Public Assessment Report

Scientific discussion

Sertraline Medreg 50 mg, 100 mg
Sertraline hydrochloride

SK/H/0297/001-002/DC

Date: 11.06.2024

This module reflects the scientific discussion for the approval of Sertraline Medreg. The procedure was finalised at 08.12.2023/D210. 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 Medreg 50mg and 100mg, film-coated tablets from Medreg s.r.o.

The product 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.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, so called generic application

II. QUALITY ASPECTS

II.1 Introduction

Sertraline Medreg 50 mg are white to off-white caplet shaped approx. 10.4 x 4.2 ± 0.2 mm biconvex film-coated tablets, with a break-line on one side and '50' debossed on either side of the break-line.
Sertraline Medreg 100 mg are white to off-white caplet shaped approx. 13.2 x 5.3 ± 0.2 mm biconvex film-coated tablets, with '100' debossed on one side.

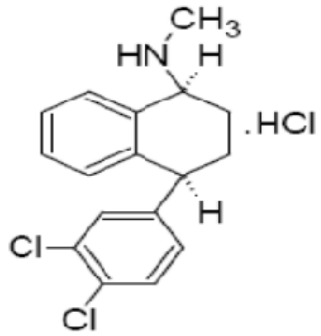
Excipients used in the medicinal product (calcium hydrogen phosphate anhydrous, cellulose microcrystalline, hydroxypropylcellulose, sodium starch glycolate (type A), magnesium stearate in tablet core; hypromellose, titanium dioxide (E171), macrogol 400, polysorbate 80 in film coating) are well known and widely used as pharmaceutical excipients.

Medicinal product is available in PVC/aluminium blisters, further packed in an outer carton.
Available in pack size: 10, 14, 28, 30, 84, 90, 98 or 100 film coated tablets.

II.2 Drug Substance

INN: Sertraline hydrochloride

Structural formula:



Molecular formula: $C_{17}H_{17}NCl_2HCl$

Chemical names:
(1S,4R)-4-(3,4-dichlorophenyl)-N-methyl-tetralin-1- amine hydrochloride
(1S,4S)-4-(3,4-Dichlorophenyl)-N-methyl-1,2,3,4- tetrahydronapthalen-1-amine hydrochloride

Appearance: White or almost white crystalline powder

Solubility: Slightly soluble in water, acetone and in isopropanol.

Chirality: Sertraline hydrochloride exhibits two polymorphic forms (Form-I & II).

Manufacturing: The CEP procedure is used for the active substance.

Specifications: The specification of the active substance sertraline hydrochloride includes the tests, limits and methods described in Ph. Eur. monograph No. 1705, together with the additional in-house tests to ensure the quality.

Stability: Sertraline hydrochloride is packed in double polyethylene bags (outer black) placed in a polyethylene drum, in accordance with CEP. Based on the available stability data the re-test period of five years has been assigned.

II.3 Medicinal Product

Manufacturing: The description of the manufacturing process has been provided in the dossier. All excipients used in manufacture process are of compendial quality. Process validation was performed on three batches in the size of 1 000 000 tablets for Sertraline tablets 100 mg and 4 500 000 for Sertraline tablets 50 mg, which are the batch sizes proposed for commercial manufacture.

Product specification: The proposed specification for the finished product is in line with ICH Q6A, where relevant, and is acceptable.

Stability: Stability data were provided for three pilot scale batches for both DP strengths under long-term and accelerated conditions. These batches were packed in opaque PVC/aluminium blisters (primary packaging). Based on the provided long-term (36 months) and accelerated (6 months) stability data the applicant proposed a shelf-life of 48 months (4 years) with recommended storage condition as “This medicinal product does not require any special storage condition” which is accepted.

II.4 Discussion on chemical, pharmaceutical and biological aspects

From a quality point of view the dossier was adequately presented.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

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

III.2 Ecotoxicity/environmental risk assessment (ERA)

The applicant has submitted an Environment Risk Assessment to support the MAA for generic medicinal product Sertraline Medreg 100 mg / 50 mg.

The consumption data were provided and presented in the dossier according to the "*Guideline on the Environmental Risk Assessment for medicinal products for human use" EMEA/CHMP/ SWP/4447/00 Rev 1)* in the time period of the years 2018 until 2021.

Since the medicinal products are intended for substitution or replacement of reference product or other already marketed generics, the authorization of these products will not increase the overall amount of consumed active substance per year in any Member State.

III.3 Discussion on the non-clinical aspects

Sufficient references to published non-clinical data were provided for this generic application, which was considered adequate.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Absorption
In man, following an oral once-daily dosage of 50 to 200 mg for 14 days, peak plasma concentrations of sertraline occur at 4.5 to 8.4 hours after the daily administration of the drug. Food does not significantly change the bioavailability of sertraline tablets.

Distribution
Approximately 98% of the circulating drug is bound to plasma proteins.

Biotransformation
Sertraline undergoes extensive first-pass hepatic metabolism.
Based on clinical and in vitro data, it can be concluded that sertraline is metabolized by multiple pathways including CYP3A4, CYP2C19 (see section 4.5) and CYP2B6. Sertraline and its major metabolite desmethylsertraline are also substrate of P-glycoprotein in vitro.

Elimination

The mean half-life of sertraline is approximately 26 hours (range 22-36 hours). Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation up to steady state concentrations, which are achieved after one week of once-daily dosing. The half-life of N-desmethylsertraline is in the range of 62 to 104 hours. Sertraline and N-desmethylsertraline are both extensively metabolized in man and the resultant metabolites excreted in faeces and urine in equal amounts. Only a small amount (<0.2%) of unchanged sertraline is excreted in the urine.

Bioequivalence study

To support the applications, the applicant has submitted as a report one bioequivalence study (Study Code: 085-20) conducted in healthy, adult, human subjects under fasting conditions as a open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover, truncated-design, oral bioequivalence study of Sertraline Film-Coated Tablets 100mg (Test Product) with Zoloft Film-Coated Tablets 100mg (Reference Product: Pfizer, Italy)

The pharmacokinetic parameters listed below were derived individually for each analysed subject from the concentration vs. time profiles of Sertraline in plasma. Actual times of sample collection were used for the estimation of pharmacokinetic parameters. The mean pharmacokinetic parameters of Sertraline for the test product (T) and reference Product (R) of 32 subjects who completed two periods and results of the comparisons of Cmax and AUC0-72h data are summarized in the following table:

Table 1. *Pharmacokinetic parameters of Test product (T) and Reference product (R) for sertraline (N = 32)*

Form	Variable	Mean	SD	Minimum	Median	Maximum	CV%
R	C_{max}	38.506	12.048	16.475	37.338	70.739	31.288
	AUC_{0-72h}	1103.392	361.632	378.945	1120.028	1947.145	32.775
	T_{max}	5.766	1.211	3.000	5.500	8.500	21.011
T	C_{max}	41.573	11.474	18.106	39.559	61.716	27.599
	AUC_{0-72h}	1161.761	390.397	407.174	1197.378	1942.359	33.604
	T_{max}	5.563	1.105	3.000	5.500	8.500	19.858

Sequence, period and formulation effect were found to be statistically non–significant for the Ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72h} at the 5% level of significance.

Concentrations of sertraline for both reference and test medicinal product in the pre-dose time point were not quantifiable. There was no Cmax observed in the first sample time point. All Cmax values were within the bio-analytical ranges. LLOQs were adequate (< 5% of minimal Cmax). It was assumed that the terminal elimination phase was reached within the sampling period. Thus, the residual AUC values were Not Applicable.

Conclusion on bioequivalence study

Based on the submitted bioequivalence study (Study Code: 085-20) Sertraline Medreg 100 mg is considered bioequivalent with Zoloft.

Biowaiver

A biowaiver was requested for 50 mg formulation of sertraline based on bioequivalence study

with the 100 mg formulation.

