open label, two period, two treatment, two sequence, single dose, crossover, comparative oral bioavailability study to establish comparative bioequivalence of Duloxetine 60 mg hard gastro resistant capsules (Mylan Laboratories India) and Cymbalta 60 mg gelule gastro resistante (MAH: Eli Lilly Nederland B.V.) in 36 healthy, adult human subjects under fasting conditions. The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety and tolerability of a single dose of Duloxetine 60 mg.

Study design

Based on the randomised schedule and following an overnight fast of at least 10 hours in both periods each volunteer received a single oral dose of Duloxetine 60mg capsule with 240ml of water in period I and either one tablet of the reference or test product in period II.

Subjects were dosed while in sitting posture and were instructed to remain seated in an upright position for the first 2 hours following drug administration. Drinking water was not permitted one hour before dosing and until one hour post dose. Subjects were confined to the clinical facility from at least 12 hours prior to each drug administration until after the 72-hour blood sample collection in each study period.

The two periods were separated by a wash-out phase of at least 17 days.

Blood samples were taken at the following time points: pre-dose and at 1.0, 2.0, 3.0, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, and 72.0 hours after dosing.

Test and reference products

Table 1: Test and Reference Product information

Product Characteristics	Reference product	Test Product
Name	Cymbalta®	Duloxetine
Strength	60 mg	60 mg
Dosage form	gelule gastro-resistante (Gastro-resistant Capsules)	Hard gastro-resistant Capsules
Manufacturer	Lilly S.A., Avda. De la Industria, 30, 28108 Alcobendas, Madrid, Spain. MA Holder: Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.	Manufactured by: UNICHEM LABORATORIES LTD. 17 & 18, Pilerne Ind.Estate, Pilerne, Bardez Goa. 403 511 Manufactured for: Mylan Laboratories Limited, India
Batch number / Lot Number	C048615	GDUV11002
Batch size (Biobatch)	-	140,000
Measured content(s) (% of label claim)	97.4 % w/w	101.1 %
Commercial Batch Size	-	--
Expiry date (Retest date)	01-2015	October - 2013
Location of Certificate of Analysis	5312-compar-ba-be-stud-rep, Appendix-16.1.6	5312-compar-ba-be-stud-rep, Appendix-16.1.6
Member State where the reference product is purchased from:	France	-
This product was used in the following trials:	Study no. ARL/13/025 and ARL/13/026	Study no. ARL/13/025 and ARL/13/026

Population studied

36 healthy adult male and female (31 males and 5 females) human subjects were enrolled as per the protocol. The study started with 36 subjects and 34 completed the study.

The population studied was considered appropriate and the main inclusion and exclusion criteria - in line with the requirements of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01). The number of subjects not completing the study would not have an effect on the results as 34 patients are enough to power the study.

With respect to product deviations, one subject was housed 23 minutes later than the protocol stipulated, some minor deviations to the blood sample time were observed in a few patients and water spillage upon taking the capsule occurred in one patients. These were not deemed to have any effect on the outcome of the study.

Analytical methods

Analysis of Duloxetine was performed using test method AMP-090-00 from 25 February to 8 March 2013.

This Ultra Performance Liquid Chromatography Method with Tandem mass spectrometry method involved the extraction of Duloxetine and the internal standard Duloxetine d5 from human plasma. The samples upon receipt from Accutest Research Laboratories Pvt. Ltd, Navi Mumbai on 22nd February 2013 were stored in a deep freezer under frozen condition at -70 ± 15°C at Bioanalytical lab of CRC from the date of their receipt until they were analysed. During transit the temperature was maintained below -55°C. Total Long term plasma stability required is 39 days however this has been provided for 71 days.

1512 blood samples were expected however 1445 were received. 1424 samples (1419 + 5 samples for safety evaluation were analysed for the 34 subjects.

