LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Sertraline Medical Valley
# (sertraline hydrochloride)

# SE/H/2396/01-05/DC

**This module reflects the scientific discussion for the approval of Sertraline Medical Valley. The procedure was finalised on 2024-10-02. 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 Medical Valley, 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, Film-coated tablet.

The active substance is sertraline hydrochloride, sertraline. 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 Medical Valley, 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, Film-coated tablet, is a generic and a hybrid application submitted according to Article 10(1) and 10(3) of Directive 2001/83/EC. Strengths 25 mg, 50 mg and 100 mg is submitted according to Article 10(1). Strengths 150 mg and 200 mg is submitted according to Article 10(3). The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE, DK, NO, IS, PL, NL 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 1993, with Upjohn EESV as marketing authorisation holder.

The reference product used in the bioequivalence study is Besitran, 100 mg, film-coated tablet from ES with Pfizer, S.L. as marketing authorisation holder.

**European Reference Product (ERP)**
A European Reference Product is used in CMS DE, NL, PL: Zoloft, 25 mg, film-coated tablet authorised in SE since 1993, with Upjohn EESV as marketing authorisation holder.
The justification to use this product is based on RMS's own files.

**Potential similarity with orphan medicinal products**
N/A

# 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

**Pharmacology, pharmacokinetics, and toxicology**
Pharmacodynamic, pharmacokinetic and toxicological properties of sertraline are well known. As sertraline is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Based on the above considerations, only a short overview on the toxicological domains of genotoxicity, carcinogenicity, and reproductive toxicity (reference to Davies et al, 1998)[1] are provided in this Overview. A genotoxicity battery of the bacterial mutation assay (Ames test), a mouse lymphoma mammalian cell mutation assay and tests for cytogenetic aberrations in mouse bone marrow (in vivo) and human lymphocytes (in vitro) has been conducted, resulting in an absence of genotoxicity (with or without metabolic systems). For oncogenicity, two 2-year feeding studies were conducted in CD-1 mice and Long-Evans rats (using 10, 20 and 40 mg/kg). No statistically significant increase in neoplasms were found in rat. In the mouse study, significant increases in the incidences of bronchioalveolar adenomas in females and hepatocellular adenomas in males were found (bronchioalveolar adenomas in females were 6/50, 2/50, 9/49, 1/50, and 12/50 in control 1, control 2, low, mid, and high dose groups, respectively). These findings have been considered non-test substance related due the lack of a clear dose response (only 1/50 in the mid dose group) and dramatic differences in the lung neoplasm incidence in the two concurrent controls. Based on these findings, it is noted in the SmPC 5.3 that there is no indication of genotoxicity and carcinogenicity-related hazards to humans.

A mouse developmental toxicity study (maternal exposure to 5, 25, or 60 mg/kg/day; Gd6 to PND15; referenced to Cabrera et al. 2020)[2] indicated that in utero exposure to sertraline at 25 and 60 mg/kg was embryotoxic, teratogenic, and fetotoxic (the animal doses correspond to 0.4, 2.0, and 4.8 mg/kg HED, respectively). There were increased resorption rates, lower embryo-foetal weight, and increased percentage of foetuses with visceral and skeletal abnormalities and cleft palates were found in the intermediate and high sertraline dose groups. These results are noted in SmPC 4.6 and 5.3. It is also noted in SmPC 4.6 that "…a substantial amount of data did not reveal evidence of induction of congenital malformations by sertraline" which is text also used in previous sertraline product SmPCs.

**Environmental risk assessment**
Regarding the provided environmental risk assessment (ERA), the applicant first chose to submit a literature-based Phase I & IIA ERA. The surface water PEC calculations were acceptable. They are based on DDD (50 mg dose) and IQVIA consumption data for the relevant member states provides Phase I surface water PEC values (PECsw) between 1,03 (Netherlands) and 4.49 ug/L (Sweden) – triggering a Phase IIA assessment.

