EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 October 2014
EMA/753230/2014
Committee for Medicinal Products for Human Use (CHMP)

Duloxetine Lilly

duloxetine

Procedure No. EMEA/H/C/004000

Applicant: Eli Lilly Nederland B.V.

Assessment report for an initial marketing authorisation application

Assessment report as adopted by the CHMP with all commercially confidential information deleted

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List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
EC	European Commission
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERA	Environmental Risk Assessment
MAH	Marketing Authorisation Holder
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 7 May 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Duloxetine Lilly, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 April 2014.

The applicant applied for the following indication

"Treatment of major depressive disorder.
Treatment of diabetic peripheral neuropathic pain.
Treatment of generalised anxiety disorder.

Duloxetine Lilly is indicated in adults".

The legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC – relating to informed consent from a marketing authorisation holder for an authorised medicinal product.

The application submitted is composed of administrative information, quality, non-clinical and clinical data with a letter from Eli Lilly Nederland B.V. allowing the cross reference to relevant quality, non-clinical and/or clinical data contained in the Cymbalta marketing authorisation dossier.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity
Not applicable

Similarity
Not applicable

Scientific Advice
The applicant did not seek scientific advice at the CHMP.

Licensing status

The cross-referred product Cymbalta was given a Community Marketing Authorisation on 17 December 2004.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

Lilly S.A.
Avda. de la Industria 30
28108 Alcobendas
SPAIN

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Arantxa Sancho-Lopez

Co-Rapporteur: Filip Josephson

CHMP Peer reviewer(s): N/A

PRAC Rapporteur: Dolores Montero Corominas

PRAC Co-Rapporteur: Qun-Ying Yue

- The application was received by the EMA on 7 May 2014
- The procedure started on 25 May 2014
- The Rapporteurs first Assessment Report was circulated to all CHMP members on 23 June 2014
- The Rapporteurs updated Assessment Report was circulated to all CHMP members on 16 July 2014
- The PRAC Rapporteur's Risk Management Plan Assessment Report was endorsed by PRAC on 10 July 2014
- During the meeting on 21-24 July 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 July 2014
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 August 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 15 September 2014
- The PRAC Rapporteur's Risk Management Plan Assessment Report was endorsed by PRAC on 10 October 2014
- During the meeting on 23 October 2014, 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 Lilly.

2. Scientific discussion

2.1. Introduction

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.

This marketing authorisation application for Duloxetine Lilly has been submitted by Eli Lilly Nederland B.V as an informed consent application in accordance with Article 10c of Directive 2001/83/EC, as amended. The resulting medicinal product, DULOXETINE LILLY, will be identical to CYMBALTA (EU/1/04/296/001-009).

As a consequence, quality, safety and efficacy of the Duloxetine Lilly medicinal product are identical to the up-to-date quality, non-clinical and clinical profile of Cymbalta. The application for Duloxetine Lilly concerns the strength and package size identical to those approved for Cymbalta and consists of only

Module 1. Information on the scientific discussion can be found in the Cymbalta CHMP assessment reports and in the European Public Assessment Report (EPAR) published on the EMA website.

The approved indication is:

"Treatment of major depressive disorder.
Treatment of diabetic peripheral neuropathic pain.
Treatment of generalised anxiety disorder.

Duloxetine Lilly is indicated in adults".

2.2. Quality aspects

Duloxetine Lilly is submitted under an informed consent application, article 10(c) of directive 2001/83/EC, only module 1 is provided and module 3 of the duplicate dossier cross-refers to the up-to-date module 3 of the original dossier (Cymbalta), which have been assessed and approved, including all post-marketing procedures. The declaration submitted by the Applicant states that Duloxetine Lilly possesses the same qualitative and quantitative composition in terms of active substances and same pharmaceutical form as Cymbalta.

2.3. Non-clinical aspects

Reference is made to the non-clinical information included in the Cymbalta EPAR (EMA/H/C/000572), which is acceptable since this is a marketing authorisation application by informed consent.

The development programme of duloxetine was long, with initial toxicology studies being conducted in early 1980s. The toxicology and toxicokinetic studies were performed in accordance with Good Laboratory Practise (GLP) regulations except for the oldest studies, since the first directive concerning the application of the Good Laboratory Practices (GLPs) in non-clinical studies carried out with chemical and pharmaceutical products dates 1987 (87/18/EEC). Studies previously conducted were carried out following Organisation of Economic Cooperation and Development (OECD) and Japanese Ministry of Health, Labour, and Welfare (MHLW) standards. No new non-clinical studies have been submitted.

