CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Escitalopram Polpharma 5 mg, 10 mg, 15 mg and 20 mg orodispersible tablets Pharmaceutical Works Polpharma S.A., Poland

escitalopram (as oxalate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2829/001-004/DC
Registration number in the Netherlands: RVG 112821-112824

17 February 2014

Pharmacotherapeutic group:	selective serotonin reuptake inhibitors
ATC code:	N06AB10
Route of administration:	oral
Therapeutic indication:	major depressive episodes; panic disorder with or without agoraphobia; social anxiety disorder (social phobia); generalised anxiety disorder; obsessive-compulsive disorder
Prescription status:	prescription only
Date of authorisation in NL:	21 May 2013
Concerned Member States:	Decentralised procedure with PL
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Esscitaxin 5 mg, 10 mg, 15 mg and 20 mg orodispersible tablets from Pharmaceutical Works Polpharma S.A. The date of authorisation was on 21 May 2013 in the Netherlands.

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 SPC.

Escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake with high affinity for the primary binding site. It also binds to an allosteric site on the serotonin transporter, with a 1000 fold lower affinity.
Escitalopram has no or low affinity for a number of receptors including 5-HT1A, 5-HT2, DA D1 and D2 receptors, α1-, α2-, β-adrenoceptors, histamine H1, muscarine cholinergic, benzodiazepine, and opioid receptors.
The inhibition of 5-HT re-uptake is the only likely mechanism of action explaining the pharmacological and clinical effects of escitalopram.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Cipralex 5 mg, 10 mg, 15 mg and 20 mg film-coated tablets which have been registered in Sweden by H. Lundbeck A/S since 7 December 2001.
The Dutch reference product is Lexapro 5, 10, 15 and 20 mg film-coated tablets (NL License RVG 30494-30497) with MAH H. Lundbeck A/S, registered since 27 April 2004 through MRP SE/H/0279/001-004. In addition, reference is made to Cipralex/Lexapro authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Cipralex 20 mg film-coated tablets, registered in Greece. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is escitalopram oxalate, an established active substance however not described in the European Pharmacopoeia (Ph.Eur.*). A USP* monograph is available. The substance is a fine, white to slightly yellow powder, which is freely soluble in methanol and in dimethyl sulfoxide, sparingly soluble in water and in alcohol, very slightly soluble in ethyl acetate and in isopropyl alcohol, and insoluble in heptane. The drug is a non-hygroscopic, phthalane derivative and S-isomer of citalopram. The polymorphic form produced by the manufacture is Form-I of escitalopram oxalate.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process has been adequately described in sufficient detail. The starting material is acceptable and controlled by satisfactory specifications. All the residual solvents of escitalopram oxalate are controlled through release specifications of the substance, or in the specification of intermediates. No class 1 solvents or metal catalysts are used in the synthesis. Acceptable specifications have been adopted for the solvents and reagents. The active substance has been adequately characterized.

Quality control of drug substance
The specification limits are in general set according to the USP monograph for escitalopram oxalate, according to the USP in general, according to the European Pharmacopeia and Quality Guidelines.
Batch analysis results have been provided for four batches of one manufacturer and two batches from the other. The results show compliance with the specification.

Stability of drug substance
Stability data on the active substance have been provided for a satisfactory amount of batches stored at 25°C/60%RH and 40°C/75%RH. Based on the available data, the proposed retest period of 5 years, and the storage conditions "No specific storage conditions. Store in the original package", are justified.

** Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and USA, respectively.*

Medicinal Product

Composition
Escitalopram Polpharma 5 mg, 10 mg, 15 mg and 20 mg are white to off-white round, flat tablets with beveled edges, a diameter of 7 mm, 9 mm, 11 mm and 12 mm and engraved with "5", "10", "15" or "20" on one side, respectively.

The orodispersible tablets are packed in peelable paper/PET/aluminium//PVC/aluminium/oPA blisters.

The excipients are: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, polacrilin potassium, acesulfame potassium, neohesperidine-dihydrochalcone, magnesium stearate, peppermint flavor [containing maltodextrin (maize), modified starch E1450 (waxy maize) and peppermint oil (mentha arvensis)], concentrated hydrochloric acid (for pH adjustment).

The four tablet strengths are fully dose proportional.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. During development, composition and process parameters were optimised until the final formulation was obtained. The composition of the batch used in the bioequivalence study is identical to the proposed final composition.

Cipralex® orodispersible tablets were not commercially available in Europe during the development of the generic product. The bioequivalence study was therefore performed versus the innovator product Cipralex 20 mg film-coated tablets. The in vitro dissolution profiles of the test biobatch versus the EU originator biobatch Cipralex® from the Greek market, were examined in dissolution media with three different pHs. Similarity of dissolution profiles was adequately demonstrated, also for the lower strengths.

The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process involves the following steps: preparation of escitalopram oxalate/polacrilin potassium suspension, filtration-centrifuge, drying, sizing, mixing, lubrication, tableting, quality control, blistering and packaging.

The manufacturing process was adequately validated for all three production sites.

Control of excipients

The excipient used and their quantities, are common for immediate release tablets. Analytical procedures for all the excipients except the flavor peppermint are performed as per requirement specified in the Ph.Eur./USP. The qualitative composition of peppermint flavor is provided, and a reference to FCC (Food Chemical Codex) as quality standard for the individual components has been given. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, diameter, thickness, identification, water content, average weight, disintegration time, dissolution, uniformity of dosage units, assay, related substances and microbiological quality. The release and end-of-shelf-life specifications are identical for the majority of the test procedures, the only exception concerns the limits for water content and total impurities, for which wider limits are applied at the end of shelf life. The analytical methods have been adequately described and validated.

