CBG MEB

Public Assessment Report

Scientific discussion

Escitalopram Bristol 5 mg, 10 mg, 15 mg and 20 mg film-coated tablets

(escitalopram oxalate)

NL/H/3079/001-004/DC

Date: 4 March 2015

This module reflects the scientific discussion for the approval of Escitalopram Bristol 5 mg, 10 mg, 15 mg and 20 mg film-coated tablets. The procedure was finalised on 5 November 2014. 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 Bristol 5 mg, 10 mg, 15 mg and 20 mg film-coated tablets from Bristol Laboratories Ltd.

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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Lexapro 5, 10, 15 and 20 mg film-coated tablets (NL License RVG 30494-30497) with MAH H. Lundbeck A/S, which has been registered in the Netherlands since 27 April 2004 through MRP SE/H/0279/001-004. In addition, reference is made to Lexapro authorisations in the individual member states (reference product). The innovator product is also registered in Europe under the trade name Cipralex. Escitalopram is a 'selective serotonin reuptake inhibitor' (SSRI), it increases intrasynaptic levels of the neurotransmitter serotonin by blocking the reuptake of the neurotransmitter into the presynaptic neuron.

The concerned member states (CMS) involved in this procedure were Germany, Ireland, Malta, Spain and the United Kingdom (only 5/10/20 mg).

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

II. QUALITY ASPECTS

II.1 Introduction

Escitalopram Bristol 5 mg is a white to off white, round, bevelled biconvex film-coated tablet debossed with 'J' on one side and '1' on the other side.
Escitalopram Bristol 10 mg is a white to off white, oval, scored, biconvex film-coated tablet debossed with 'J' on one side and '2' on the other side.
Escitalopram Bristol 15 mg is a white to off white, oval, scored, biconvex film-coated tablet debossed with 'J' on one side and '3' on the other side.
Escitalopram Bristol 20 mg is a white to off white, oval, scored, biconvex film-coated tablet debossed with 'J' on one side and '4' on the other side.

The 10 mg, 15 mg and 20 mg tablet can be divided into equal doses.

The film-coated tablets are packed in PVC/PE/PVdC clear triplex blisters, PVC/PE/PVdC white opaque triplex blisters and High Density Polyethylene (HDPE) tablet containers.

The excipients are:
Tablet core - microcrystalline cellulose, silica colloidal anhydrous, croscarmellose sodium, talc, magnesium stearate
Tablet coating - Opadry White-YS-1-7003 (consists of titanium dioxide (E171), hypromellose 2910, macrogol 400, polysorbate 80)

The tablet strengths are dose proportional.

II.2 Drug Substance

The drug substance is escitalopram oxalate, an established drug substance. Escitalopram is the S enantiomer of citalopram, which is also established. The substance is not described in the Ph.Eur. The USP contains a monograph for this substance. Escitalopram is soluble across the physiological pH range. The drug substance exhibits polymorphism. Form I is used.

The Active Substance Master File (ASMF) procedure is used for 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 of escitalopram oxalate involves seven stages. The proposed starting materials used in the process are acceptable. The manufacturing process is sufficiently described.
The drug substance is sufficiently characterized with regard to chemical structure and polymorphic form. The intended polymorphic form (Form I) is consistently manufactured.

Quality control of drug substance
The drug substance specification of the MAH is identical to the drug substance specification of the ASMF holder with some additional tests (particle size, polymorphic form and microbiological purity). The proposed drug substance specification limits are acceptable.
Batch analysis data have been submitted of several drug substance batches, complying to the specification limits.

Stability of drug substance
Stability data on the active substance have been provided for three production-scale batches stored at 25°C/60% RH (24 months), 30°C/65%RH (12 months) and 40°C/75% RH (6 months). No significant changes were observed in the currently available stability data. Based on the provided stability data, the proposed re-test period of 36 months is justified.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The qualitative composition of the generic product is the same as of the innovator/reference product. The dissolution is similar, for all the tablet strengths.
Manufacturing process development is adequately explained. A bioequivalence study was carried out with the 20 mg strength. The batch used in the bioequivalence study has the same composition and is manufactured in the same way as the future commercial batches. The dissolution profiles obtained of the test and reference product were rapid and similar across the physiological range (pH=1, pH=4.5, pH=6.8). Bioequivalence was shown.
A biowaiver was requested for the 5 mg, 10 mg and 15 mg strengths. The biowaiver is acceptable from a chemical-pharmaceutical point of view, considering the quantitative proportional compositions and the similar dissolution profiles of all the tablet strengths of the generic product across the physiological pH range. Functionality of the score lines of the tablets has been adequately demonstrated.

Manufacturing process
The manufacturing process includes dry blending, compression, and film-coating. This is considered a standard process. The description of the manufacturing process is sufficiently detailed. The process has been sufficiently validated. Process evaluation data were presented for (semi-)production batches of each strength (three tablet batches per strength), manufactured from three production common blend batches, at the proposed manufacturing site. All batches complied with the predefined acceptance criteria, including content uniformity. Acceptable process validation protocols have been provided for the next production batches after product approval.

Control of excipients
All individual excipients comply with the Ph.Eur. where relevant. The specifications of the excipients are acceptable. The quantitative and qualitative composition of the Opadry mixture is laid down.

Quality control of drug product
The product specification includes tests for appearance, tablet dimensions, identification, titanium dioxide identification, average weight, water content, dissolution, uniformity of dosage units, degradation products, assay, breakability test, and microbial limits. The proposed drug product specification is acceptable. Analytical methods are adequately described, and have been sufficiently validated.
Batch analysis data showing compliance with the proposed release specification have been provided for (semi-)production batches of each strength (three tablet batches per strength), manufactured from three production common blends batches.

Stability of drug product
Stability data on the product was provided for three batches of each strength at semi-industrial size stored at 25°C/60% RH (18 months), 30°C/65% RH (12 months)and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Tablets were stored in the proposed packages.
No significant changes were observed, except regarding degradation products at 40°C/75% RH. Photostability was studied according to the applicable Note for Guidance. The tablets were demonstrated to be photostable. Based on the provided stability data, the proposed shelf life of 36 months when stored below 30°C is approvable.
Based on the in-use stability data, the claim of 4 months in-use for the HDPE container is justified.

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 member states consider that Escitalopram Bristol 5 mg, 10 mg, 15 mg and 20 mg film-coated tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:
- The MAH committed to generate dissolution profiles at pH range pH = 1 – 6.8 (i.e. pH 1.2, pH 4.5 and pH 6.8) of the first three production batches of the 20 mg tablet strength, complying to the dissolution profile of the test batch.
- The MAH committed to evaluate if the specifications for water content and related compounds can be tightened based on the further data available from the proposed commercial batches.

The MAH should submit an appropriate variation application within 6 months after completion of this procedure to confirm whether the above mentioned commitments have been fulfilled.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Escitalopram Bristol 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 Lexapro, 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

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, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Escitalopram Bristol 20 mg (Bristol Laboratories Ltd., UK) is compared with the pharmacokinetic profile of the reference product Cipralex® 20 mg film-coated tablets (H. Lundbeck A/S Denmark).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
A biowaiver for the additional strengths 5, 10 and 15 mg can be granted, as all products were manufactured by the same process, the composition of the different strengths is qualitatively the same and quantitatively proportional. All strengths have a similar *in-vitro* dissolution profile (>85% dissolved within 15 min at 0.1N HCl, pH 4.5 and pH 6.8) as the 20 mg strength. Therefore, the conclusion of the bioequivalence study with the 20 mg strength can be extrapolated to the lower strengths of 5 mg, 10 mg and 15 mg.

Bioequivalence study
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects (28.0 ± 7.19 years of age). Each subject received a single dose (20 mg) of one of the 2 escitalopram formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. Water was allowed *ad libitum* until 1 hour pre-dose and 1 hour after drug administration. The washout period is 14 days between two treatments.

Blood samples were collected pre-dose and at 1.0, 2.0, 2.5, 3.0, 3.333, 3.667, 4.0, 4.333, 4.667, 5.0, 5.5, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours after administration of the products.

The study design is acceptable. Taking into account the expected time to peak concentration (3-4 hours) and the elimination half-life of escitalopram (about 30 hours), the sampling schedule and the sampling time period of 72 hours are adequate. The AUC truncated at 72 hours (AUC(0-72h)) is acceptable. The wash-out period of 14 days is considered to be adequate.

Escitalopram is almost completely absorbed and independent of food intake. 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
One was withdrawn from the study on the grounds of emesis in Period-I. A total of twenty-three subjects completed the clinical phase, were analysed and considered in the statistical analysis.

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

Treatment N=23	**AUC_{0-72}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	691.64 ± 185.96	--	20.55 ± 3.72	5.5 (2.5-8.0)	--
Reference	726.34 ± 226.72	--	21.81 ± 5.85	5.0 (3.0-8.0)	--
***Ratio (90% CI)**	0.96 (0.92-1.00)	--	0.95 (0.89-1.03)	-	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Escitalopram Bristol 20 mg is considered bioequivalent with Cipralex® 20 mg film-coated tablets.

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).

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 Bristol.

- 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
Missing information	Off-label use Use in pregnancy and lactation

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 Lexapro. 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. 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 daughter (Escitalopram Bristol) and parent PL (Venlafaxine Bristol, national registration in UK) belong to the same therapeutic class and have similar key safety messages. Although not all key messages are identical, the readability data for the parent PL demonstrate that patients would be able to locate and understand a similar message for the daughter PL. The design and layout of the PL of Escitalopram Bristol are identical to that approved for the PL of Venlafaxine Bristol and the language used in both PLs is comparable. Moreover, the content of the PL is in line with the reference product Lexapro. In conclusion, the bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Escitalopram Bristol 5 mg, 10 mg, 15 mg and 20 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Lexapro 5, 10, 15 and 20 mg film-coated tablets. Lexapro 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 Escitalopram Bristol with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 November 2014.

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