Public Assessment Report

Scientific discussion

Escitalopram +pharma 5 mg Filmtabletten,
Escitalopram +pharma 10 mg Filmtabletten,
Escitalopram +pharma 20 mg Filmtabletten

Escitalopram oxalate

AT/H/0400/001-003/MR

Date: 28.06.2016

This module reflects the scientific discussion for the approval of Escitalopram +pharma 5 mg Filmtabletten, Escitalopram +pharma 10 mg Filmtabletten and Escitalopram +pharma 20 mg Filmtabletten. The procedure was finalised at 07.08.2013. 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 +pharma 5 mg Filmtabletten, Escitalopram +pharma 10 mg Filmtabletten and Escitalopram +pharma 20 mg Filmtabletten, from +pharma arzneimittel GmbH.
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.

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

Escitalopram is the pure S-enantiomer of R,S-citalopram and has been demonstrated to be the only pharmacologically active component in the racemate.
Racemic citalopram is a potent, selective serotonin re-uptake inhibitor (SSRI) and has been used worldwide for more than 10 years for the treatment of major depressive disorders. Citalopram is a racemate with a single chiral centre that comprises an S(+)-enantiomer (S-citalopram, escitalopram) and an R(-)-enantiomer (R-citalopram). Escitalopram is the main effective isomer of citalopram, whereas the R-citalopram is considered to be inactive. Thus, escitalopram is also a selective and potent SSRI and is used worldwide as an antidepressant drug (ATC-Code: N06AB10).

II. QUALITY ASPECTS

II.1 Introduction

Escitalopram +pharma is a film-coated tablet which is presented in a blister.

II.2 Drug Substance

The active substance in Escitalopram +pharma is escitalopram (as oxalate). The specification of the active substance meets the current scientific requirements. The adequate quality of the active substance has been shown by submitting the appropriate control data. The stability of the active substance has been tested under ICH conditions. The results of the stability studies support the established retest-period.

II.3 Medicinal Product

Escitalopram +pharma contains the following excipients:
Tablet core:
Cellulose, microcrystalline
Croscarmellose sodium
Silica, colloidal anhydrous

Magnesium stearate

Tablet film coating:
Hypromellose
Titanium dioxide (E 171)
Macrogol 400

The development of the product has been sufficiently made and deemed appropriate. The usage of all the excipients has been described.
The release specification includes the check of all parameters relevant to this pharmaceutical form. Appropriate data concerning the control of the finished product support the compliance with the release specifications.
The packaging of the medicinal product complies with the current legal requirements.
Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SmPC, with a shelf life of 36 months.

The pharmaceutical quality of Escitalopram +pharma has been adequately shown.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of active substance and medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of escitalopram are well known. As escitalopram is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Escitalopram +pharma 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

To support the application, the applicant has submitted as report one bioequivalence study.

IV.2 Pharmacokinetics

Biowaiver
The 5 mg and 10 mg dosage strengths were exempted from conducting bioequivalence studies

based on the principles stated in Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98).
All test tablets with different dosage strengths (5 mg, 10 mg and 20 mg) applied for marketing authorisation are manufactured by the same manufacturer and the same manufacturing process.
The qualitative composition of the different strengths is the same, and the composition of the strengths is quantitatively proportional, i.e. the ratio between the amount of active ingredient and excipients is identical among the various strengths.
Pharmacokinetics of escitalopram have been shown to be linear over the therapeutic dose range.
According to data presented, the dissolution profiles of the lower strengths (5 mg and 10 mg) were similar to the 20 mg strength used in the bioequivalence study. Generic products and reference products dissolved rapidly (dissolution > 85% in 15 minutes) in all media that had been tested (pH 1.2, 4.5 and 6.8). Therefore, it could be concluded, that all strengths of the test formulation and the reference product formulation showed very similar dissolution profiles.

Bioequivalence studies
Test product: Escitalopram 20 mg film-coated tablets
Reference product: Cipralex® 20 mg tablets

In a single-centre, single-dose, three-period crossover study, healthy female and male subjects received either test or reference in randomised order after controlled fasting. Study periods were separated by a washout of fourteen days. Blood samples were collected at appropriate intervals up to 192 hours post-dose, and, for reason of safety evaluation, adverse events were recorded adequately. A statement on GCP-compliance has been provided, and the study was performed in agreement with the current Helsinki Declaration.
The study population was chosen according to relevant guidelines, and, therefore, can be considered appropriate. Subjects that dropped out and protocol deviations are prescribed adequately.

Results:
In accordance with the guidelines of the European Committee for Proprietary Medicinal Products (CPMP) bioequivalence was concluded if the calculated 90% confidence interval of the ratios of primary pharmacokinetic parameters was completely within the accepted bioequivalence interval (80-125 %).
Results of AUC_{0-t}, $AUC_{0-\infty}$, C_{max} (primary pharmacokinetic variables) and of t_{max} and $T_{1/2}$, respectively, are presented in Table 1 (S-citalopram) and Table 2 (S-desmethylcitalopram).

Table 1. Pharmacokinetic parameters for S-citalopram (non-transformed values; arithmetic mean ± SD, t_{max} : mean ± SD)

Treatment	AUC_{0-t} (ng/mL/h)	$AUC_{0-\infty}$ (ng/mL/h)	C_{max} ng/mL	t_{max} hours	$T_{1/2}$ hours
Test	725.170 ± 308.387	753.044 ± 320.804	26.186 ± 7.387	2.982 ± 0.887	37.156 ± 9.188
Reference	752.577 ± 340.217	788.233 ± 361.458	25.748 ± 8.143	3.000 ± 0.758	41.892 ± 21.780
*Ratio (90% CI)	98.115 (92.076-104.549)	97.477 (91.248-104.132)	102.047 (96.163-108.291)	-	-

CV (%)	14.1	14.6	13.2	-	-

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 concentration
$T_{1/2}$ half-life
*ln-transformed values

Table 2. Pharmacokinetic parameters for S-desmethylcitalopram (non-transformed values; arithmetic mean ± SD, t_{max} : mean ± SD)

Treatment	AUC_{0-t} (ng/mL/h)	$AUC_{0-\infty}$ (ng/mL/h)	C_{max} ng/mL	t_{max} hours	$T_{1/2}$ hours
Test	443.300 ± 174.803	495.533 ± 202.866	5.372 ± 1.763	14.107 ± 15.456	52.279 ± 14.629
Reference	444.029 ± 189.186	494.991 ± 213.397	5.375 ± 2.137	17.647 ± 18.639	50.712 ± 16.821
*Ratio (90% CI)	100.711 (94.458-107.378)	100.934 (94.560-107.737)	101.826 (96.140-107.847)	-	-
CV (%)	14.2	14.5	12.7	-	-

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 concentration
$T_{1/2}$ half-life
*ln-transformed values

The 90% confidence interval of both escitalopram and S-desmethylcitalopram lies within the acceptance interval of 80-125 %.

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study, Escitalopram +pharma 20 mg Filmtabletten is considered bioequivalent with Cipralex® 20 mg tablets.

The results of the bioequivalence study with the 20 mg formulation can be extrapolated to the other strengths 5 mg and 10 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The justification for BCS (Biopharmaceutics Classification System) - based biowaiver can be accepted.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: antidepressants, selective serotonin re-uptake inhibitors
ATC-code: N06AB10

The pharmacodynamic profile of escitalopram is well established. No additional pharmacodynamic study has been submitted and none is required.

IV.4 Clinical efficacy / Clinical safety

Efficacy and safety of escitalopram in the proposed indications are known and assessed as being scientifically based considering recent knowledge, guidelines, and recommendations.
The safety profile of the test product is comparable with the safety profile of the reference product.

IV.5 Discussion on the clinical aspects

The dossier contains an adequate review of published clinical data and bioequivalence has been shown.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The dossier contains an adequate review of published (non)clinical data and bioequivalence has been shown for the 20 mg dosage strength. The biowaver justification for the 5 mg and 10 mg dosage strengths has been accepted.
The pharmaceutical quality of Escitalopram +pharma has been adequately shown.
There are no non-clinical or clinical concerns.
The benefit/risk relation is considered positive.

User consultation

The applicant did not provide a user testing and justified this that in the Public Assessment Report of the originator Cipralex it is stated that for the PL user testing was performed. In the PL for this generic application for Escitalopram +pharma the wording of the Cipralex PL was even adopted literally.
The justification for the absence of user testing has been accepted.

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product Information affected	Date of start of the procedure
Renewal of the marketing authorisation	AT/H/0400/001-003/R/001	Y	16.05.2014

Date of end of procedure	Approval/ non approval	Assessment report attached
20.08.2014	Approved	N

Scope	Procedure number	Product Information affected	Date of start of the procedure
Update of the ASMF from an API manufacturer	AT/H/0400/001-003/II/004/G	N	05.11.2015

Date of end of procedure	Approval/ non approval	Assessment report attached
28.04.2016	Approved	N