Validation of the test method

The method has been validated (VR-090-00) in July 2012 and partially revalidated once in August 2012. The following parameters were addressed; selectivity and specificity of Duloxetine and the internal standard (IS), calibration curve (linearity), carryover test, blank matrix specificity, selectivity and LOQ, recovery of both the analyte and the internal standard, precision, accuracy, dilution integrity accuracy and precision, stability of the stock solution (short and long term stability in the biological matrix, bench top, freeze-thaw, dry extract, auto sampler storage, and short and long term stock solution stability), haemolysis effect accuracy and precision, ruggedness (different analyst, column, instrument) and matrix effect. Each parameter has been assessed and the limits are justified. This is deem5ed acceptable.

The lower limit of quantification (LLOQ) of this method for the estimation of Duloxetine concentrations in plasma was 0.401ng/ml (Precision 0.90%, Accuracy 102.24%). The linearity range of Duloxetine was from 0.401g/ml to 100.372ng/ml. (9 point curve)

Pharmacokinetic Variables

Primary parameters: $AUC_{0-t,}$ AUC_{0-inf} and C_{max}

Secondary parameters: T_{max}, Residual area, Elimination rate constant, AUC_{0-t} /AUC_{0-inf}

Bioequivalence criteria; Bioequivalence was concluded if the 90% confidence interval of geometric mean of Cmax, AUC0-t and AUC0-inf between test and reference products fall within the range of 80.00 % to 125.00 % for Duloxetine.

Statistical methods

Analysis of variance (ANOVA) was performed on the log-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-inf an alpha level of 0.05. The analysis of variance model included sequence, subjects nested within sequence, period and treatment as factors. Each analysis of variance also included calculation of least-square means (LSM's), adjusted differences between formulation means and the standard errors associated with these differences. All effects were tested against the residual error (mean square error) from the ANOVA model as the error term. The sequence effect was tested at the 10% level of significance and all other main effects were tested at the 5% level of significance against the residual error (mean square error) from the ANOVA model as the error term.

Results

Table 2 Pharmacokinetic parameters for Duloxetine 60mg (non-transformed values)

Pharmacokinetic parameter	Arithmetic Means (± SD) (N=34)	
	Test Product	Reference product
*Tmax (h)	5.50 (4.50-9.00)	5.00 (4.50- 8.00)
Cmax (ng/mL)	61.26 ± 27.12	63.35 ± 25.11
AUC0-t	1176.84 ± 578.38	1149.26 ± 556.55
AUC0-inf	1229.91 ± 652.29	1214.71 ± 659.31
AUC0-t/ AUC0-inf Ratio (%)	96.35 ± 3.27	95.87 ± 4.57
Extrapolation Area (%)	3.65 ± 3.27	4.13 ± 4.57
Kel (1/h)	0.06 ± 0.01	0.06 ± 0.01
t½ (h)	12.89 ± 2.76	12.73 ± 2.47
* For Tmax median (Range)		

Table 3 Statistical analysis for Duloxetine 60mg (ln-transformed values)

Parameters	*Geometric mean		% Ratio	% Power	% Intra-Subject Variability	90 % Confidence Interval for Log-transformed data	
	Test (A)	Reference (B)	A/B			Lower Limit	Upper Limit
AUC_{0-inf}	1090.23	1070.16	101.8754	96.94	25.68	91.8113	113.0427
AUC_{0-t}	1049.96	1024.45	102.4902	97.44	25.08	92.5855	113.4544
C_{max}	55.89	58.34	95.8054	94.89	27.72	85.6576	107.1553

*Geometric mean was taken as the antilog (exponential) of the Least square mean of the log-transformed data.

Safety data

Both formulations were well tolerated, with no major side effects and no relevant differences in safety profiles were observed between the preparations.

A total of six adverse events were reported during the study, of which one adverse event was observed in the test product treated subjects, one adverse event was observed in the reference product treated subjects and four adverse events were observed during the post-study evaluation. As the subjects had received both the treatments, it was difficult to attribute the adverse events during Post study evaluation to either of the treatments. From the total of six adverse events were reported during the study, one adverse event was expected and definitely related, three adverse events were expected and probably related and two adverse events were unexpected and unrelated to the study drug. The adverse events were mild in severity and were resolved.

The adverse events were mild in severity and were resolved. One adverse event was observed in the test product treated subjects and another was observed in a reference product treated subject. Four adverse events were observed during the post-study evaluation.

