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Public Assessment Report

Scientific discussion

Escitalopram Medreg
escitalopram

SK/H/0292/001/DC

Date: 11/2023

This module reflects the scientific discussion for the approval of Escitalopram Medreg. The procedure was finalised on 07 August 2023. 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 Escitalopram Medreg, film-coated tablets, 10 mg from Medreg s.r.o., Czechia.
The product is indicated for*:*

Treatment of major depressive episodes.
Treatment of panic disorder with or without agoraphobia.
Treatment of social anxiety disorder (social phobia).
Treatment of generalised anxiety disorder.
Treatment of obsessive-compulsive disorder.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The drug product is a film-coated tablet containing 10 mg of escitalopram, with following description: White to off white, oval, approx. 7.8 x 5.3 - 8.2 x 5.7 mm biconvex film-coated tablet with 'C4' embossed on one side and notch break-line on other side.
Active substance is escitalopram oxalate; other ingredients are cellulose microcrystalline, croscarmellose sodium, talc, silica colloidal anhydrous, magnesium stearate, hypromellose, titanium dioxide, macrogol and purified water. The selected excipients are well known and established for use in manufacturing process of solid dosage form.
Film-coated tablets are packed in clear PVdC coated PVC/Alu blisters.

II.2 Drug Substance

Chemical Names:

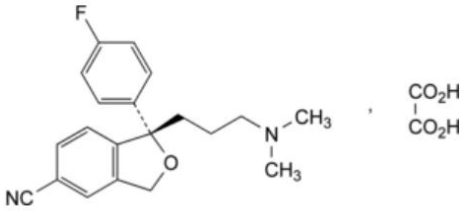
(1S)-1-[3-(Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3- dihydro-2-benzofuran-5-carbonitrile hydrogen oxalate (Ph.Eur)

S-(+)-5-Isobenzofurancarbonitrile, 1-[3-(dimethylamino)
propyl]-1-(4-fluorophenyl)-1,3-dihydro-, oxalate (USP)

S-(+)-1-[3-(Dimethylamino)propyl]-1-(p-fluorophenyl)-5- phthalancarbonitrile Oxalate (USP)

(+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3- dihydroosobenzofuran-5-carbonitrile oxalate (In-house)

Structural formula:



Molecular Formula:	$C_{22}H_{23}FN_2O_5$
Molecular Weight:	414.4
Description:	A white or almost white crystalline powder
Solubility:	Sparingly soluble in water, freely soluble in methanol and slightly soluble in methylene chloride
Specific Optical Rotation:	+10.0° to +13.0°
Solubility at different buffers:	pH (Solubility definition is as per EP)

Buffer pH	*pH of the product in buffer solution*	*Concentration*
2.00	2.10	soluble
4.01	3.64	soluble
6.86	3.86	non soluble
9.18	5.09	soluble

pH of 1.0% aqueous solution:	3.02 - clear solution is obtained
Isomerism:	escitalopram is S-enantiomer of citalopram
Bulk Density:	Untapped: NLT 0.20 – 0.40 g/ml tapped: 0.40 – 0.70 g/mL
Polymorphism:	escitalopram oxalate exhibits polymorphism, the polymorph is Form-I
Hygroscopicity:	non-hygroscopic

Manufacturing: Information on the manufacturing process and process controls has been supplied to, and approved by, the European Directorate for the Quality of Medicines (EDQM).

Specifications: The specifications of escitalopram are in line with the active pharmaceutical ingredient (API) monograph no. 2733 published under Ph. Eur.

Stability: The re-test period of the drug substance is presented in the CEP (Certificate of suitability issued by EDQM). Re-test period for API is 60 months if stored in double polyethylene bags, placed in a polyethylene drum.

II.3 Medicinal Product

Pharmaceutical development: The aim of the development of the finished product was to develop a formulation pharmaceutically equivalent to the reference medicinal product Cipralex 10 mg from H. Lundbeck A/S Denmark. A number of excipients were studied with the drug substance at accelerated temperatures and humidity condition to assess the compatibility of the excipients with the drug substance. The excipients provisionally selected were those, which were known to be present in the reference product. In addition several other excipients were also tried.

Manufacturing: The finished product is manufactured by direct compression and a description of the process has been provided in the dossier. In brief, it involves sifting, dry mixing of blend, lubricating, compressing and film coating. The process validation was conducted on three maximum commercial batches of proposed product. Process validation protocols for pilot batches manufactured were provided as well.

Product specification: The proposed specification for the finished product is in line with ICH Q6A. The finished product release and shelf life specifications include appropriate tests and limits for description (in house), identification (HPLC, UV), average weight of tablet (in house), uniformity of dosage unit (Ph.Eur), assay (in house), dissolution (in house), loss on drying (in house), related substances (in house), and microbial limits (in house). The specification limit for impurities (A, B, C, E) and limit for unknown impurity is set in line with the ICH Q3B guideline.

