LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Escitalopram Grindeks
(escitalopram oxalate)

SE/H/2239/01-03/DC

This module reflects the scientific discussion for the approval of Escitalopram Grindeks. The procedure was finalised on 2023-05-17. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Escitalopram Grindeks, 5 mg, 10 mg, 20 mg, Film-coated tablet.

The active substance is escitalopram oxalate, escitalopram. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Escitalopram Grindeks, 20 mg, 5 mg, 10 mg, Film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, BG, CZ, DE, EE, EL, ES, FR, HR, HU, IE, IT, LT, LU, LV, NL, NO, PL, PT, RO, SI, SK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Cipralex 5 mg Film-coated tablet authorised in SE since 2001, with H. Lundbeck A/S as marketing authorisation holder.

The reference product used in the bioequivalence study is Cipralex 20 mg Film-coated tablet from DK with H. Lundbeck A/S as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS CZ, EE, DE, HR, HU, LT, LU, LV, RO, SI, SK: Cipralex 5 mg, Film-coated tablet; and in CMS HR, HU, PL, RO, SI, SK: Cipralex 20 mg, Film-coated tablet, both authorised in SE since 2001, with H. Lundbeck A/S as marketing authorisation holder.
The justification to use this product is based on RMS's own files. The ERP information from SE was circulated during the validation period.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of escitalopram oxalate are well known. As escitalopram oxalate is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Escitalopram Grindeks is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Escitalopram Grindeks from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the Applicant has conducted one bioequivalence study comparing Escitalopram Grindeks (Escitalopram) with the reference product Cipralex.

Pharmacokinetic properties of the active substance
Absorption: As with racemic citalopram, the absolute bioavailability of escitalopram is expected to be about 80 %. Mean time to maximum concentration (mean T_{max}) is 4 hours after multiple dosing.

The pharmacokinetics of escitalopram is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.

Linearity: There is linear pharmacokinetics.

Elimination: The elimination half-life ($t_{½\,\beta}$) after multiple dosing is about 30 hours. The major metabolites have a significantly longer half-life.

Study 126-08
Methods
This was a single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Escitalopram, 20 mg, tablets with Cipralex, 20 mg, tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 168 hours post-dose. Plasma concentrations of escitalopram and metabolite S-desmethylcitalopram were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2008-08-29 and 2008-09-27.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for escitalopram, n=30.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1135.08 ± 366.10**	**1228.19 ± 448.13**	**24.21 ± 4.15**	**4.33 (2.00-8.00)**
Reference	**1147.97 ± 432.23**	**1234.18 ± 483.75[#]**	**24.76 ± 5.28**	**4.67 (2.00-10.00)**
***Ratio (90 % CI)**	**100.4 (96.93-103.93)**	**100.3 (96.89-103.84)**	**98.6 (94.56-102.77)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*
[#]The extrapolated AUC was > 20% for two subjects. Hence, the number of subjects used for computation was 28.

For AUC_{0-t} and C_{max} the 90 % confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %.

A biowaiver was sought for the additional strengths of 5 mg and 10 mg.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1). Evaluation of bioequivalence was based upon measured concentrations of the parent compound and the bioanalytical methods were adequately validated. Bioequivalence was shown.

The quantities of several excipients differ between the biobatch product and the finished product intended for marketing. Although the differences in the content of silica and magnesium stearate are larger than the limits given for a BCS3 waiver by ICH M9, the risk for inequivalence in this case is assessed to be very low. The Applicant has shown data from different formulations of escitalopram showing bioequivalence despite substantial differences in composition, and the absolute amounts of the differing excipients are low. In addition, the Applicant has submitted data from *in vitro* dissolution tests carried out at three different pH:s (0.1 N HCl, pH 4.5 and pH 6.8, using paddle 50 rpm), comparing the dissolution profiles of the reference product (Cipralex 20 mg tablets), initial/biobatch product (escitalopram 5 mg, 10 mg, 20 mg) and revised finished product (escitalopram 5, 10, 20 mg). Comparable dissolution profiles were concluded, as ≥85% drug release was constantly achieved within 15 minutes. Thus, the final formulation can be accepted without further in vivo data.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system
The Applicant 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 Escitalopram Grindeks.

Safety specification
The MAH has submitted the version 1.1 RMP dated 2022-08-17 and proposed the following summary safety concerns:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	*None*
Important potential risks	*None*
Missing information	*None*

The proposed RMP for Escitalopram Grindeks is in line with the most recent escitalopram RMP, the RMP for the medicinal product Escitalopram Mylan, approved in 2019, which is endorsed.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 1.1 signed 2022-08-17 is considered acceptable.

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.

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

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 PL was Latvian.
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

The quality of the generic product, Escitalopram Grindeks, is found adequate. There are no objections to approval of Escitalopram Grindeks, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Escitalopram Grindeks, 5 mg, 10 mg, 20 mg, Film-coated tablet was positively finalised on 2023-05-17.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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