Decentralised Procedure

Public Assessment Report

Duloxetin HEXAL 30/ 60 mg magensaftresistente Hartkapseln

Duloxetine hydrochloride

DE/H/4512/001-002/DC

Applicant: HEXAL AG, Germany

Reference Member State	DE

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product(s) in the RMS	Duloxetin HEXAL 30/ 60 mg magensaftresistente Hartkapseln
Name of the drug substance (INN name):	Duloxetine hydrochloride
Pharmaco-therapeutic group (ATC Code):	N06AX21
Pharmaceutical form(s) and strength(s):	Gastro-resistant capsules, hard 30; 60 mg
Reference Number(s) for the Decentralised Procedure	DE/H/4512/001-002/DC
Reference Member State:	DE
Concerned Member States:	AT, DK, EL, HU, PL, SI, SK
Applicant (name and address)	Hexal Aktiengesellschaft Industriestr. 25, D-83607 Holzkirchen, Germany

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for *"Duloxetin HEXAL 30/ 60 mg magensaftresistente Hartkapseln",* indicated in the treatment of major depressive disorder, diabetic peripheral neuropathic pain and generalised anxiety disorder in adults, is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

N/A

II.2 About the product

Duloxetine is a serotonin and noradrenaline reuptake inhibitor that weakly interferes with dopamine reuptake and does not exert significant affinity on histaminergic, dopaminergic, cholinergic and adrenergic receptors. Duloxetine is indicated for the treatment of major depressive disorder, diabetic peripheral neuropathic pain and generalised anxiety disorder in adults.

II.3 General comments on the submitted dossier

This application according to Art. 10.2(b) of Dir. 2001/83/EC is in line with prevailing European regulatory requirements for essentially similar medicinal products.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory 'issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance

Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

The data submitted on the quality of the drug substance and drug product reflect well researched and well defined products.

A valid Certificate of suitability is provided for the active substance manufacturer A. The residual content of 2-propanol used in the last steps of the synthesis is limited by the test for loss on drying according to Ph.Eur. monograph with a limit of NMT 0.5%. The re-test period of the substance is 60 months if stored in double polyethylene bags placed in fibre drums.

An Active Substance Master File (ASMF) is submitted for manufacturer B. The ingredients, the manufacturing process and the in-process controls of the drug product correspond to the current standard of pharmaceutical technology and are suitable to guarantee an appropriate product quality. The description of the analytical test methods is adequate. The validation results are plausible.

All relevant quality criteria are specified in accordance with internationally acknowledged pharmacopoeias. The specified limits are in line with the requirements of the CHMP Guidelines and are guarded by the finished product.

A shelf-life of 2 years for Duloxetine 30 mg and 60 mg gastro-resistant capsules packed in PA/Alu/PVC/Alu blisters, PVC/PE/PCTFE/Alu blisters, and HDPE bottles with screw cap with special storage conditions "Do not store above 30ºC" is justified by available stability data.

III.2 Non-clinical aspects

The pharmacological and toxicological properties of duloxetine are well known and have been summarised based on publicly available information in the Non-clinical Overview. The instructions on use of the compound during pregnancy and lactation and the preclinical safety data contained in the proposed SmPC and PL, respectively, essentially reflect these properties and have been adequately harmonised with the currently approved product information of the reference product *"Cymbalta"* (EMEA/H/C/572-WS/758), which is acknowledged.

Environmental Risk Assessment (ERA)

Since *"Duloxetin HEXAL 30 / 60 mg magensaftresistente Hartkapseln"* are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Clinical aspects

Pharmacokinetics

To support the application, the applicant has submitted reports of two pivotal bioequivalence studies under fasting and fed conditions:

Single dose fasting study (Code: BA13541245-01)

Study Title: An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study of Duloxetine Hard Gastro-Resistant Capsules 60 mg and 'CYMBALTA' Hard Gastro-Resistant Capsules 60 mg in healthy adult human subjects under fasting conditions.

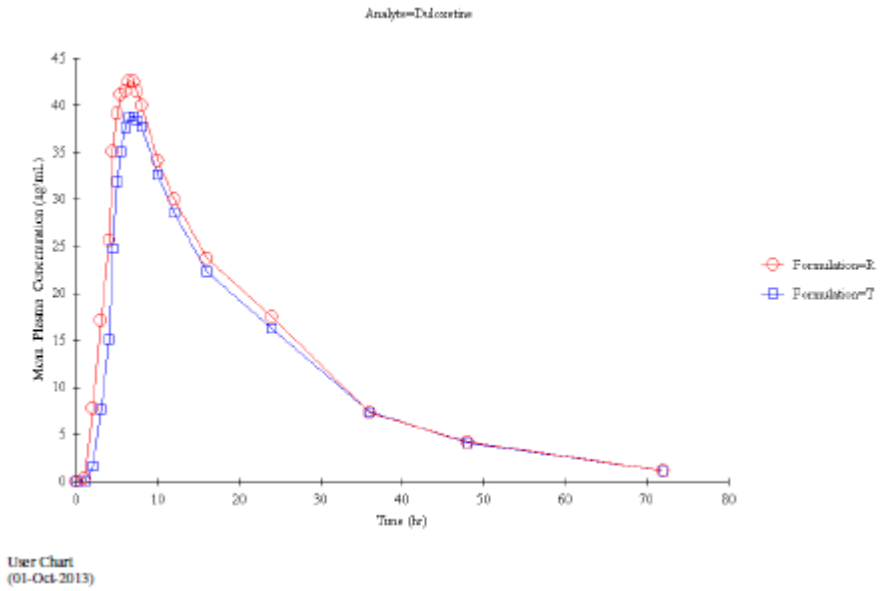
Results:

Pharmacokinetic data for Duloxetine (n=30)

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test product	Reference Product
$AUC_{(0-t)}$ (hr*ng/mL)	810.452 ± 377.2165	882.413 ± 404.8640
$AUC_{(0-\infty)}$ (hr*ng/mL)	841.722 ± 392.7974	915.198 ± 423.5756
C_{max} (ng/mL)	43.310 ± 18.9512	46.971 ± 19.8324
t_{max} (Median (Min, Max))	6.750 (4.50 - 10.00)	6.500 (4.50 - 8.00)
K_{el}	0.0589 ± 0.01335	0.0598 ± 0.01543
$t_{½}$	12.375 ± 2.8494	12.290 ± 2.9590
AUC_%Extrap_obs	3.802 ± 2.2115	3.474 ± 1.6387
AUC_t/AUC_i	0.962 ± 0.0221	0.965 ± 0.0164

Bioequivalence evaluation of Duloxetine:

Pharmacokinetic parameter (n=30)	Geometric Mean Ratio Test/Ref	90% Confidence Intervals	Intra subject CV%[1]
$AUC_{(0-t)}$ (hr*ng/mL)	92.09	82.98% - 102.21%	24.01
C_{max} (ng/mL)	91.72	83.05% - 101.29%	22.84



Single dose fed study (Code: BA13541246-01)

Study Title: An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study of Duloxetine Hard Gastro-Resistant Capsules 60 mg and 'CYMBALTA' Hard Gastro-Resistant Capsules 60 mg in healthy adult human subjects under fed conditions.

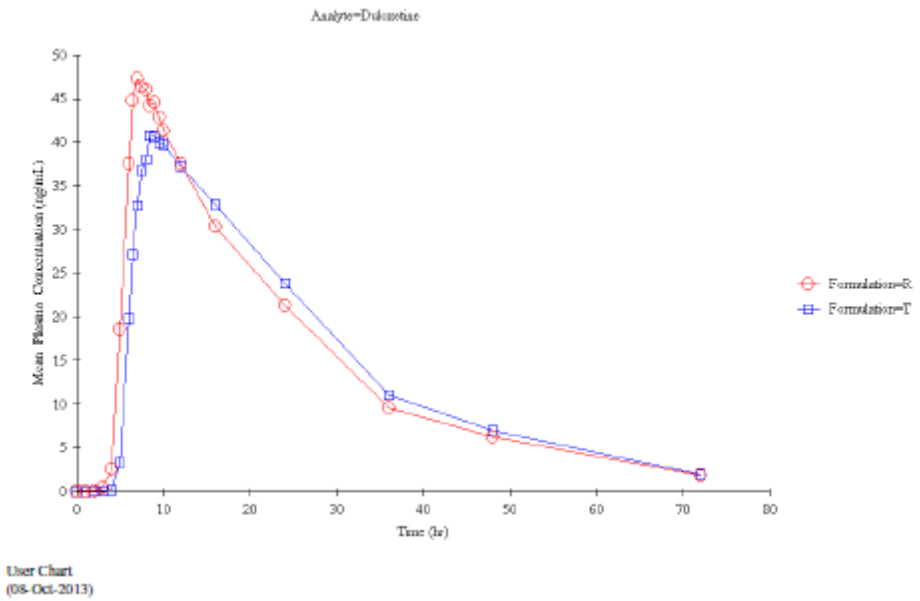
Results:

Pharmacokinetic data for Duloxetine (n=33):

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test product	Reference Product
$AUC_{(0-t)}$ (hr*ng/mL)	1015.008 ± 728.7549	1007.355 ± 762.3045
$AUC_{(0-\infty)}$ (hr*ng/mL)	1069.963 ± 795.9889	1061.946 ± 845.1074
C_{max} (ng/mL)	48.582 ± 32.0021	49.768 ± 28.0713
t_{max} (Median (Min, Max))	9.000 (6.00 - 24.00)	7.500 (6.00 - 10.00)
K_{el}	0.0582 ± 0.01627	0.0580 ± 0.01452
$t_{½}$	12.718 ± 3.1403	12.729 ± 3.2855
AUC_%Extrap_obs	4.808 ± 2.6924	4.562 ± 2.5047
AUC_t/AUC_i	0.952 ± 0.0269	0.954 ± 0.0250

Bioequivalence evaluation of Duloxetine:

Pharmacokinetic parameter (n=33)	Geometric Mean Ratio Test/Ref	90% Confidence Intervals	Intra subject CV%[1]
$AUC^{2}_{(0-t)}$ (hr*ng/mL)	101.01	95.82% - 106.47%	12.53
C_{max} (ng/mL)	94.78	87.56% - 102.59%	18.93



Conclusion: For both studies the confidence intervals of C_{max} and AUC_{0-t} are within the bioequivalence acceptance limits of 80.00 to 125.00%.

Biowaiver for additional strength 30 mg:
The results of the two pivotal studies BA13541245-01 and BA13541246-01 with 60mg gastro resistant formulation can be extrapolated to the other strength 30 mg, as all requirements according to the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6., are fulfilled.

Legal Status
For prescription only

Assessment of User Testing
Overall, the test methodology follows the guidelines of the European Commission (*Guideline on the readability of the label and package leaflet of medicinal products for human use*, Revision January 2009; Update of Directive 2001/83/EC as amended by Directive 2004/27/EC / *Guidance concerning consultations with target patient groups for the packet leaflet*, May 2006). Both the first and the second test round met the success criteria of over 90% of the subjects being able to locate the requested information, and of those, more than 90% being able to give the correct answer, to indicate that they understood the information presented. The general impression of the PL (Content, language and layout) was mostly positive. In conclusion, the user test is considered acceptable.

Summary Pharmacovigilance system
The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to duloxetine.

Important identified risks	• Hepatic risks • Suicidality • Hyperglycemia • Stevens-Johnson Syndrome • Gastrointestinal Tract Bleeding • Serotonin Syndrome
Important potential risks	• Cardiovascular events including those with concomitant use of NSAIDs (including myocardial infarction, heart failure, and stroke) • Upper gastrointestinal tract (UGIT) bleeding events with concomitant use of NSAIDs • Renal Failure
Missing information	• Characterization of the safety and tolerability of duloxetine in pediatric patients • Prospective data about potential risks of exposure to duloxetine during Pregnancy • Characterization of drug utilization in unapproved indications and populations • Safety of duloxetine in elderly patients ≥75 years old with concomitant NSAIDs use • Long term safety data in chronic pain patients

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 RMS;
- 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.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:
- PSURs shall be submitted 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. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

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

IV. BENEFIT RISK ASSESSMENT

Based on the review of the data on quality, safety and efficacy, the application for *"Duloxetin HEXAL 30/ 60 mg magensaftresistente Hartkapseln"* is approved. For intermediate amendments see current product information.