There were several issues with the submitted literature ERA. The Phase I & II ERA came without the

[1] Davies TS and Kluwe WM. Preclinical toxicological evaluation of sertraline hydrochloride. Drug Chem Toxicol. 1998 May; 21(2): 163-79.
[2] Cabrera RM, Linda Lin Y, Law E et al. The teratogenic effects of sertraline in mice. Birth Defects Res. 2020 Aug; 112(13): 1014-1024

underlying articles that are referenced to and/or are the basis for the empirical data. The possibility for terrestrial exposure via sewage sludge nor the need for sediment-dweller toxicity testing was not assessed. The ERA also missed a microorganism toxicity study (OECD TG209 or similar) and a relevant fish toxicity study (OECD TG210 or similar). Interestingly, a 70d developmental (metamorphosis) toxicity study in frog (Conners et al, 2009, LOEC 0.1 ug/L for body mass reduction, where all three concentrations [0.1 to 10 ug/L] used in the test caused statistically significant body mass reduction) was the most sensitive toxicity test of relevance to Aquatic toxicology (more sensitive than the 21d Daphnia study with NOEC 32 ug/L that the applicant proposes to use for PNEC selection in the risk characterization).

An generics approach (sensu the CHMP 2006 ERA-GL) was also submitted, but the provided IQVIA dales data show that there has been substantial increase in consumption over the last 4 years in especially Poland and Germany. As such, the generics approach - based on a roughly unchanged total environmental exposure across the previous years - for waiving the ERA is not possible.

The applicant considers that the generics approach is sufficient for Sertraline Medical Valley, mainly based on claim that the percentage of increase cannot be considered significative, especially considered globally across the EU – which is contradicted by the submitted IQVIA data for some of the specific member states concerned – and that the competent authorities were satisfied for the reference product ERA (Zoloft tablets). Under the 2006 CHMP ERA framework (which this procedure formally is subordinate to), the demonstrated increase in specific member state consumption would negate the ‘generics ERA waiver’ approach and necessitate a new/full ERA (with new experimental studies for those elements that literature cannot cover; see above comments on the literature ERA).

The 2024 CHMP ERA framework opens up for some additional options. The argument that the ERA of this procedure would be in line with the content of the reference product ERA could possibly be resolved by following Figure 2 in the 2024 CHMP ERA-GL (questions Q2A to Q2D) but it requires at a minimum an attempt at applying for data-sharing. It is legally not possibly to simply refer to another products ERA, so if a proper ERA is available for the reference product or from another equivalent sertraline product owner, then it is recommended that the applicant applies for data sharing (a ‘Letter-of-Access ERA’, see Q2B in the 2024 CHMP ERA-GL). As the present procedure is in its final stages, a committment to conduct such an approach and resolve the ERA issue is appropriate. The alternative is to commit to submit a future ERA following the 2024 CHMP ERA GL recommendations. Such a commitment has been provided by the applicant (see section VIII.2). Until the ERA-issue is resolved, no conclusions can be made regarding the environmental risk status of the product.

Overall, there are no remaining issues for this procedure from a non-clinical perspective.

# IV. CLINICAL ASPECTS

**Pharmacokinetics**
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Sertraline Medical Valley with the reference product Besitran.

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, and therefore there are no restrictions with respect to food in the SmPC of the originator.

*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 C1B01935

*Methods*

This was a single-dose, two-way crossover study conducted in 34 healthy volunteers, comparing Sertraline Hydrochloride, 100 mg, tablets with Besitran, 100 mg, tablets 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 an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for $AUC_{0-72}$ and $C_{max}$. The study was conducted between 2022-06-02 and 2022-06-19.

*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=34.**

| Treatment | $AUC_{0-72}$ ng*h/ml | $C_{max}$ ng/ml | $t_{max}$ h |
|---|---|---|---|
| **Test** | **926.324 ± 377.524** | **32.862 ± 11.078** | **6.33 (4.33-16.00)** |
| **Reference** | **888.736 ± 382.153** | **29.622 ± 10.503** | **8.33 (4.33-12.00)** |
| ***Ratio (90% CI)** | **104.52 (99.39-109.91)** | **111.09 (104.56-118.03)** | **-** |

**$AUC_{0-72}$** 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 %.

A biowaiver was sought for the additional strengths of 25 mg, 50 mg, 150 mg and 200 mg.

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.

