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Public Assessment Report

Scientific discussion

Duloxetin Krka 90 mg hard gastro-resistant capsules
Duloxetine hydrochloride

SK/H/0156/003/DC

Date: December 2017

This module reflects the scientific discussion for the approval of Duloxetin Krka 90 mg. The procedure was finalised at 25.07.2017. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for *Duloxetin Krka 90 mg hard gastro-resistant capsules*, from *Krka, d.d., Slovenia.*
The product is indicated for *the treatment of major depressive disorder (MDD) and generalised anxiety disorder (GAD).*
A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Duloxetine 90 mg hard gastro-resistant capsules are white to almost white pellets in a hard gelatine capsule size 0. The capsule body is light orange and the cap is white. On capsule body "90" by black ink is imprinted.
Blister used as primary packaging consists of:
- Aluminium forms foil: OPA/Alu/[HDPE/PE + DES of CaO/HDPE]
- Aluminium sealing foil: Alu/PE

Carton box as secondary packaging has been chosen.
The drug is sensitive to moisture. To protect the capsules the blister with desiccant has been chosen.

II.2 Drug Substance

Duloxetine hydrochloride is described in Ph. Eur.. Duloxetine hydrochloride is white or almost white powder, sparingly soluble in water, freely soluble in methanol, practically insoluble in hexane. Solubility of duloxetine hydrochloride is pH dependent.
Manufacturing process is performed in multi-step synthesis of the chiral key intermediate DLT19 following the condensation step with 1-fluoronaphtalene resulting in duloxetine free base.
The control tests and specifications for drug substance product are adequately drawn up. Specifications for active substance have been set in accordance with Ph. Eur. monograph for duloxetine hydrochloride and for basic and specific tests in line with ICH Q6A guideline with acceptable limits.
Duloxetine hydrochloride drug substance is controlled in accordance with the current European Pharmacopoeia monograph (2594).
The same analytical methods as for drug substance release have been used in the stability program. All monitored parameters have remained within the limits of specifications for all tested batches at long-term and accelerated testing conditions. Microbiological quality complies with the requirements. The proposed retest period of 24 months is justified.

II.3 Medicinal Product

The aim of the development has been to develop a product essential similar to the reference medicinal product, easily and consistently manufactured and showing stable formulation.
Excipients in the formulation of the generic product are substantially the same as in the reference product except of enteric layer, where different excipient providing gastro resistant properties of the 3rd layer of pellets in generic (hypromellose phthalate) and reference product (hypromellose acetate succinate) has been used.
Coating of pellets, encapsulation, packaging of capsules and equipment have been shortly described. Flowchart with IPC has been incorporated.
The excipients chosen on the basis of the reference product formulation are well known and widely used. All excipients are covered by Ph. Eur. The selection has been carried out to gain good physical characteristics of the formulation, a comparable dissolution profile with respect to reference medicinal product and acceptable impurity profile.

Shelf-life of 24 months is acceptable with proposed storage conditions: Do not store above 25°C. Store in the original packaging in order to protect from moisture.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of duloxetine are well known. As duloxetine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Grounds for non-providing new non-clinical data are justified adequately. Overview based on literature review is, thus, appropriate.

Ecotoxicity/environmental risk assessment (ERA)
The following sentence can be used in case no ERA has been submitted:
Since Duloxetine 90 mg is intended for substitution of 30 mg + 60 mg strengths, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Applicant submitted application for marketing authorisation for duloxetine 90 mg in order to increase the compliance in patients with MDD and GAD who need more than 60 mg of duloxetine per day (as stated in clinical overview). This 90 mg formulation is indeed appropriate only for patients with MDD and GAD, based on posology of duloxetine. In the third indication of strengths 30 mg and 60 mg – diabetic peripheral neuropathic pain – 90 mg strength cannot be use, as in this indication, doses above 60 mg should be administered as evenly divided.

IV.2 Pharmacokinetics

Bioequivalence studies

Applicant submitted two bioequivalence studies with 90 mg strength of duloxetine compared to 60 mg + 30 mg strength of Cymbalta. Initially a possibility of biowaiver for 90 mg strength based on the existent studies with 60 mg capsules was evaluated by applicant. However, as safety reasons were not fully accepted as an argument for the waiver of bioequivalence study with the highest 90 mg strength, it was, in agreement with the Scientific Advice from BfArM,

decided to conduct also the studies with 90 mg capsules. To prevent nausea as the most frequent adverse event in duloxetine treatment the anti-emetic drug was administered to study subjects in both bioequivalence studies.

