COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Citalopram 40 mg/ml Focus, oral drops, solution

(citalopram hydrochloride)

NL License RVG 124834

Date: 16 December 2020

This module reflects the scientific discussion for the approval of Citalopram 40 mg/ml Focus, oral drops, solution. The procedure was finalised at 14 July 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Citalopram 40 mg/ml Focus, oral drops, solution, from Focus Care Pharmaceuticals B.V.

The product is indicated for:

- treatment of major depression episodes
- treatment of panic disorders, with or without agoraphobia

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

This national procedure concerns a generic application claiming essential similarity with the innovator product Cipramil 40 mg/ml oral drops, solution which has been registered in the Netherlands by Lundbeck B.V. since 9 February 1999.

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

II. QUALITY ASPECTS

II.1 Introduction

Citalopram Focus is a clear and colourless liquid (drop solution). 1 ml drop solution contains citalopram hydrochloride, equivalent to 40 mg citalopram. (1 ml equals 20 drops equals 40 mg citalopram; 1 drop equals 2 mg citalopram).

The drop solution is packed in brown type III glass bottle with a white HDPE child-resistant screw cap and a colourless LDPE drop cap, containing 15 ml of liquid dropper.

The excipients are: methyl paraben (E128), propyl paraben (E216), hydroxyethyl cellulose, alcohol 96% and purified water. The solution contains 9.0% v / v alcohol.

II.2 Drug Substance

The active substance is citalopram hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to almost white crystalline powder and is very soluble in water and freely soluble in ethanol. The molecule contains one chiral centre and the racemate is provided.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances

for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. The absence of a test for microbial purity has been justified. Batch analytical data demonstrating compliance with this specification have been provided for five production scaled batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The development studies were mainly performed to show equivalence to the innovator product Cipramil 40 mg/ml oral drops. Comparison of dose and dose uniformity, assay, impurities, pH, appearance and microbial count has been done. The pharmaceutical development of the product has been adequately performed.
A biowaiver has been requested based on the qualitative composition, the product being an aqueous solution at time of administration, containing the same concentration of active substance and no excipients which influence bioavailability.

Manufacturing process
The process is divided into preparing a solution of hydroxyethyl cellulose and purified water and a solution of the active substance and preservatives in ethanol. Both solutions are mixed, the pH adjusted with NaOH if necessary and the bulk solution is filled into bottles. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production scaled batches. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, assay, related substances, pH, average volume, dose and uniformity of dose, and microbial quality. The shelf-life specification does not have tests for average volume and dose/uniformity of dose. This is acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from six production scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for thee production scaled batches stored at 25°C/65% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies were performed and show compliance with the specification when packed in the immediate packaging. No out of specification results of significant changes are observed hence the shelf-life of 24 months can be approved. No specific storage restrictions are necessary.
Stability data has been provided demonstrating that the product remains stable for 16 weeks following first opening of the container when stored at room temperature (25 °C).

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Citalopram Focus has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Citalopram Focus is 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Cipramil which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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 MEB agrees that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Citalopram hydrochloride 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 MEB agrees that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver

The generic drug product has the same qualitative and quantitative composition in active substances, and the same pharmaceutical form as the reference medicinal product Cipramil 40 mg/ml oral drops. In addition, the drug product Citalopram contains the same excipients as the reference drug product Cipramil. In addition, all of the excipients are commonly used in pharmaceutical presentations, and are pharmacologically inert and therefore pose no risk in terms of safety. As the oral bioavailability of citalopram from tablets is about 80% after ingestion, and the relative bioavailability of citalopram from the oral drops solution is approximately 25% greater, it is concluded that the oral bioavailability of citalopram from the oral drops solution is almost complete. Therefore, the absence of bioequivalence studies is agreed and a biowaiver has been granted.

The absence of bioequivalence studies is agreed since the product is an aqueous oral solution and contains the same concentration of active substance and excipients as the reference product and also, the excipients used in the formulation have no effects on the gastrointestinal absorption.

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 Citalopram Focus.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	– Electrocardiogram QT prolonged
Important potential risks	– Suicide related events – Seizures – Serotonin syndrome – Diabetes Mellitus – Ventricular arrhythmia including Torsades de Pointes
Missing information	– Off label use – Use in pregnancy and lactation

The MEB agrees that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Cipramil. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Cipramil 40 mg/ml oral drops, solution. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Citalopram 40 mg/ml Focus, oral drops, solution has a proven chemical-pharmaceutical quality and is a generic form of Cipramil 40 mg/ml oral drops. Cipramil is a well-known medicinal product with an established favourable efficacy and safety profile.

The absence of bioequivalence studies is agreed since the product is an aqueous oral solution and contains the same concentration of active substance and excipients as the reference product and also, the excipients used in the formulation have no effects on the gastrointestinal absorption. A biowaiver has been granted.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Citalopram Focus with the reference product, and has therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 14 July 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse