CBG MEB

Public Assessment Report

Scientific discussion

Sertraline Accord 50 mg and 100 mg film-coated tablets

(sertraline hydrochloride)

NL/H/3385/001-002/DC

Date: 2 December 2016

This module reflects the scientific discussion for the approval of Sertraline Accord 50 mg and 100 mg film-coated tablets. The procedure was finalised on 8 January 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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
EDQM	European Directorate for the Quality of Medicines
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 Sertraline Accord 50 mg and 100 mg film-coated tablets from Accord Healthcare Ltd.

Sertraline is indicated for the treatment of:

- Major depressive episodes. Prevention of recurrence of major depressive episodes
- Panic disorder, with or without agoraphobia
- Obsessive compulsive disorder (OCD) in adults and paediatric patients aged 6-17 years
- Social anxiety disorder
- Post traumatic stress disorder (PTSD)

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 Lustral 50 mg and 100 mg film-coated tablets which has been registered in the UK by Pfizer Ltd. since 19 November 1990. The innovator product is registered in several European countries under various trade names. The Dutch reference product is called Zoloft 50 mg and 100 mg (NL License RVG 16292 and 105255, Pfizer B.V.), and is subject of MRP NL/H/1732/002-003. Lustral is part of this MRP as well.

The concerned member states (CMS) involved in this procedure were Austria, Bulgaria, Cyprus, Denmark, Estonia, Finland, Hungary, Ireland, Italy, Latvia, Poland, Sweden and Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

Sertraline Accord 50 mg is a white coloured, biconvex, capsule shaped, film coated tablet debossed with 'I' and 'C' on either side of a score line on one side and plain on other side. The tablet can be divided into equal doses. Each tablet contains 56 mg sertraline hydrochloride equivalent to 50 mg sertraline.

Sertraline Accord 100 mg is a white coloured, biconvex, capsule shaped, film coated tablet debossed with 'IJ' on one side and plain on other side. Each tablet contains 112 mg sertraline hydrochloride equivalent to 100 mg sertraline.

The film-coated tablets are packed in white opaque PVC - Aluminium blister packs

The excipients are:
Tablet core - calcium hydrogen phosphate dihydrate (E341), cellulose microcrystalline (E460), hydroxypropylcellulose (E463), sodium starch glycolate (Type A) (E468) and magnesium stearate (E470b).
Film-coating – Opadry White containing: hypromellose 2910 (5mPa.s) (E464), macrogol 400 (E1521), polysorbate-80 (E433) and titanium dioxide (E171).

The two tablet strengths are fully dose proportional.

II.2 Drug Substance

The active substance is sertraline hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white to off-white crystalline powder. The substance is slightly soluble in water, sparingly soluble in ethanol and slightly soluble in acetone and isopropanol. It

shows polymorphism, and is produced in Form I. Sertraline hydrochloride exhibits both geometrical and optical isomerism; the active substance is the S-cis enantiomer.

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 CEP holder. Batch analytical data demonstrating compliance with this specification have been provided.

Stability of drug substance
Stability data on the active substance have been provided for three commercial batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The retest period of 5 years is accepted. No additional storage condition is necessary.

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 effectivity of the score line on the 50 mg tablet is shown; the tablet can be broken into two equal halves. The pharmaceutical development of the product has been adequately performed.

One *in vivo* bioequivalence study was submitted to demonstrate bioequivalence between Sertraline Accord 100 mg film-coated tablets and reference product, Lustral 100 mg film-coated tablets registered in the UK. The bioequivalence study test batch was manufactured according to the finalised manufacturing process and composition.

For the lower strength a biowaiver is requested. Comparative dissolution data in media with different pH (1.2, 4.5, and 6.8) between 100 mg tablets and the 50 mg strength have been provided. The results show that the two tablet strengths have comparable dissolution characteristics throughout the physiological pH range.

Manufacturing process
The manufacturing process uses a wet granulation process consisting of a combination of screening, mixing, granulation, drying, blending, lubrication, and compression and coating steps. The manufacturing process is considered a standard process.
The manufacturing process has been adequately validated for both manufacturing sites, according to relevant European guidelines. Process validation data on the product has been presented for two or more commercial scaled batches per strength and for each manufacturing site.

Control of excipients
All ingredients of the tablet core and coating mixture are listed and adequately controlled by pharmacopoeial or in-house 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 appearance, uniformity of dosage units, identification, assay, water content, dissolution rate, related substances and microbiological purity. 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 analysis results of six commercial batches for the 50 mg tablet and three commercial batches for the 100 mg tablet have been provided for manufacturer-I. Batch analysis results of two commercial batches per strength have been provided for manufacturer-II. Compliance with the release specification is demonstrated.

Stability of drug product
Stability data on the products have been provided for three commercial scaled batches per strength and per manufacturing site, stored at 25°C/60% RH (2 batches for 6 months, 4 batches for 12 months, 2 batches for 24 months and 2 batches for 36 months) and 40°C/75% RH (4 batches for 6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored packed in the proposed packaging. The results of photostability studies remained within acceptable criteria. Therefore, the product is considered photostable. On basis of the data submitted, a shelf life was granted of 3 years without special storage conditions.

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 Sertraline Accord 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 Sertraline Accord 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 Zoloft 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

Sertraline 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 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.

IV.2 Pharmacokinetics

Bioequivalence study

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Sertraline Accord 100 mg film-coated tablets (Accord Healthcare Ltd, United Kingdom) is compared with the pharmacokinetic profile of the reference product Lustral 100 mg film coated tablets (Pfizer Ltd, UK).

The choice of the reference product

The choice of the UK reference product Lustral in the bioequivalence study has been justified. It is registered through NL/H/1732/002-003/MR. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The results of the bioequivalence study with the 100 mg strength can be extrapolated to the 50 mg strength as the biowaiver criteria are fulfilled:

- The products are manufactured by the same manufacturing process
- The qualitative composition of the different strengths is the same
- The composition of the strengths is quantitatively proportional
- The *in vitro* dissolution test in support of the biowaiver is acceptable

Design

An open label, balanced, randomised, two-treatment, two-sequence, two-period, single oral dose, crossover bioequivalence study was carried out under fasted conditions in 44 healthy male subjects, aged 28±6 years. Each subject received a single dose (100 mg) of one of the 2 sertraline hydrochloride formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre dose and at 1.0, 2.0, 3.0, 3.5, 4.0, 4.3, 4.67, 5.0, 5.3, 5.67, 6.0, 6.33, 6.67, 7.0, 7.3, 7.7, 8.0, 8.3, 8.7, 9.0, 9.5, 10.0, 10.5, 11.0, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable considering the absorption rate and half-life. Also the washout period is acceptable. As this product can be taken regardless food intake, a study under fasted conditions is justified.

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 subject was withdrawn from the study on medical grounds in Period-I. Three subjects were withdrawn from the study on medical grounds in Period-II and one subject discontinued from the study on his own accord in Period-II. As a result, 39 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=39	**AUC_{0-72}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	926 ± 274	34.5 ± 8.6	4.7 (3.0 - 11.0)
Reference	924 ± 272	34.4 ± 8.1	5.0 (3.5 - 10.5)
***Ratio (90% CI)**	1.01 (0.96 - 1.04)	1.01 (0.96 - 1.06)	--
CV (%)	10.4	13.0	--

AUC_{0-72}	area under the plasma concentration-time curve from time zero to 72 hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
CV	coefficient of variation

**ln-transformed values*

Safety
The clinical portion of the study was completed with 3 significant adverse events (AEs). The investigational products were well tolerated by healthy subjects, as a single dose administration. 17 AEs were reported during the conduct of the study. 10 AEs were mild in nature and 7 AEs were moderate in nature. The subjects were followed up until resolution of their AEs.

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-72}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Sertraline Accord 100 mg film-coated tablets are considered bioequivalent with Lustral 100 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 Sertraline Accord.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Serotonin syndrome • Suicidality
Important potential risks	• Diabetes mellitus • Use in pregnancy • Abnormal bleeding/haemorrhage
Missing information	• Use in paediatric patients, especially under age of 6 years

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 Zoloft. 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 bridging reports. The bridging is applied in following in two ways.
Firstly, between the proposed PL of Sertraline Accord 50 mg and 100 mg film coated tablets and the approved PL of reference product Lustral 50 mg and 100 mg film coated tablets for text content.
Secondly between the proposed PL of Sertraline Accord 50 mg and 100 mg film coated tablets and one of the satisfactory user tested PL of Mycophenolic acid 180 mg and 360 mg gastro-resistant tablets (ES/H/0183/001-002/DC) for design, layout and style of writing.
The bridging reports submitted by the MAH have been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sertraline Accord 50 mg and 100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Zoloft 50 mg and 100 mg film-coated tablets. Zoloft 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 Sertraline Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 January 2016.

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