Study conclusion

The 90% confidence intervals calculated for the primary parameters C_{max} and AUC_{0-t} for Duloxetine fell within the 80 – 125% acceptance range after single dose administration under fasting conditions.

Based on the presented bioequivalence study Duloxetine 60mg hard gastro resistant capsules manufactured for Mylan by Unichem Laboratories was considered bioequivalent with Cymbalta 60mg gastro resistant capsules of Eli Lilly Nederland B.V. under fasting conditions.

Study ARL-13-026

Methods

This was a randomized, balanced, open label, two period, two treatment, two sequence, single dose, crossover, comparative oral bioavailability study to establish comparative bioequivalence of Duloxetine 60 mg hard gastro resistant capsules (Mylan Laboratories India) and Cymbalta 60 mg gelule gastro resistante (MAH: Eli Lilly Nederland B.V.) in 36 healthy, adult male and female human subjects under fed conditions. The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety and tolerability of a single dose of Duloxetine 60 mg.

Study design

Based on the randomised schedule and following an overnight fast of at least 10 hours in both periods all subjects were given high fat and high calorie non-vegetarian breakfast of approximately 800-1000 calories (27.7% carbohydrate, 16.2% protein and 55.9% fat) 30 minutes prior to dosing. Each volunteer received a single oral dose of Duloxetine 60mg capsule with 240ml of water in period I and either one tablet of the reference or test product in period II.

Subjects were dosed while in sitting posture and were instructed to remain seated in an upright position for the first 2 hours following drug administration. Drinking water was not permitted one hour before dosing and until one hour post dose. At all other times water was given any time. Subjects were confined to the clinical facility from at least 12 hours prior to each drug administration until after the 48-hour blood sample collection in each study period.

Standardized meal was given to subjects during check-in night (in such a way to maintain 10 hrs fasting before high-fat and high-calorie non-vegetarian breakfast which was started by the subject 30 minutes prior to drug administration).

Standardized meals were provided to the subjects at 4 hours post-dose (12:00 hours, standard lunch), at 9 hours post-dose (17:00 hours, standard snacks), at 13 hours post-dose (21:00 hours, standard dinner), at 24 hours post-dose (08:00 hours, standard breakfast), at 28 hours post-dose (12:00 hours, standard lunch), at 33 hours post-dose (17:00 hours, standard snacks) and at 37bn hours post-dose (21:00 hours, standard dinner) in each study period.

The two periods were separated by a wash-out phase of at least 10 days.

Blood samples were taken at the following time points: pre-dose and at 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 13.0, 14.0, 16.0, 20.0, 24.0, 36.0, 48.0, and 72.0 hours after dosing.

Test and reference products

Table 4: Test and Reference Product information

Product Characteristics	Reference product	Test Product
Name	Cymbalta®	Duloxetine
Strength	60 mg	60 mg
Dosage form	gelule gastro-resistante (Gastro-resistant Capsules)	Hard gastro-resistant Capsules
Manufacturer	Lilly S.A., Avda. De la Industria, 30, 28108 Alcobendas, Madrid, Spain. MA Holder: Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.	Manufactured by: UNICHEM LABORATORIES LTD. 17 & 18, Pilerne Ind.Estate, Pilerne, Bardez Goa. 403 511 Manufactured for: Mylan Laboratories Limited, India
Batch number / Lot Number	C048615	GDUV11002
Batch size (Biobatch)	-	140,000
Measured content(s) (% of label claim)	97.4 % w/w	101.1 %
Commercial Batch Size	-	--
Expiry date (Retest date)	01-2015	October - 2013
Location of Certificate of Analysis	5312-compar-ba-be-stud-rep, Appendix-16.1.6	5312-compar-ba-be-stud-rep, Appendix-16.1.6
Member State where the reference product is purchased from:	France	-
This product was used in the following trials:	Study no. ARL/13/025 and ARL/13/026	Study no. ARL/13/025 and ARL/13/026

Population studied

36 healthy adult human subjects (33 males and 3 females) were enrolled as per the protocol. The study started with 36 subjects and 31 completed the study.