The ERA provided for this application consists of an adequate justification for the absence of specific study data.

A full environmental risk assessment conforming to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00, 2006) has been previously submitted to the EMA to support a Type II variation extending the indication of Cymbalta to include generalized anxiety disorder (EMEA/H/C/572/27) and a Type II Variation to include the use of Cymbalta to prevent recurrence of major depressive episodes (EMEA/H/C/572/36). The data showed that duloxetine would not persist or accumulate in aqueous, sediment or soil compartments. Additionally, the predicted environmental concentrations of duloxetine were lower than the predicted no-effect concentrations calculated from ecotoxicity data with sentinel species. The conclusions in the environmental risk assessments state that human excretion of duloxetine and its metabolites is not expected to result in any significant environmental risk.

The current dossier does not propose any new indications, increased doses or an expanded indicated population to that already authorized for Cymbalta. Additionally, the resulting medicinal product is not intended to be marketed in any European countries for which Cymbalta is not already marketed. Therefore, approval of this dossier is not expected to result in a significant increase in the extent of use of duloxetine. Therefore, the CHMP was of the view that it should not result in an increase of risk to the environment during storage, distribution, use and disposal.

The nonclinical documentation is acceptable. No further nonclinical data are required.

2.4. Clinical aspects

Since this application is an informed consent of the Cymbalta application, the clinical data in support of the Duloxetine Lilly application are identical to the up-to-date clinical data of the Cymbalta dossier, which have been assessed and approved (including all post-marketing procedures).

So no additional clinical data have been submitted and reference has been made to Module 5 data for Cymbalta.

2.5. Pharmacovigilance

Summary of the Pharmacovigilance System

The applicant has provided the Summary of the Pharmacovigilance System, version 4.0 (PSMF reference MFL6).

The MAH was requested to update the Summary of the PSMF including the version date. A version 6 of the summary of the PSMF was provided with the signatures dated.

The CHMP considered that the Pharmacovigilance system summary submitted by the applicant fulfilled the legislative requirements.

2.6. Risk Management Plan

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

The PRAC considered that the risk management plan version 11.2 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update.

The applicant implemented the changes in the RMP during the procedure as requested by the rapporteur, and they submitted a new version (11.2) with the track changes highlighted from the version that was being evaluated (11.1). This version, was considered acceptable by the PRAC

The CHMP endorsed the Risk Management Plan version 11.2 with the following content:

Safety concerns

Summary of Safety Concerns	
Important Identified Risks	• Hepatic risks • Suicidality • Hyperglycaemia • Stevens-Johnson Syndrome • Gastrointestinal tract bleeding
Important Potential Risks	• Cardiovascular events including those with concomitant use of NSAIDs (including myocardial infarction, heart failure, and stroke) • Upper gastrointestinal tract bleeding events with concomitant use of NSAIDs • Renal failure
Missing Information	• Characterization of the safety and tolerability of duloxetine in paediatric patients • Prospective data about potential risks of exposure to duloxetine during pregnancy • Safety of duloxetine in elderly patients ≥75 years old with concomitant NSAIDs use

Pharmacovigilance plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
F1J-MC-B034 Cymbalta Pregnancy Registry Category 3	To develop and maintain a prospective, observational pregnancy exposure registry study conducted in the United States that compares the pregnancy and foetal outcomes of women exposed to Cymbalta during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, and any serious adverse pregnancy outcomes. These events will be assessed	Prospective information about potential risks of exposure to duloxetine during pregnancy; missing information	Ongoing	Final report Q4 2016

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
	among the enrolled women throughout the pregnancy. The events will also be assessed among infants through at least the first year of life. Annual interim reports will be submitted until FDA has acknowledged that sufficient data has been collected.			
Study F1J-MC-B035 General Practice Research Database (GPRD) -Feasibility assessment for a further analysis of suicidality in SUI patients. Category 3	Follow on assessment to determine if exposure numbers are sufficient for a further analysis to be conducted to study to investigate the association between duloxetine exposure and suicide-related behaviors and ideation in women with SUI.	Suicidality	Planned	Feasibility assessment Q4 2014

Abbreviations: FDA = Food and Drug Administration; GPRD = General Practice Research Database; PSUR = Periodic Safety Update Report; Q = quarter; SUI = stress urinary incontinence.

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Hepatic risks	Appropriate labelling (sections of the SmPC: 4.2 Posology and method of administration; 4.3 Contraindications; 4.4 Special warnings and precautions for use; 4.8 Undesirable effects; 5.2 Pharmacokinetic properties). The language covers the identified risks of mild-to-moderate liver enzyme elevations and also more severe (>10X ULN) transaminase elevations.	None
Suicidality	Appropriate labelling (sections of the SmPC: 4.4 Special	None

	warnings and precautions for use; 4.8 Undesirable effects; 5.1 Pharmacodynamic properties). The language takes into account the available data within Lilly as well as the FDA meta-analyses of antidepressant class-related association with suicidality.	
Hyperglycaemia	Appropriate labelling (section 4.8 of the SmPC, Undesirable effects). The language provides information from DPNP clinical trial data and also states that hyperglycaemia is an undesirable effect.	None
Stevens-Johnson Syndrome	Appropriate labelling (section 4.8 of the SmPC, Undesirable effects). Stevens-Johnson Syndrome is a listed event in the postmarketing adverse event section.	None
Gastrointestinal tract bleeding	Appropriate labelling (sections of the SmPC: 4.4 Special warnings and precautions for use; 4.5 Interaction with other medicinal products and other forms of interaction; 4.8 Undesirable effects).	None
Cardiovascular events including those with concomitant use of NSAIDs (including myocardial infarction, heart failure, and stroke)	Appropriate labelling (sections of the SmPC: 4.3 Contraindications; 4.4 Special warnings and precautions for use; 4.8 Undesirable effects; 4.9 Overdose). Duloxetine Lilly is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis.	None
Renal failure	None; a potential risk.	None
UGIT Bleeding Events with Concomitant Use of NSAIDs	Appropriate labelling. Section 4.4 of the SmPC, Special warnings and precautions for use, advises caution in patients taking anticoagulants and/or medicinal products known to affect platelet function (eg, NSAIDs or ASA), and in patients with known bleeding tendencies.	None
Characterisation of the safety and tolerability in paediatric patients	Appropriate labelling (sections of the SmPC: 4.2 Posology and method of administration; 4.8 Undesirable effects; 5.1 Pharmacodynamic properties;	None

	5.2 Pharmacokinetic properties).	
Prospective data about potential risks of exposure to duloxetine during pregnancy	Appropriate labelling (sections of the SmPC: 4.6 Fertility, pregnancy, and lactation; 5.3 Preclinical safety data). Section 4.6 advises that duloxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.	None
Elderly patients ≥75 years old with concomitant NSAIDs use	Appropriate labelling (sections of the SmPC: 4.2 Posology and method of administration; 4.4 Special warnings and precautions for use; 4.8 Undesirable effects; 5.1 Pharmacodynamic properties; 5.2 Pharmacokinetic properties).	None

2.7. Product information

The MAH was requested to align the PI of Duloxetine 30 mg and 60 mg hard gastro-resistant capsules with those of Cymbalta 30 mg and 60 mg hard gastro-resistant capsules.

The MAH submitted a new version of the product information that included the changes made in the recently approved text for Cymbalta from procedure EMEA/H/C/000572/WS0490/0061.The CHMP agreed with this revised PI.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons: There are no changes to the text with respect to Cymbalta except for the invented name. The results of user testing of the Cymbalta patient leaflet were last submitted to the EMA in December 2008 as part of variation EMEA/H/C/572/37. Since the proposed Package Leaflet for the current application is essentially identical to the Package Leaflet of Cymbalta, no further testing is warranted.

3. Benefit-Risk Balance

Since this application has been submitted by Eli Lilly Nederland B.V as an informed consent application to Cymbalta in accordance with Article 10c of Directive 2001/83/EC, as amended, the CHMP considered that the benefit-risk balance of Duloxetine Lilly 30 mg and 60 mg Gastro-resistant capsules was favourable and therefore recommended the granting of the marketing authorisation for the following indication:

"Treatment of major depressive disorder.
Treatment of diabetic peripheral neuropathic pain.
Treatment of generalised anxiety disorder.

Duloxetine Lilly is indicated in adults".

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Duloxetine Lilly in the treatment of major depressive disorder, diabetic peripheral neuropathic pain, generalised anxiety disorder is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreeed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The product does not have any additional RMMs in place.

- **Obligation to complete post-authorisation measures**

No conditions are necessary.

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

Not applicable.