Stability: Stability data were provided for three pilot batches under long-term and accelerated conditions, which were packed in clear PVDC coated PVC/Aluminium blister as proposed for marketing. The proposed shelf-life of 3 years with no special storage condition was considered acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

From a quality point of view the dossier was adequately presented.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of escitalopram are well known. As escitalopram is a widely used, well-known active substance, the applicant has not provided additional studies and further studies were not required. The non-clinical overview referred to 73 publications up to year 2021.
Overview based on literature review was considered appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

The applicant presented and summarized the data for escitalopram from the PubChem Compound Summary and EDQM Safety Data Sheet. The log Kow value for escitalopram was determined to be 3.74, which is below the action limit of > 4.5. Although this evidence was not complete in terms of Phase I assessment, it was accepted as relevant justification of the absence of significant increase of the environmental exposure for this specific product.

Since Escitalopram Medreg is intended for generic substitution, this will not lead to an increased exposure to the environment. Thus, it could be deemed that Escitalopram Medreg is not likely to pose an environmental risk when used as recommended.

III.3 Discussion on the non-clinical aspects

Sufficient references to published non-clinical data were provided for this generic application, which was considered adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

To support the application, the applicant has submitted as report one bioequivalence study, an open-label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, two-way crossover, comparative oral bioavailability study of escitalopram tablets 20 mg in healthy, adult, human, male subjects under fasting conditions.

IV.2 Pharmacokinetics

Biowaiver
Biowaiver for the 10 mg strength has been requested.

The Applicant has demonstrated that the qualitative composition of the different strengths of escitalopram was the same, and the composition of 10 mg and 20 mg strengths was quantitatively proportional. Furthermore, the dissolution test has shown that the strengths were comparable.

Bioequivalence studies

The pharmacokinetic parameters C_{max}, AUC_{0-t}, AUC_{0-inf} were taken as primary variables.

Table of Geometric Means and 90% Confidence Interval for Escitalopram (N=26)

Parameters	*Geometric mean		% Ratio	90 % Confidence Interval for Log-transformed data	
	Test (A)	Reference (B)	A/B	Lower Limit	Upper Limit
AUC_{0-inf}	1003.87	993.35	101.05	96.21	106.15
AUC_{0-t}	891.71	873.60	102.07	95.78	108.77
C_{max}	20.83	20.75	100.38	96.53	104.38

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

C_{max} was not observed in first time-point in any of the cases.

No statistically significant sequence, treatment and period effect was observed for Log transformed C_{max}, AUC_{0-t} and $AUC_{0-inf.}$ Also, the subject within the sequence effect was found to be significant ($p<0.05$) for Logtransformed pharmacokinetic parameter (C_{max}, AUC_{0-t} and AUC_{0-inf}) for escitalopram. This statistical difference was not likely to have any clinical significance, as significant subject effect will always be present. It simply tells that subjects do differ from each other.

The sampling schedule covered the plasma concentration time curve long enough to provide a reliable estimate of the extent of exposure. The study demonstrated that Escitalopram Medreg was bioequivalent to reference product Cipralex under fasting conditions as the 90% confidence interval for the ratio of geometric means for the test and reference formulations for C_{max}, AUC_t and $AUC_{0-\infty}$ were within the 80.00% - 125.00% interval. Justification of significant subject effect was acceptable.

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 Escitalopram Medreg.

- Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

IV.4 Discussion on the clinical aspects

The application contained an adequate review of published clinical data and the bioequivalence has been shown.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This was an application for a marketing authorisation of a medicinal product for human use as it is defined in Article 10(1) (generic application) of the European Directive 2001/83/EC as amended. Decentralised procedure according to Article 28(3) of Directive 2001/83/EC as amended with Slovak Republic acting as RMS. The applicant Medreg s.r.o. has submitted this MAA under procedural number SK/H/0292/001/DC; CMSs were Czech Republic, Poland and Romania.

The reference medicinal product referred to as authorised not less than 10 years in European Economic Area was Cipralex 10 mg film-coated tablets, authorised in Sweden since 07 December 2001, by H. Lundbeck A/S (MA number 17085).

To support the application, the applicant has submitted as report one bioequivalence study, an open-label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, two-way crossover, comparative oral bioavailability study of escitalopram tablets 20 mg in healthy, adult, human, male subjects under fasting conditions. The results of this study conducted with 20 mg strength were extrapolated for 10 mg strength (biowaiver).

Quality aspects of the dossier were adequately described; specifications of API escitalopram were in line with monograph no. 2733 published under Ph. Eur and that of finished medicinal product were in line with ICH Q6A, where relevant.