Main inclusion criteria:

Healthy, adult, human male and non pregnant female subjects having the age ranging from 18 to 45 years and Body Mass Index between 18 kg/m2 – 28 kg/m2 were eligible for enrollment in the study.

The subjects were included in the study after undergoing the demographic examination, clinical history, physical examination (including vital signs), 12 lead ECG, breath alcohol test, clinical laboratory tests [haemogram, biochemistry, urinalysis, and infectious disease screening (HIV, Hepatitis B and Hepatitis- C)], urine test for drug of abuse and meeting the inclusion criteria and none of the exclusion criteria. The subjects who participated in the study had age ranging from 20 to 40 years and BMI ranging from 18.29 to 27.99 kg/m^2.

Protocol deviations

Subject no. 22 was withdrawn due to adverse event after dosing in period I. Subject nos. 20 and 32 were withdrawn due to adverse event after dosing in period II. Subject no.36 was withdrawn due to non compliance to high fat high calorie breakfast noted before dosing in period I. Subject no.15 was dropped out as subject did

not report to study centre for enrolment of period II. Subject nos. 20, 22 and 32 were analyzed for safety reasons but concentrations obtained were not considered for pharmacokinetic and statistical analysis.

Analytical methods

Analysis of Duloxetine was performed using test method AMP-090-00 from 13 March 2013 to 26 March 2013.

This Ultra Performance Liquid Chromatography Method with Tandem mass spectrometry method involved the extraction of Duloxetine and the internal standard Duloxetine d5 from human plasma. The samples upon receipt from Accutest Research Laboratories Pvt. Ltd, Navi Mumbai on 01 March 2013 were stored in a deep freezer under frozen condition at -70 ± 15°C at Bioanalytical lab of CRC from the date of their receipt until they were analysed. During transit the temperature was maintained below -55°C. Total Long term plasma stability required is 39 days however this has been proved for 71 days.

1440 blood samples were expected however 1308 were received. 1287 samples (1233 + 54 samples for safety evaluation were analysed for the 31 subjects.

Validation of the test method

The test method was been validated (VR-090-00) in July 2012 and revalidated once in August 2012. The same test method was used for both studies. The same validation results achieved in study ARL-13-025 also pertain to this study.

Partial validation was carried out in order to amend the long term stability in the stock solution and human plasma. The long term stability is covered for up to 71 days.

Pharmacokinetic variables

Primary parameters: $AUC_{0-t,}$ AUC_{0-inf} and C_{max}

Secondary parameters: T_{max}.

Bioequivalence criteria; Bioequivalence was concluded if the 90% confidence interval of geometric mean of Cmax, AUC0-t and AUC0-inf between test and reference products fall within the range of 80.00 % to 125.00 % for Duloxetine.

Statistical methods

Analysis of variance (ANOVA) was performed on the log-transformed pharmacokinetic parameters

Cmax, AUC0-t and AUC0-inf at _ level of 0.05. The analysis of variance model included sequence, subjects nested within sequence, period and treatment as factors. Each analysis of variance also included calculation of least-square means (LSM's), adjusted differences between formulation means and the standard errors associated with these differences. All effects were tested against the residual error (mean square error) from the ANOVA model as the error term. The sequence effect was tested at the 10% level of significance and all other main effects were tested at the 5% level of significance against the residual error (mean square error) from the ANOVA model as the error term.

Results

Table 5 Pharmacokinetic parameters for Duloxetine 60mg (non-transformed values)

Formulations		C_{max} (ng/mL)	AUC_{0-t} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	T_{max} (hrs)	K_{el} (hrs^{-1})	$t_{1/2}$ (hrs)	AUC_{0-t}/ AUC_{0-inf} Ratio
Test Product A (N=31)	Arithmetic Mean ± SD	65.80 ± 22.32	1340.17 ± 471.19	1401.05 ± 512.74	8.87 ± 2.35	0.06 ± 0.01	12.68 ± 2.46	96.11 ± 3.33
Reference Product B (N=31)	Arithmetic Mean ± SD	65.42 ± 16.22	1221.12 ± 354.20	1267.51 ± 382.81	7.16 ± 1.70	0.06 ± 0.01	12.75 ± 2.61	96.59 ± 2.70
% Ratio (A/B)	Arithmetic Mean	100.58	109.75	110.54	-	-	-	-