To support the application, the applicant has submitted as report 2 bioequivalence studies:

1. A Single-Dose, Comparative Bioavailability Study of Duloxetine 90 mg Hard Gastro-Resistant Capsules and an Equivalent Dose of Cymbalta Hard Gastro-Resistant Capsules under Fasting Conditions. This study was designed as single center, open label, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, 2-treatment, cross over study in healthy male and female volunteers under fasting state.

The results of the study show bioequivalence between test and reference product when administered under fasted condition. The pharmacokinetic parameters are summarized in Table 1.

Table 1. Pharmacokinetic parameters

Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
C_{max}	**A**	32	90.388 (47)	82.529	**A vs B**	93.13	86.49 - 100.27	17
(ng/mL)	**B**	32	95.547 (40)	88.619				
AUC_t	**A**	32	1592.183 (50)	1431.662	**A vs B**	98.37	93.05 - 103.98	13
(ng·h/mL)	**B**	32	1604.327 (45)	1455.434				
AUC_{inf}	**A**	32	1675.158 (52)	1497.249	**A vs B**	98.49	93.17 - 104.10	13
(ng·h/mL)	**B**	32	1683.570 (46)	1520.258				
		n	***Median***	***Range***				
T_{max}	**A**	32	5.00	3.00- 7.50				
(h)	**B**	32	5.00	3.00- 6.52				

Treatment A (Test)	*Duloxetine 90 mg hard gastro-resistant capsules, Batch No.: R42170 (Krka, d.d., Novo mesto, Slovenia, EU)*
Treatment B (Ref)	*Cymbalta® (duloxetine) 30 mg + 60 mg hard gastro-resistant capsules, Lot No.: C488357/C505808 (Eli Lilly Nederland B.V., The Netherlands, EU)*

A Single-Dose, Comparative Bioavailability Study of Duloxetine 90 mg Hard Gastro-Resistant Capsules and an Equivalent Dose of Cymbalta Hard Gastro-Resistant Capsules under Fed Conditions. This study was designed as single center, open label, randomized, single dose, laboratory-blinded, 2-period, 2-sequence, 2-treatment, cross over study in healthy male and female volunteers under fed conditions.

The results of the study show bioequivalence between test and reference product when administered under fed condition. The pharmacokinetic parameters are summarized in Table 2.

Table 2. Pharmacokinetic parameters

Parameter	Trt	n	Arithmetic Mean (CV%)	Geometric Mean	Contrast	Ratio (%)	90% Confidence Interval	Intra-Sbj CV(%)
C_{max}	A	35	90.394 (49)	80.320	A vs B	100.69	93.70 - 108.19	18
(ng/mL)	B	35	91.491 (55)	79.772				
AUC_t	A	35	1670.806 (72)	1355.955	A vs B	105.11	98.43 - 112.24	16
(ng·h/mL)	B	35	1655.999 (85)	1290.041				
AUC_{inf}	A	35	1794.982 (79)	1419.835	A vs B	105.54	98.77 - 112.77	16
(ng·h/mL)	B	35	1771.332 (94)	1345.324				
		n	Median	Range				
T_{max}	A	35	8.00	5.50-12.00				
(h)	B	35	7.00	5.50-11.00				

Treatment A (Test)	*Duloxetine 90 mg hard gastro-resistant capsules, Batch No.: R42170 (Krka, d.d., Novo Mesto, Slovenia, EU)*
Treatment B (Ref)	*Cymbalta® (duloxetine) 30 mg + 60 mg hard gastro-resistant capsules, Batch No.: C488357+C505808 (Eli Lilly Nederland B.V., The Netherlands, EU)*

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence studies Duloxetin Krka 90 mg is considered bioequivalent with reference medicinal product.
The reference medicinal product is Ariclaim 30 mg, 60 mg gastro-resistant capsule, hard by Eli Lilly Netherland B.V., registered since 11.08.2004. To the same global marketing authorization belongs also medicinal product Cymbalta, 30 mg, 60 mg, gastro-resistant capsule, hard, that is used in the bioequivalence study.

IV.3 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 the medicinal product Duloxetin Krka 90 mg.

