Public Assessment Report

Scientific discussion

Sertraline Apotex 50 mg and 100 mg, film-coated tablets (sertraline hydrochloride)

NL/H/2800/001-002/DC

Date: 6 May 2014

This module reflects the scientific discussion for the approval of Sertraline Apotex 50 mg and 100 mg, film-coated tablets. The procedure was finalised on 28 October 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 Sertraline Apotex 50 mg and 100 mg, film-coated tablets from Apotex Europe BV.

The product is indicated for:

- 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 Dutch reference product is called Zoloft 50 mg and 100 mg (NL License RVG 16292 and 105255), which is subject of MRP NL/H/1732/002-003.

The concerned member states (CMS) involved in this procedure were Belgium, Czech Republic, Luxembourg, Poland and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Sertraline Apotex 50 mg is a bluish purple, oval, scored film-coated tablet engraved “APO” on one side, “SE” bisect “50” on the other side.
Sertraline Apotex 100 mg is a yellow, oval, scored film-coated tablet engraved “APO” on one side, “SER” bisect “100” on the other side.
The tablets can be divided into equal doses.

The tablets are packed in Aluminium/PVC/PVDC blisters.

The excipients are:
Core – microcrystalline cellulose (E460), methylcellulose (E461), colloidal anhydrous silica (E550), magnesium stearate (E572)
Coating - hypromellose (E464), hydroxypropylcellulose (E463), macrogol 8000 (E1521), titanium dioxide (E171); 50 mg tablets: Indigo carmine (E132), lake; 100 mg tablets: Ferric Oxide (Yellow Iron Oxide) (E172)

The tablet strengths are qualitatively and quantitative 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, which is slightly soluble in water, sparingly soluble in ethanol and slightly soluble in acetone and isopropanol. It shows polymorphism, the commercial form is II. Sertraline HCl exhibits both geometrical and optical isomerism; the active ingredient 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 European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The specification of sertraline hydrochloride is in line with the specification of the Ph. Eur. and CEP holder. As compendial analytical methods are used, submission of validation data is not required. Batch analyses of the active substance manufacturer have been reviewed in relation to the approval of the Certificates of Suitability. Batch analysis results have also been submitted by the MAH.

Stability of drug substance
The active substance is stable for 5 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 development of the product has been described, the choice of excipients is justified and their functions explained. A biowaiver was submitted to extrapolate the results from the bioequivalence study on the 100 mg strength to the 50 mg strength. The biowaiver criteria are fulfilled.
In 0.1 N HCl and pH 4.6 buffer, the dissolution profiles of Apotex 50 mg Tablets and 100 mg Tablets were demonstrated to be similar. In pH 6.8 buffer, the dissolution profiles are similar for the same dose (2 tablets of 50 mg vs. 1 tablet of 100 mg). The UK reference product used in the bioequivalence study is part of the MRP NL/H/1732/MR, and therefore representative for the member states involved in this DCP. The Ph.Eur. requirement for subdivision of tablets is included in the release specification to confirm that the tablets can be divided into equal halves. Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process
The method of manufacturing for the 50 mg and 100 mg tablets uses a dry mix/direct compression process consisting of a combination of screening, mixing, compaction and compression and coating steps. The manufacturing process is considered a standard process.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three blends and three pilot-scale batches per strength.

Control of excipients
All ingredients within the tablet core comply with relevant Ph.Eur. monographs. All ingredients of the coating mixture are listed, and are adequately controlled by pharmacopoeial or in-house requirements. The specifications are acceptable.

Quality control of drug product
The drug product specifications includes tests on appearance, content uniformity, uniformity of mass, uniformity of mass of subdivided tablets, identification, assay, dissolution rate, related substances and microbiological purity. The methods used have been adequately described and validated.
Batch analysis data have been provided for three commercial batches per strength. Compliance with the release specification was demonstrated.

Stability of drug product
Stability data on the products have been provided for three pilot-scale batches per strength stored at 25°C/60% RH (36 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. The batches were stored packed in the proposed blister packs materials.
A photosensitivity study shows that no significant change was observed in degradation products for the 50 mg and 100 mg tablets that were directly exposed. Protection from light is not necessary. In view of the results the proposed shelf life (3 years) and storage conditions (No special precautions for storage) are acceptable for the 50 mg and 100 mg strengths.

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 Apotex 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 Apotex 50 mg and 100 mg, film-coated tablets are 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 Lustral film-coated tablets, which are available on the European market. Reference is made tot 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 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 Sertraline Apotex 100 mg (Apotex Europe BV, the Netherlands) 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 in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

<u>Biowaiver</u>
A biowaiver has been granted for the 50 mg strength, based on the following:

- The formulation of Sertaline Apotex 50 mg tablets and 100 mg tablets is dose proportional;
- The pharmacokinetics of sertraline are linear across the dose range 50 to 200 mg;
- In 0.1 N HCl and pH 4.6 buffer, the dissolution profiles of Sertraline Apotex 50 mg tablets and 100 mg tablets are similar (f2 > 50);
- In pH 6.8 buffer, the dissolution profiles are similar for the same dose (2 tablets of 50

- mg vs. 1 tablet of 100 mg);
- Sertraline does not have a narrow therapeutic range.

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, aged 19-39 years. Each subject received a single dose (100 mg) of one of the 2 sertraline formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 2 weeks.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 15, 24, 36, 48, 60 and 72 hours after administration of the products.

The study design is acceptable. Sampling scheme is adequate to estimate the pharmacokinetic parameters reliably. The wash-out period of 2 weeks is acceptable, in the light of the $t_{1/2}$ of up to 36 h. The study in fasting state with the highest strength is sufficient, as food does not significantly change the bioavailability of sertraline.

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

Two subjects were withdrawn due to adverse events (functional aphasia and loose stools), one subject did not report for the 60 and 72 h ambulatory sample and one subject was withdrawn due to a dosing failure. Twenty subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=20	**AUC_{0-72}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1309 ± 477	1779 ± 850	41.8 ± 14.6	6.0 (3.0-9.0)	--
Reference	1367 ± 501	1816±840	42.4 ± 11.9	5.0 (2.0-11.0)	--
***Ratio (90% CI)**	0.95 (0.90-1.01)	0.97 (0.91-1.03)	0.96 (0.88-1.06)	--	--
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}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Sertraline Apotex 100 mg is considered bioequivalent with Lustral 100 mg film-coated tablets.

There were 15 adverse events in the study (7 for test, 8 for reference), all were mild. The reported events for the test formulation were loose stools (4), functional aphasia, agitation and headache. The reported adverse events for the reference formulation were loose stools (4), decreased haemoglobin, abnormal urine analysis, common cold and dizziness.

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 Apotex.

Summary table of safety concerns as approved in RMP

Important identified risks	- Hypersensitivity - Concomitant treatment with MAOIs - Concomitant use with pimozide - Serotonin Syndrome - Neuroleptic Malignant Syndrome - Suicide related events - Abnormal bleeding / haemorrhage - Persistent pulmonary hypertension of the newborn (PPHN) - Bone fractures
Important missing information	- Use in Children under 6 years of age - Use in patients with severe hepatic impairment - Long term safety and efficacy data in children (6-12 years old) and adolescents (13-17 years old)

No other risk minimisation measures than the information provided in the SmPC is proposed. This is acceptable, as no additional measures are applicable to the innovator.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Lustral. 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

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sertraline Apotex 50 mg and 100 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Lustral 50 mg and 100 mg. Lustral 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 Apotex with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 October 2013.

The following post-approval commitment has been made during the procedure:

- The MAH committed to implement SmPC changes three months following approval thereof for the innovator.

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