From a pharmacokinetic point of view, it is sufficient to establish bioequivalence with only one strength since 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.

For drugs with linear pharmacokinetics the bioequivalence study should in general be conducted at the highest strength. In case the drug substance is highly soluble, selection of a lower strength than the highest is also acceptable. The applicant performed own solubility study and high solubility was shown for sertraline. Thus, absence of studies with the additional strengths of 25 mg, 50 mg, 150 mg and 200 mg is acceptable.

Based on the submitted bioequivalence study, Sertraline Medical Valley is considered bioequivalent with Besitran.

**Pharmacodynamics/Clinical efficacy/Clinical safety**

The product in this application is claimed to be essentially similar to the reference medicinal product. The only difference between the Applicant's product and the reference product is the additional strengths. The indications, dosage, and route of administration are the same as those of the reference medicinal product.

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted in this application. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary. Sertraline is a widely used active substance and the pharmacodynamic, clinical efficacy and safety properties of sertraline are well known. The Applicant provided a clinical overview based on literature review. This is considered appropriate. The overview revealed no new concerns.

**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 Medical Valley.
The MAH submitted version 1.0, DLP 26 April 2023, signed 18 May 2023.

Part II Safety specification

Table SVIII.1 Summary of Safety Concerns

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | • Serotonin syndrome<br>• Suicidality |
| Important potential risks | • Diabetes mellitus<br>• Use in pregnancy<br>• Abnormal bleeding/haemorrhage |
| Missing information | • Use in paediatric patients, especially under age of 6 years |

The safety specification is in line with that of other approved sertraline medicinal products and considered acceptable.

Part III Pharmacovigilance Plan

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

Part V Risk minimisation measures

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

Part VI Summary of the RMP

The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 1.0 signed 18 May 2023 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

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 PL was Spanish.

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

There are no objections to approval of Sertraline Medical Valley, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and 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**

The applicant has not provided an acceptable ERA so no conclusion can be made on the environmental risks for this product. The applicant's argument that the ERA of this procedure would be in line with the content of the reference product ERA could possibly be resolved by following Figure 2 in the 2024 CHMP ERA-GL (questions Q2A to Q2D) but it requires at a minimum an attempt at applying for data-sharing. It is legally not possibly to simply refer to another products ERA, so if a *proper* ERA is available for the reference product *OR* from another equivalent sertraline product owner, then it is recommended that the applicant applies for data sharing (a 'Letter-of-Access ERA', see Q2B in the 2024 CHMP ERA-GL).

A committment to conduct such a data-sharing approach in order to resolve the ERA issue is appropriate. The alternative is to commit to submit a future ERA following the 2024 CHMP ERA GL recommendations (which will also be needed if an invoked Letter-of-Access ERA turns out to be non-satisfactory). In the latter case of submitting a new full ERA, such a commitment should have a due date of 2 to 3 years, at the latest Autumn 2027).

The applicants has provide a Letter of Commitment that they will try to get a proper Letter-of-Access to ERA in order to look for a data-sharing scenario and share the updated ERA with the authorities within 1 year after EoP. In case this approach would not be possible, the applicant commits to submit a full ERA in line with 2024 CHMP ERA-GL within 3 years after EoP.

| Description | Due date |
|---|---|
| Attempt to procure and submit an Letter of Access ERA | 1 year after EoP : ~2025 |
| [OR, if needed] Submit a full ERA in line with 2024 CHMP ERA-GL | Within 3 years after EoP: ~2027 |
| | |

**Quality**

CEP 2018-292-Rev 01 was submitted and assessed during the procedure. However, it has been noted, 2024-10-01, that a new version of the CEP is available. According to the EDQM knowledge database, the current version, CEP 2018-292-Rev 02, was issued 2024-06-26 (Procedure type minor revision). The applicant was not able to provide the current valid version of the CEP within the timeline for the procedure.
A Letter of Commitment stating that the applicant will submit variation to update the CEP within the next 3 months after EoP has been provided.

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

N/A

# VII. APPROVAL

The decentralised procedure for Sertraline Medical Valley, 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, Film-coated tablet was positively finalised on 2024-10-02.

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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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