IPAR

Public Assessment Report

Scientific discussion

Escitotab / Escivriens / Escitomar / Escithon / Escitalopram Glenmark
10, 15 & 20mg Film-coated Tablets
Escitalopram (as oxalate)

IE/H/198/1-3/DC Escitotab
IE/H/199/1-3/DC Escivriens
IE/H/200/1-3/DC Escitomar
IE/H/201/1-3/DC Escithon
IE/H/202/1-3/DC Escitalopram Glenmark

This module reflects the scientific discussion for the approval of Escitotab / Escivriens / Escitomar / Escithon / Escitalopram Glenmark. These procedures were finalised on 11/08/10. 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, a generic version of escitalopram, under the trade names of Escitotab 10mg, 15mg & 20mg film coated tablets, Escivriens 10mg, 15mg & 20mg film coated tablets, Escitomar 10mg, 15mg & 20mg film coated tablets, Escithon 10mg, 15mg & 20mg film coated tablets and Escitalopram Glenmark 10mg, 15mg & 20mg film coated tablets.

The product is indicated for the:

- 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 Summary of Product Characteristics (SmPC).

Escitalopram (as hydrogen oxalate) is a selective serotonin reuptake inhibitor (SSRI) and increases serotonin levels in the synaps by inhibiting the reuptake mechanism. Escitalopram is the S-enantiomer of racemic citalopram, which is also a marketed SSRI. Escitalopram has a 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 %-HT1A, 5-HT2, DA D1 and D2 receptors, alpha1-, alpha 2-beta-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.
Both escitalopram and citalopram belong to the SSRI subgroup of antidepressants, ATC code NO6AB10 and NO6AB04 respectively.

This Marketing Authorisation Application (MAA) states that escitalopram (as hydrogen oxalate) tablets are a generic form of the currently available innovator and reference product, Cipralex (escitalopram (as hydrogen oxalate)) tablets. Escitalopram is the active enantiomer in the racemic citalopram.

The MA is granted based on Article 10(1) of Directive 2001/83EC as amended.

The Applicant has submitted one bioequivalence study to document similarity with the innovator product.
The bioavailablity of the proposed escitalopram 20mg (as hydrogen oxalate) film coated tablets (Synthon BV, The Netherlands) was compared to the reference product Cipralex 20mg film coated tablets (Lundbeck GmbH) from the German market.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the reference medicinal product.

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

II QUALITY ASPECTS

II.1 Introduction

These applications are for Escitotab / Escivriens / Escitomar / Escithon / Escitalopram Glenmark 10, 15 & 20mg Film-coated tablets. Each tablet contains 10, 15 or 20mg of escitalopram (as oxalate) and the tablets are packaged in blister packs.

II.2 Drug Substance

The active substance is Escitalopram (as oxalate) an established active substance. The drug substance is manufactured

in accordance with the principles of Good Manufacturing Practice (GMP).

Escitalopram is a chiral drug substance and is the S-enantiomer of citalopram. The level of the R-enantiomer is suitably controlled in the active substance specifications.

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided. Stability studies have also been provided and the results support the proposed retest period.

II.3 Medicinal Product

P.1 Composition
Each film-coated tablet contains 10, 15 or 20mg of escitalopram (as oxalate) and the following excipients:

Tablet core:
Microcrystalline cellulose
Colloidal anhydrous silica
Talc
Croscarmellose sodium
Magnesium stearate

Coating:
Hypromellose
Macrogol 400
Titanium dioxide (E 171)

The 5mg tablets are white, oval, film-coated tablets, debossed with ‘E9CM’ on one side and on the other side scored and debossed with‘10’ (one number on each side of the scoring line).

The 10mg tablets are white, oval, film-coated tablets, debossed with ‘E9CM’ on one side and on the other side scored and debossed with ‘15’ (one number on each side of the scoring line).

The 20mg tablets are white, oval, film-coated tablets, debossed with ‘E9CM’ on one side and on the other side scored and debossed with ‘20’ (one number on each side of the scoring line).

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur.

P.5 Control of Finished Product

The Finished Product Specification is based on the Ph. Eur. monograph for tablets and the tests and control limits are

considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented as PVC/PE/PVdC/Aluminium blisters or as oPA/Aluminium/PVC/Aluminium blisters.

Evidence has been provided that the blisters comply with EU legislation for use with foodstuffs.

A range of pack sizes are proposed for each strength – however not all pack sizes may be marketed.

P.7 Stability of the Finished Product

Stability data for all strengths of the finished product in each of the proposed blisters have been provided in accordance with EU guidelines demonstrating the stability of the product for 3 years with no special precautions for storage.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Escitotab / Escivriens / Escitomar / Escithon / Escitalopram Glenmark 10, 15 & 20mg Film-coated tablets.

III NON-CLINICAL ASPECTS

Escitalopram is an orally administered SSRI, indicated for the treatment of major depressive disorder and for the treatment of GAD. Non-clinical data generated by the reference product Lexapro 15 mg or Cipralex 15/20 mg (escitalopram as hydrogen oxalate) film coated tablets marketed by H. Lundbeck A/S was used to support this application.
The impurity C citalopram (H#1703) (citalopram related compound C - Chemical Name: 3-[3-(dimethylamino)-1-propyl](4- fluorophenyl)-6-cyano-1(3H)-isobenzofuranone oxalate) is a degradation product thought to be formed during the wet granulation process in the production of Escitalopram tablets and increases during stability studies. Based on the maximum daily dose of 20 mg/kg, the level of H#1703 is above the applicable qualification limit of ≤0.5% as described in the ICH guideline on impurity levels in drug products, CPMP/ICH/2738/99. The applicant has therefore performed a toxicity prediction assessment and genotoxicity studies to evaluate the potential toxicity posed by H#1703.

III.1 Pharmacology

The pharmacology of Escitalopram is well established and is extensively reviewed in the literature. No additional pharmacology studies with Escitalopram were performed.

III.2 Pharmacokinetics

The pharmacokentics of Escitalopram are well established and are extensively reviewed in the literature. No additional pharmacokinetic studies with Escitalopram were performed.

III.3 Toxicology

The toxicology of Escitalopram is well established and is extensively reviewed in the literature. No additional toxicology studies with Escitalopram were performed. However, an impurity H#1703 is formed during the wet granulation process in the production of Escitalopram tablets and exceeds the applicable qualification limit of 0.5%. In qualifying this impurity, the applicant has predicted through DEREK analysis that impurity H#1703 might cause alpha-2-mu-globulin nephropathy in rodents or phospholipidosis. The relevance of alpha-2-mu-globulin nephropathy is not considered significant to humans given that it appears to be species and sex-specific. The relevance of phospholipidosis to human is unknown but is also apparent with the parent compound, citalopram.

Impurity H#1703 was not mutagenic in the Salmonella typhimurium and in the Escherichia coli reverse mutation assay and it was not clastogenic in the human lymphocyte assay and so is not considered genotoxic.

III.4 Ecotoxicity/environmental risk assessment

No separate environmental risk assessment has been performed with Escitalopram as it is a generic product whose introduction on the market will not cause any significant increase in environmental exposure to the drug substance.

III.5 Discussion on the non-clinical aspects

Overall, the non-clinical studies which includes a toxicity prediction assessment and genotoxicity studies for the impurity H#1703 supports the rationale that Escitalopram will be well tolerated and will potentially have a similar safety profile to that of the reference tablet product.

IV CLINICAL ASPECTS

IV.1 Introduction

The Applicant has provided the results of a bioequivalence study in support of this application based on essential similarity

IV.2 Pharmacokinetics

The study is a randomised single dose, two period crossover bioequivalence study comparing escitalopram 20mg (as hydrogen oxalate) film coated tablets (Synthon BV, The Netherlands) to the reference product Cipralex 20mg film coated tablets (Lundbeck GmbH) from the German market, in healthy volunteers, under fasting conditions and with a washout period of 14 days.