- Summary table of safety concerns as approved in RMP

Important identified risks	Hepatic risks Suicidality Hyperglycemia 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) Renal Failure
Missing information	Prospective data about potential risks of exposure to duloxetine during pregnancy Use of duloxetine 120 mg in elderly patients

- Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Important Identified Risks		
Hepatic risks	(Proposed) content in SPC Section: **Sections 4.2** (Posology and method of administration) and **4.3** (Contraindications) state that duloxetine must not be used in patients with substantial liver disease. **Section 4.4** (Special warnings and precautions for use) states that cases of liver injury have been reported with duloxetine, especially during the first months of treatment and that duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury. **Section 4.8** (Undesirable effects): listed in this section. **Section 5.2** (Pharmacokinetic properties): data in this section. **Prescription only medicine.**	None proposed
Suicidality	(Proposed) content in SPC Section: **Section 4.4** (Special warnings and precautions for use) states that depression is associated with an increased risk of suicidal thoughts and selfharm and that this risk persists until significant remission occurs and that the risk of suicide may increase in the early stages of recovery and in patients less than 25 years old. **Section 4.8** (Undesirable effects): listed in this section. **Prescription only medicine.**	None proposed
Hyperglycemia	(Proposed) content in SPC Section: **Section 4.8** (Undesirable effects): listed in this section. Mentioning of study. **Prescription only medicine.**	None proposed
Stevens-Johnson Syndrome	(Proposed) content in SPC Section: **Section 4.8** (Undesirable effects): listed in this section. **Prescription only medicine.**	None proposed
Gastrointestinal Tract Bleeding	(Proposed) content in SPC Section: **Section 4.4** (Special warnings and precautions for use) states that there have been reports of various bleeding abnormalities and that caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function and in patients with known bleeding tendencies. **Section 4.8** (Undesirable effects): listed in this	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	section. **Prescription only medicine.**	
Important Potential Risks		
Cardiovascular events including those with concomitant use of NSAIDs (including myocardial infarction, heart failure, and stroke)	(Proposed) content in SPC Section: **Sections 4.3** (Contraindications) states that the initiation of treatment with duloxetine is contraindicated in patients with uncontrolled hypertension and potential risk of hypertensive crisis. **Section 4.4** of the SmPC (Special warnings and precautions for use) states that duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients, including cases of hypertensive crisis, especially in patients with preexisting hypertension. Blood pressure monitoring is recommended, especially during the first month of treatment. Caution should also be exercised when duloxetine is used with medicinal products that may impair its metabolism (see section 4.5). For patients who experience a sustained increase in blood pressure while receiving duloxetine, either dose reduction or gradual discontinuation should be considered (see section 4.8). **Section 4.8** (Undesirable effects): listed in this section. **Prescription only medicine.**	None proposed
Renal Failure	The relatedness of risk of renal failure to duloxetine administration has not been confirmed yet. Proposed) content in SPC Section: **Sections 4.2** (Posology and method of administration) *Renal impairment* No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). <Invented name> must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min; see section 4.3). **4.3** (Contraindications) states that duloxetine must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min). **Section 4.4** (Special warnings and precautions for use) *Renal impairment* Increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 ml/min). For patients with severe renal	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	impairment, see section 4.3. See section 4.2 for information on patients with mild or moderate renal dysfunction. **Section 5.2** (Pharmacokinetic properties): Protein binding is not affected by renal or hepatic impairment. *Renal impairment*: End stage renal disease (ESRD) patients receiving dialysis had 2-fold higher duloxetine Cmax and AUC values compared with healthy subjects. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.	
Missing Information		
Prospective data about potential risks of exposure to duloxetine during pregnancy	(Proposed) content in SPC Section: **4.6 Fertility, pregnancy and lactation** Warning about no adequate well-controlled trials in pregnant women and that duloxetine should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to foetus. Discontinuation symptoms may occur after maternal duloxetine use near term. Duloxetine is weakly excreted into human milk therefore the patients are advised not to breastfeed if they are taking duloxetine. **Prescription only medicine.**	None proposed
Use of duloxetine 120 mg in elderly patients	(Proposed) content in SPC Section: **Section 4. 2** (Posology and method of administration) *Elderly* No dosage adjustment is recommended for elderly patients solely on the basis of age. However, caution should be exercised when treating the elderly, especially with 120 mg duloxetine per day. **Section 4.4** (Special warnings and precautions for use) *Elderly* Data on the use of 120 mg duloxetine in elderly patients with major depressive disorder and generalised anxiety disorder are limited and caution should be exercised when treating the elderly with the maximum dosage. **Section 5.2** (Pharmacokinetic properties): *Information that p*harmacokinetic differences have been identified between younger and elderly females, although the magnitude of these changes is not sufficient to justify adjustments to the dose. Recommendation	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	about caution when treating the elderly.	

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Duloxetine 30 mg and 60 mg, SK/H/0156/001-002/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit risk assessment was considered positive. Therefore the RMS and CMSs recommended approval of Duloxetin Krka 90 mg hard gastro-resistant capsules.