Both strengths are manufactured by the same manufacturing process, equipment, and in-process controls analyzed by the same validated analytical methods in the same analytical laboratory.

The qualitative composition of the different strengths is the same.
Both strengths of Sertraline tablets, i.e. 50 mg and 100 mg are equivalent in terms of ingredients. The compositions of all strengths are proportional

Following single or multiple oral once-daily doses of 50 to 400 mg/day, the average terminal elimination half-life is approximately 26 hours. Linear dose proportionality has been demonstrated over the clinical dose range of 50 to 200 mg/day. Sertraline exhibits dose-proportional pharmacokinetics in the range of 50 to 200 mg. Humans follow an oral once-daily dosage of 50 to 200 mg for 14 days, peak plasma concentrations of sertraline occur at 4.5 to 8.4 hours after the daily administration of the drug. Food does not significantly change the bioavailability of sertraline tablets. Following oral administration of a single 50 mg sertraline dose after an overnight fast, the mean plasma level of 0.05-0.2 μg/mL was achieved after 6.9 hours.

The Applicant provided in vitro dissolution data to confirm the adequacy of waiving additional in vivo bioequivalence testing.

Given the calculation provided, the biowaiver request for 50 mg strengths of sertraline tablets can be accepted.

IV.2 Pharmacodynamics

Sertraline is a potent and specific inhibitor of neuronal serotonin (5-HT) uptake in vitro, which results in the potentiation of the effects of 5-HT in animals. It has only very weak effects on norepinephrine and dopamine neuronal reuptake. At clinical doses, sertraline blocks the uptake of serotonin into human platelets. It is devoid of stimulant, sedative or anticholinergic activity or cardiotoxicity in animals. In controlled studies in normal volunteers, sertraline did not cause sedation and did not interfere with psychomotor performance. In accordance with its selective inhibition of 5-HT uptake, sertraline does not enhance catecholaminergic activity. Sertraline has no affinity for muscarinic (cholinergic), serotonergic, dopaminergic, adrenergic, histaminergic, GABA or benzodiazepine receptors. The chronic administration of sertraline in animals was associated with down-regulation of brain norepinephrine receptors as observed with other clinically effective antidepressants and antiobsessional drugs.

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 Medreg.

Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

IV.4 Discussion on the clinical aspects

Submitted clinical dossier was of sufficient quality. Submitted data supported the chosen legal basis "generic application". The application contained an adequate review of published clinical data and the bioequivalence has been shown.

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 language used for the purpose of user testing the PIL was English.
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.

Bridging report has been submitted for the purpose to bridge Sertraline Medreg 50 mg, 100 mg film-coated tablets (three columns PIL) to Sertraline Medreg 50 mg, 100 mg film-coated tablets (two columns PIL), i.e different design and layout. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This was an application for a marketing authorisation of a medicinal product for human use as it is defined in Article 10(1) (generic application) of the European Directive 2001/83/EC as amended.
Decentralised procedure according to Article 28(3) of Directive 2001/83/EC as amended with Slovak Republic acting as RMS. The applicant Medreg s.r.o. has submitted this MAA under procedural number SK/H/0292/001-002/DC; CMSs were Czech Republic, Poland and Romania.

The reference medicinal product referred to is Zoloft 50/100 mg film-coated tablets, authorised in Czech Republic since 1994, held by Upjohn EESV (MA number 30/1093/94-A/C and 30/1093/94-B/C).

To support the application, the Applicant has submitted one bioequivalence study with reference medicinal product Zoloft 100 mg film-coated tablets, Viatris Pharma S.r.l., Italy. Based on the submitted bioequivalence study, test product Sertraline Medreg 100 mg was considered bioequivalent with the reference medicinal product Zoloft 100 mg. Biowaiver for the 50 mg strength has been accepted.

The legal basis is considered acceptable as the reference products are considered to fall under the notion of same global marketing authorisation and the data protection period has expired in all Member States.