Table 6 Statistical analysis for Duloxetine 60mg (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref (%)	Confidence Intervals		CV %
		Lower%	Upper%	
Cmax (ng/mL)	97.6108 %	91.0158%	104.6837%	16.10 %
AUC0-t (ng.h/mL)	106.3941 %	100.1822 %	112.9911 %	13.82 %
AUC0-inf (ng.h/mL)	107.0394 %	101.0920 %	113.3366 %	13.13 %

Safety data

Both formulations were well tolerated, with no major side effects and no relevant differences in safety profiles were observed between the preparations.

A total of nine adverse events were reported during the study, of which two adverse events were observed in the test product treated subjects, four adverse events were observed in the reference product treated subjects and three adverse events were observed during the post-study evaluation. As the subjects had received both the treatments, it was difficult to attribute the adverse events during Post study evaluation to either of the treatments. A total of three adverse events were expected and definitely related, four adverse events were expected and probably related and two adverse events were unexpected and unrelated to the study drug.

The adverse events were mild in severity and were resolved. No statistical significant differences between the test and reference treatments, for the incidence of subjects having experienced adverse events and for the incidence of adverse events were seen.

Study conclusion

Based on the presented bioequivalence study Duloxetine 60mg hard gastro resistant capsules manufactured for Mylan by Unichem Laboratories is considered bioequivalent with Cymbalta 60mg hard gastro resistant capsules of Eli Lilly Nederland B.V. under fed conditions.

2.4.3. Pharmacokinetic conclusion

The 90% confidence intervals calculated for the primary parameters $AUC_{0-t,}$ AUC_{0-inf} and AUC_{0-t} for Duloxetine fll within the 80 – 125% acceptance range after single dose administration under both fed and fasting conditions.

2.4.4. Pharmacodynamics

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

2.4.5. Post marketing experience

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

2.4.6. Discussion on clinical aspects

The applicant has presented two bioequivalence studies using the 60mg hard gastro resistant capsules. The results of these two studies concluded that the 60mg strength is bioequivalent to the chosen reference product in both fed and fasting conditions. The proposed biowaiver for the 30 mg strength was properly justified and accepted by the CHMP.

2.4.7. Conclusions on clinical aspects

Based on the submitted bioequivalence study results Duloxetine 60mg hard gastro resistant capsules of Mylan Laboratories India are considered bioequivalent with Cymbalta 60mg hard gastro resistant capsules of Eli Lilly Nederland B.B in healthy adult male and female patients under both fed and fasting conditions.

The results of studies ARL-13-025 and ARL-13-026 with the 60mg hard gastro resistant capsule can be extrapolated to Duloxetine 30mg hard gastro resistant capsule as all of the conditions in the Guideline on the Investigation Bioequivalence CPMP/EWP/QWP/1401/98 Rev 1 are met.

2.5. Pharmacovigilance

Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC. The applicant's pharmacovigilance system summary includes a reference to the location where the pharmacovigilance system master file for the medicinal product is kept and provides proof that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC.

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 3.0 is acceptable. The PRAC advice is attached.

2.7. PSUR submission

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

2.8. Product information

2.8.1. User consultation

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

3. Benefit-risk balance

This application concerns a generic version of duloxetine hard capsule. The reference product Cymbalta is indicated for the treatment of major depressive disorder, diabetic peripheral neuropathic pain, and generalised anxiety disorder in adults. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence studies form the pivotal basis with a two way crossover comparative bioavailability design under fasting and fed conditions. These were considered adequate to evaluate the bioequivalence of this formulation and were in line with the respective European requirements. Choice of dose, sampling points, overall sampling time, as well as wash-out period were adequate. The analytical methods were validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Duloxetine Mylan met the protocol-defined criteria for bioequivalence when compared with the reference product. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range. Bioequivalence of the two formulations was demonstrated.

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 Mylan in the "Treatment of major depressive disorder. Treatment of diabetic peripheral neuropathic pain. Treatment of generalised anxiety disorder. Duloxetine Mylan is indicated in adults.

For further information see section 5.1." 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 submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.