COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Citalopram Amarox 10 mg, 20 mg, 30 mg and 40 mg film-coated tablets (citalopram hydrobromide)

NL/H/5181/001-004/DC

Date: 21 December 2021

This module reflects the scientific discussion for the approval of Citalopram Amarox 10 mg, 20 mg, 30 mg and 40 mg film-coated tablets. The procedure was finalised at 25 August 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AE	Adverse Event
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 Member States have granted a marketing authorisation for Citalopram Amarox 10 mg, 20 mg, 30 mg and 40 mg film-coated tablets, from Amarox Pharma B.V.

The product is indicated for

- Treatment of major depressive episodes
- Treatment of panic disorder with or without agoraphobia

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Cipramil 10 mg, 20 mg, 30 mg and 40 mg film-coated tablets which have been registered in the EEA by Lundbeck Limited since 1995. For the 20 mg and 40 mg strengths of the product, reference is made to Cipramil 20 mg and 40 mg authorised in the Netherlands (RVG 19593 and 19594). The 10 mg (RVG 19592) and 30 mg strengths are currently not authorised in the Netherlands.

The concerned member states (CMS) involved in this procedure were Germany and (except for the 40 mg strength) Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Citalopram Amarox is a film-coated tablet.

- Citalopram Amarox 10 mg film-coated tablets are white to off-white coloured, round biconvex, debossed with “Z and 6” on one side and “H” on the other side. Each tablet contains as active substance 10 mg citalopram (as citalopram hydrobromide).
- Citalopram Amarox 20 mg film-coated tablets are white to off-white coloured, oval biconvex, debossed with “Z and 7” on either side of the score line and “H” on the other side. The tablet can be divided into equal doses. Each tablet contains as active substance 20 mg citalopram (as citalopram hydrobromide).
- Citalopram Amarox 30 mg film-coated tablets are white to off-white coloured, oval biconvex, debossed with “Z and 8” on either side of the score line and “H” on the other side. The tablet can be divided into equal doses. Each tablet contains as active substance 30 mg citalopram (as citalopram hydrobromide).

- Citalopram Amarox 40 mg film-coated tablets are white to off-white coloured, oval biconvex, debossed with “Z and 9” on either side of the score line and “H” on the other side. The tablet can be divided into equal doses. Each tablet contains as active substance 40 mg citalopram (as citalopram hydrobromide).

The film-coated tablets are packed in white opaque PVC/PVdC Aluminium foil blister packs.

The excipients are:
Tablet core - lactose monohydrate, maize starch, copovidone (E1208), microcrystalline cellulose (Grade 102) (E460), croscarmellose sodium and magnesium stearate
Coating - titanium dioxide (E171), hypromellose 3 & 6 mPas (E464), macrogol (E1521) and polysorbate 80 (E433)

The four tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is citalopram hydrobromide, an established active substance described in the European Pharmacopoeia (Ph. Eur.). Citalopram hydrobromide is a white powder, sparingly soluble in water. It has one chiral centre and is used as racemic mixture. It does not show polymorphism. The substance manufactured is crystalline citalopram hydrobromide.

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. and the CEP, with additional requirements for particle size distribution and microbial quality. The proposed limits for particle size distribution are in line with those of the batches of the drug substance used in the biobatch. Sufficient information is provided about the reference standard in use for citalopram hydrobromide and the policy to establish them. The primary reference standard will be the European Pharmacopoeial Commission of Reference Substances (EPCRS) for future qualification. Information about the reference standards for the impurities is provided.

Batch analytical data from both the supplier and the drug product manufacturer, demonstrating compliance with the drug substance specification, have been provided for two full scale batches from the proposed supplier. As no other results were available and the substance is covered by a CEP, this is acceptable.

Stability of drug substance

The re-test period of the active substance is five 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. Compatibility studies of the drug substance with the chosen excipients have been performed and showed no incompatibility issues. The pharmaceutical development is based on reference product Cipramil 10 mg, 20 mg, 30 mg and 40 mg film-coated tablets, which have been adequately characterised.

Several test batches have been produced during formulation and manufacturing process development, which are adequately described. Also the formulation and manufacturing process development have been generally adequately performed and described.

The development of the quality control dissolution test method is adequately discussed. The discriminatory power of the method is adequately demonstrated for the 40 mg strength product and an adequate justification is provided for extrapolating these conclusions to the lower strengths. Comparative dissolution profiles at three pH values (between 1.2 and 6.8) between the reference product and the final formulation of the test product have been performed. The active substance is very soluble in water at all pHs, therefore in all conditions dissolution was very fast (>85% in 15 minutes) for both reference and test products, of all strengths. Similarity is confirmed and the biobatch is considered acceptable from a pharmaceutical point of view.

The bioequivalence (BE) study has been performed with the highest strength (40 mg) and the MAH has been provided a justification for a biowaiver for the 10 mg, 20 mg and 30 mg tablets.

Manufacturing process

Only one blend batch size is presented. For the process validation batches, each common blend batch has been divided in different batches for all different strengths. For commercial use, a common blend batch can be used for only one strength or a combination, depending on commercial needs. The maximal and minimal batch size per strength are stated.

Manufacturing process description and flow chart are provided. The manufacturing process consists of dry mixing, followed by wet granulation. After drying and sizing, the granulate is mixed with the extra-granular excipients and then lubricated, to obtain the final common blend. The following steps are compression, coating and packaging. The level of details provided in the manufacturing process description is sufficient. Holding time and conditions for the bulk product are clearly stated, the other intermediates are not held for prolonged

times. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three blend batches, each divided in four tablet batches, one of each strength, in accordance with the relevant European guidelines. The products are manufactured using conventional manufacturing techniques. As larger tablets batch sizes are to be produced based on the proposed maximal batch size of each strength, the MAH commits to perform process validation at maximal commercial batch size, when produced. The protocol for process validation at maximal batch size is acceptable.

Control of excipients

All excipients used in the drug product manufacturing are reported in a Ph. Eur. monograph, except for the coating Opadry White. For specification, analytical methods, their validation and justification of specification, reference is made to the Ph. Eur. monographs. For some excipients additional parameters and functionality related characteristics are included in the specifications. These specifications are acceptable. Also the documentation provided about the non-compendial excipient Opadry White is adequate.

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 appearance, identity, average mass, uniformity of dosage units, dissolution, assay, related substances, water content, identification of titanium dioxide and microbial quality control. Release and shelf-life specifications are identical except for the limits for water content and total impurities. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

The MAH provided the results of the test for subdivision of tablets performed as per Ph. Eur. 0478 on three batches of each strength (the process validation batches). All results comply to the limits. Further, in the process validation protocol of the 20 mg, 30 mg and 40 mg strengths a study on tablet splitting (weight loss and dissolution behaviour) was performed on both tablets produced with high and low hardness, to show that the tablets in the proposed hardness range can be adequately divided. Based on the presented results, the tablets can be adequately divided in two equal doses. The claim can be held on the SmPC and a routine control for subdivision of tablets at drug product release is not considered necessary.

Satisfactory validation data for the analytical methods have been provided. Validation reports are provided for the methods for assay, related substances, dissolution and identity of titanium dioxide. These methods are adequately validated in line with ICH Q2 requirements. Stability indicating nature of the high-pressure liquid chromatography methods for assay and related substances is demonstrated by means of forced degradation studies. Proof of suitability of the methods for water content and microbial quality in presence of the finished product has been provided.
Batch analytical data from the proposed production site on three validation batches of each strength have been provided, demonstrating compliance with the release specification. A risk assessment on elemental impurities is provided, which is performed in line with ICH Q3D

Option 2b, concluding that no control for elemental impurities is needed at release is agreed. A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been provided, the conclusion that no risk is identified is endorsed.

Stability of drug product

Stability data on the product have been provided for three validation batches of each strength, in accordance with applicable European guidelines demonstrating the stability of the product stored at 25°C/60%RH (up to 12 months) and at 40°C/75%RH (up to 6 months). The batches were stored in the proposed blister packs and bulk packaging. Additional results of dissolution after 23 months storage at long term conditions have been provided for one batch of each strength, after adjustment of the dissolution test specification limit. No significant change or trend is observed in the provided results at all conditions. On basis of the data submitted, a shelf life was granted of two years. No specific storage conditions need to be included in the SmPC or on the label. Photostability studies according to Guideline ICH Q1B have been performed and show that the product is not sensitive to light.