Batch analytical data from three batches per strength were provided. All batches comply with the proposed specification.

Stability of drug product

The following stability data on the product has been provided per strength: one batch for up to 18 months at 25°C±2°C/60%±5%RH (long term) and 6 months at 40°C±2°C/75%±5%RH (accelerated conditions), two batches up to 18 months long term and 6 months accelerated conditions. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Aluminium/peelable Aluminium blisters. At both accelerated and long term conditions, an increase in impurities is seen. However, the results remain well within the proposed limits. Based on the available data, the proposed shelf life of 30 months is justified.

Photo-stability testing was performed according to ICH on one 5 mg pilot batch, and shows out of specification results when the tablet is directly exposed, but stable in the proposed packaging material. Hence the following storage condition is acceptable: “This medicinal product does not require any special temperature storage conditions; store in the original package to protect from moisture and light”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
BSE/TSE statements from representative manufacturers regarding the safety and compliance of lactose monohydrate, and a statement for the vegetable origin of magnesium stearate, have been provided. Only lactose monohydrate is of animal origin. TSE risk for the lactose used can be considered negligible.

II.2 Non-clinical aspects

This product is a generic formulation of Cipralex, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of escitalopram released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Escitalopram is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Escitalopram Polpharma 20 mg orodispersible tablets (Pharmaceutical Works Polpharma S.A., Poland) is compared with the pharmacokinetic profile of the reference product Cipralex 20 mg film-coated tablets (H. Lundbeck A/S, from the Greek market).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 20 healthy male and female subjects, aged 24-64 years. Each subject received a single dose (20 mg) of one of the 2 escitalopram formulations. Prior to drug administration the study subjects fasted for at least 10 hours. Prior to test drug (orodispersible tablet) administration each subject rinsed their mouth for approximately 5 seconds with approximately 20 mL of room temperature water, and then swallowed this water. Subsequently, staff placed the tablet from the blister unit directly onto the subject's tongue and asked the subject to close their mouth in a natural way, without chewing, biting or breaking the study drug. Once the tablet was completely dissolved or up to a maximum of 60 seconds after being placed on the tongue, the subject swallowed the saliva. The reference drug (film-coated tablet) was administered with 240 ml water. There were 2 dosing periods, separated by a washout period of 10 days.

Blood samples were collected pre-dose and at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, 16, 24, 36, 48 and 72 hours after administration of the products.

The study design is approvable, with correct test product administration without water. Sampling scheme is adequate to estimate the pharmacokinetic parameters reliably. The wash-out period of 10 days is acceptable, in the light of the $t_{1/2}$ of 30 h.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Seventeen subjects completed the study and were included in the analysis. One subject was dismissed due to experiencing diarrhoea within 8 hours of dosing, one subject was dismissed due to experiencing emesis within 4 hours after dosing and one subject withdrew due to personal reasons. Out of the 17 volunteers, 9 were males and 8 females.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of escitalopram under fasted conditions.

Treatment N=17	**AUC_{0-72h}** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h
Test	721.17 ± 203.61	24.73 ± 5.55	4.00 (3.00-8.00)
Reference	731.51 ± 203.16	25.20 ± 6.05	3.50 (2.00-7.00)
***Ratio (90% CI)**	0.98 (0.94 – 1.02)	0.98 (0.94 – 1.03)	--
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 h **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration			

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. Based on the pharmacokinetic parameters of escitalopram under fasted conditions, it can be concluded that Escitalopram Polpharma 20 mg orodispersible tablets and Cipralex 20 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Escitalopram may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of escitalopram. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Safety
There were 27 adverse events reported in the study (9 for test, 18 for reference), none were serious. The most common adverse events were nausea and catheter site swelling.

Biowaiver
A biowaiver was granted for the lower strengths is requested based on the following:
- Pharmacokinetics are linear over the dose range of 5 to 20 mg.
- All strengths are manufactured by the same manufacturing process
- The qualitative composition of the different strengths is the same
- The composition of strengths is quantitatively proportional
- Appropriate *in vitro* dissolution data are available covering the pH range of 1.2 – 6.8

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan

Escitalopram was first approved in 2001, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of escitalopram can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Cipralex. The MAH updated SPC in line with the current Core Safety Profile (CSP), as established in Worksharing procedure SE/H/PSUR/0016/002, which was finalised in December 2012.

Readability test

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 test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Overall, each and every question met the criterion of 81% correct answers. Therefore the test was deemed successful and no adaptations are necessary to the package leaflet. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Escitalopram Polpharma 5 mg, 10 mg, 15 mg and 20 mg orodispersible tablets have a proven chemical-pharmaceutical quality and are generic forms of Cipralex 5 mg, 10 mg, 15 mg and 20 mg film-coated tablets. Cipralex is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Escitalopram Polpharma 5 mg, 10 mg, 15 mg and 20 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 1 May 2013. Escitalopram Polpharma 5 mg, 10 mg, 15 mg and 20 mg orodispersible tablets is authorised in the Netherlands on 21 May 2013.

The date for the first renewal will be: 1 May 2018.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to continue the stability studies up to 36 months. In addition, the first three commercial production-scale batches per strength of the drug product will be tested for their stability under both long-term (25°C±2°C/60%±5%RH for 36 months) and accelerated conditions (40°C±2°C/75%±5%RH for 6 months). Annually, one commercial production scale batch of each strength of the drug product will be tested for stability under long-term conditions (25°C±2°C/60%±5% RH), up to 36 months.
- The MAH committed to re-evaluate the limit for water content as soon as the long term stability data of 3 batches stored up to the proposed storage period is available.
- The MAH committed to re-evaluate the limits for impurities when more stability data has become available.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached