LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Sertraline Orifarm
# (sertraline hydrochloride)

# SE/H/2168/01/DC

**This module reflects the scientific discussion for the approval of Sertraline Orifarm. The procedure was finalised on 2022-04-13. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Sertraline Orifarm, 25 mg, Film-coated tablet.

The active substance is sertraline hydrochloride. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Sertraline Orifarm, 25 mg, Film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orifarm Generics A/S, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Zoloft 25 mg Film-coated tablet authorised in SE since 2001, with PFIZER AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Zoloft, 100 mg, Film-coated tablet from DE with Pfizer Pharma PFE GmbH as marketing authorisation holder.

**Potential similarity with orphan medicinal products**
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

# II. QUALITY ASPECTS

## II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

## II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

# III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of active substance are well known. As active substance is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

**Environmental Risk Assessment (ERA)**
Since Sertraline Orifarm is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Sertraline Orifarm from a non-clinical point of view.

# IV. CLINICAL ASPECTS

**Pharmacokinetics**
To support the marketing authorisation application the applicant submitted one bioequivalence study with 100 mg strength (not applied for in the current application) in the fasting state. A biowaiver was sought for the addtional strength of 25 mg.

Pharmacokinetic properties of the active substance
*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.

*Linearity:* Sertraline exhibits dose proportional pharmacokinetics in the range of 50 to 200 mg.

*Elimination:* The mean half-life of sertraline is approximately 26 hours (range 22-36 hours).

Study 003-20

*Methods*
This was a single-dose, two-way crossover study conducted in 36 healthy volunteers (26 completed), comparing Sertraline, 100 mg, film-coated tablet with Zoloft, 100 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of sertraline were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for $AUC_{0-72}$ and $C_{max}$.

*Results*
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

**Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range) for sertraline, n=26.**

| Treatment | $AUC_{0-72}$ ng*h/ml | $C_{max}$ ng/ml | $t_{max}$ h |
|---|---|---|---|
| **Test** | **1322.631 ± 439.634** | **50.472 ± 15.215** | **5.00 (2.000-8.330)** |
| **Reference** | **1235.407 ± 398.622** | **44.760 ± 13.314** | **5.50 (3.000-11.000)** |
| ***Ratio (90% CI)** | **106.65 (98.35-115.64)** | **112.38 (103.70-121.77)** | **-** |

**$AUC_{0-72}$** area under the plasma concentration-time curve from time zero to 72 hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum plasma concentration

**calculated based on ln-transformed data*

For $AUC_{0-72}$ and $C_{max}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **). The bioanalytical method was adequately validated.

Based on the submitted bioequivalence study Sertraline, 100 mg film-coated tablet is considered bioequivalent with Zoloft, 100 mg, film-coated tablet of Pfizer Pharma PFE GmbH, under fasting conditions.

No further literature references with regard to dose proportionality in the range below 50 mg were submitted. However, sertraline exhibits dose-proportional pharmacokinetics in the range of 50 to 200 mg and there are no indications of non-linear pharmacokinetics (less than proportional increase in AUC with increasing dose) over the dose interval 25-50 mg that would require an additional study of the lowest strength. The absence of studies with the applied strength of 25 mg is thus acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **) are fulfilled.

**Pharmacodynamics/Clinical efficacy/Clinical safety**
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

**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 Orifarm.

Safety specification
The MAH has submitted an RMP version 1.0 dated 10/03/2021 and proposed the following summary safety concerns:

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

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 1.0 signed 10/03/2021 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

# V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report: making reference to:

**Content**
Sertraline Apotex 50 mg and 100 mg,film-coated tablets, NL/H/2800/001-002/DC. The bridging report submitted by the applicant has been found acceptable.

**Layout**
The applicant has proposed a bridging to a user test carried out on the product Kaliumklorid Orifarm 750 mg depottabletter, DK/H/2347/001.

The bridging has been assessed and accepted.

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Sertraline Orifarm, is found adequate. There are no objections to approval of Sertraline Orifarm, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product with 100 mg strength has been adequately demonstrated. The absence of studies with the applied strength of 25 mg is acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **) are fulfilled. The product information is acceptable. The application is therefore recommended for approval.

**List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment**

N/A

**List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC**

N/A

# VII. APPROVAL

The decentralised procedure for Sertraline Orifarm, 25 mg, Film-coated tablet was positively finalised on 2022-04-13.

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# Public Assessment Report – Update

| Procedure number* | Scope | Product Information affected (Yes/No) | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
|---|---|---|---|---|---|
| | | | | | |

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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