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

For lactose, a certificate of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated. No other materials derived from animal and/or human origin are used in the manufacture of the finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Citalopram Amarox 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 Amarox 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Citalopram hydrobromide 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 one bioequivalence study, which is discussed below. A biowaiver is applied for the additional lower strengths of 10, 20 and 30 mg.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product, Citalopram Amarox 40 mg film-coated tablets (Amarox Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Cipramil 40 mg film-coated tablets (Lundbeck B.V., the Netherlands).

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

Biowaiver

The MAH requested for a biowaiver for the 10 mg, 20 mg and 30 mg tablets. The tablets of different strengths are manufactured by the same manufacturer. The composition of the different strengths is qualitative the same and quantitatively proportional. To support the biowaiver of strength, the applicant provided data on comparative dissolution. The comparative dissolution experiments showed that the dissolution for the 10 mg, 20 mg, 30 mg and 40 mg is very rapid (> 85% within 15 minutes) for all strengths at three different pH levels. Furthermore, the pharmacokinetics of citalopram is dose-linear in the range of 10 – 60 mg. Therefore, one bioequivalence study at the highest strength of 40 mg is sufficient.
Based on the above, a biowaiver of strength can be granted for the Citalopram Amarox 10 mg, 20 mg and 30 mg tablets.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy Asian male subjects, aged 20-41 years. Each subject received a single dose (40 mg) of one of the two citalopram hydrobromide formulations. The tablet was orally administered with water after a fasting period of at least ten hours before and 4 hours after administration of the products. There were two dosing periods, separated by a washout period of 18 days.

Blood samples were collected before dosing and 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.50, 7, 8, 10, 12, 16, 24, 48, 72, 96, 144 and 192 hours after administration of the products.

The design of the study is acceptable.

Citalopram hydrobromide may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of citalopram hydrobromide. 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.

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

Five subjects dropped out from the study due to adverse events (AEs) or not checking in for period 2. The other 23 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=23	**AUC_{0-t} (h/ng/ml)**	**$AUC_{0-\infty}$ (h/ng/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	3044 ± 709.1	3353 ± 886.4	60.75 ± 12.61	2.67 (1.33 – 5.67)
Reference	2959 ± 698.9	3297 ± 918.9	57.45 ± 11.15	3.00 (1.67 – 6.00)
***Ratio (90% CI)**	1.03 (1.01 – 1.05)	1.02 (1.00 – 1.04)	1.06 (1.01 – 1.11)	-

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

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Citalopram Amarox is considered bioequivalent with Cipramil.

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).

The results of the bioequivalence study are extrapolated to the lower strengths of 10 mg, 20 mg and 30 mg. The dissolution requirements in the bioequivalence study guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, 2010) for granting a biowaiver are fulfilled as well.

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 Amarox.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• None
Important potential risks	• None
Missing information	• Long-term safety in children and adolescents concerning growth, maturation and cognitive and behavioural development

The member states agreed 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. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. The biowaiver of strength for the 10 mg, 20 mg and 30 mg citalopram hydrobromide tablets can be granted. 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. The MAH bridges the content (key safety messages) with the

PI of the reference product Citalopram Generis Phar (PT/H/1711/001-003/DC). The design and layout are bridged with another product of the MAH: Levetiracetam Hetero (PT/H/0515/001-004/DC). As the proposed PL is identical to the reference product, bridging for the content to the PL of the reference product is agreed.
Regarding the design and layout, critical issues like font, text size and headings are the same in both PLs. Therefore, bridging for the design and layout to the PL of Levetiracetam Hetero also is agreed.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Citalopram Amarox 10 mg, 20 mg, 30 mg and 40 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Cipramil 10 mg, 20 mg, 30 mg and 40 mg film-coated tablets. Cipramil 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 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 Citalopram Amarox with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 August 2021.

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