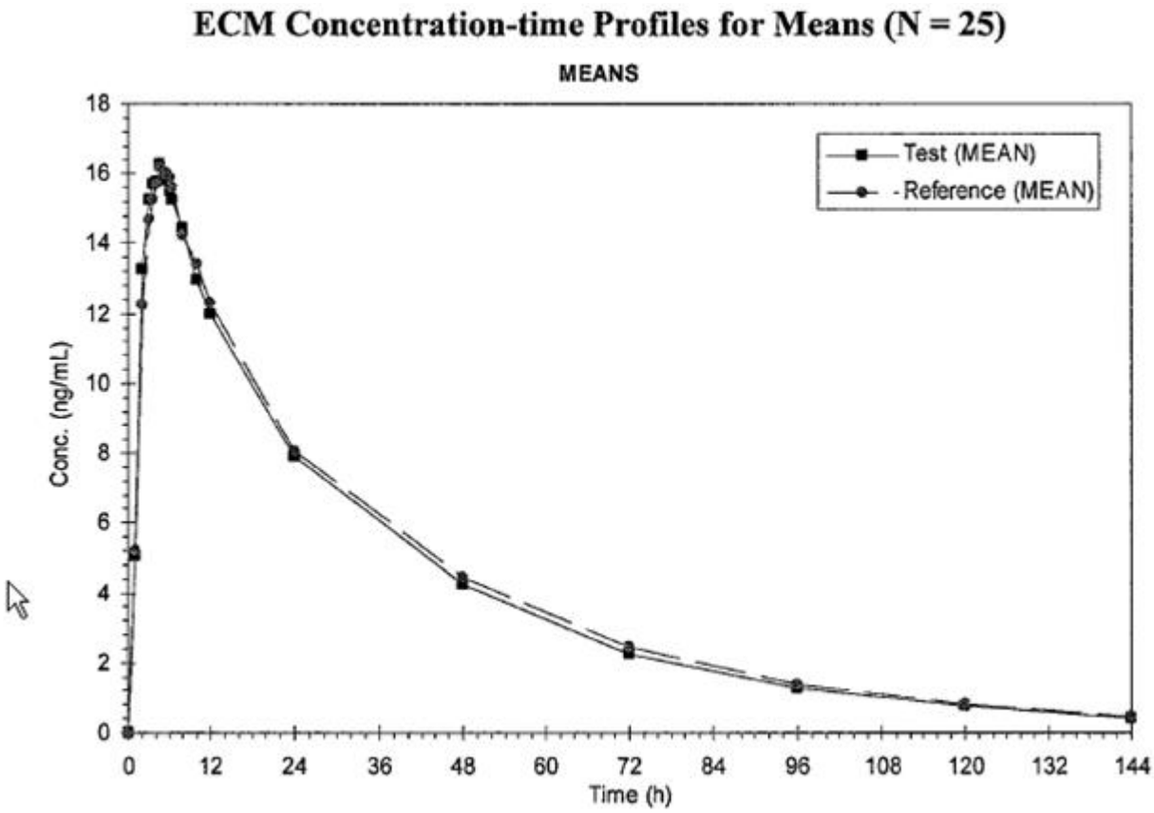
Results

The 90% confidence intervals for Test to Reference ratios of Least Squares Means based on In-transformed data for AUCo-t, AUCo-inf and Cmax were found within the bioequivalence acceptance range of 80 – 125%, as detailed below.

Based on these results, it can be concluded that test escitalopram 20mg film coated tablet and reference product Cipralex 20mg film coated tablet are bioequivalent with respect to the rate and extent of absorption of escitalopram.

Statistical Summary of Comparative Bioavailability Data for the Fasting Bioequivalence Study (N=25)

Parameter	GEOMETRIC LEAST SQUARES MEANS		RATIO T/R (%)	90% CONFIDENCE LIMITS (%)	
	T	R		Lower	Upper
AUC_{0-t} (ng·h/mL)	561.31	576.82	97.31	94.37	100.35
$AUC_{0-\infty}$ (ng·h/mL)	582.44	598.57	97.31	94.34	100.36
C_{max} (ng/mL)	16.78	16.59	101.15	98.60	103.78



IV.3 Pharmacodynamics

No additional pharmacodynamic studies were submitted and none are required for such an application. The pharmacodynamic profile of escitalopram is well known.

IV.4 Clinical efficacy

No new data were submitted and none is required for such an application.
In the dossier, the Applicant discusses several literature references of clinical trials conducted to determine the safety and efficacy of escitalopram in patients with major depressive disorder.
The Applicant has also discussed published literature in relation to the efficacy and safety of escitalopram in the treatment of generalised anxiety disorder, panic disorder, social anxiety disorder and obsessive compulsive disorder.
It is considered that the Applicant has provided sufficient literature references to support the indications proposed for this generic product.

IV.5 Clinical safety

This medicinal product has not been marketed in any country. The reference medicinal product Cipralex has been widely used in the EU market for many years and the safety profile is well known.
In the dossier, the Applicant discusses the issues of hyponatraemia, driving performance, serotonin syndrome, suicide and suicidal thoughts, withdrawal, interactions, pregnancy and lactation, overdose, contraindications and post marketing surveillance associated with the use of escitalopram.

IV .6 Other Clinical issues

Readability test

The package leaflet has been evaluated by means of a User consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83EC as amended. The readability test has been adequately performed.

Pharmacovigilance System

The Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

Not necessary.

V OVERALL CONCLUSIONS

Escitalopram film coated tablets are a generic form of Cipralex film coated tablets. Cipralex is a well known medicinal product with a proven chemical – pharmaceutical quality and an established favourable efficacy and safety profile. On the basis of the data submitted, the IMB and the other Member States involved in the procedure, considered that bioequivalence has been demonstrated for escitalopram 20mg film coated tablets with the reference product and have therefore granted a marketing authorisation. Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. The SmPC is consistent with that of the reference product.

VI REVISION DATE

November 2010