COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sempavox 100 mg tablets

(sildenafil citrate)

NL/H/4137/004/DC

Date: 7 March 2019

This module reflects the scientific discussion for the approval of Sempavox 100 mg tablets. The procedure was finalised at 24 September 2018. 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
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
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 Sempavox 100 mg tablets from Sandoz BV.

The product is indicated in adult men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

In order for sildenafil to be effective, sexual stimulation is required.

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 Viagra 100 mg tablets (EU/1/98/077) which has been registered in The Netherlands by Pfizer since 14 September 1998 (original product).

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Germany, Denmark, Estonia, Greece, Spain, France, Italy, Lithuania, Latvia, Portugal, Slovenia, United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Sempavox 100 mg tablets are light blue round slightly dotted tablets, with cross breaking notch on both sides and embossment “100” on one side.

And contains as active substance 100 mg of sildenafil, as 140.4 mg of sildenafil citrate.

The tablets are packed in polyvinylchloride-Aclar/aluminium blisters.

The excipients are microcrystalline cellulose (E460), calcium hydrogen phosphate anhydrous (E341), copovidone, croscarmellose sodium (E468), magnesium stearate (E470b), saccharin sodium (E954) and indigo carmine.

II.2 Drug Substance

The active substance is sildenafil citrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white, slightly hygroscopic, crystalline powder. The anhydrous form is manufactured.

The CEP procedure is used for the active substance by both manufacturers. 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. Batch analytical data demonstrating compliance with this specification have been provided for sufficient batches.

Stability of drug substance

The active substance is stable for five years (manufacturer I) and three years (manufacturer II) 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 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. Breakability data is provided for two batches, of which one is manufactured by each manufacturer. The results demonstrate that the requirements of the Ph.Eur. monograph 'Tablets' under 'Subdivision of Tablets', are met. The hardness of the tested tablets complies with the IPC on hardness for all strengths, and is therefore acceptable.

One bioequivalence study has been submitted comparing the 100 mg test product with the reference product.

Pharmaceutical development has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are production of the granules, preparation of the final blend, compression of the tablets, packaging. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for two batches from one manufacturing site in accordance with the relevant European guidelines.

Control of excipients
For the colourant indigo carmine the in-house specification complies with Directive 95/45, regulation 231/2012 and the Ph.Eur. monograph which is considered acceptable. The other excipients comply with the requirements of their respective Ph.Eur. monographs. 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 and includes tests for appearance, identity, dissolution, assay, related substances, uniformity of dosage units 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 analytical data from sufficient batches from the one proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on full scale batches has been provided for batches manufactured at both manufacturing sites. For the one manufacturing site, three batches were placed on stability. 24 months long term stability data (30°C/75% RH) is available. For this manufacturing site, also six months accelerated stability data (40°C/75% RH) is available. No significant up or downward trends are observed. For the other manufacturing site no stability data on of the proposed drug product have been provided. On basis of the data submitted, a shelf life was granted of 36 months.

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 Sempavox has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- As and when the MAH manufactures batches as per registered composition at the second manufacturing site in near future, they will put them on FUST study and will provide the data in case of unexpected results.
- As and when the MAH will manufacture batches as per registered composition at the second manufacturing site, they will generate batch analytical data as per current registered specification prevailing at that time.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Sempavox 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 Viagra 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

Sildenafil citrate 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

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Sempavox 100 mg tablets (Sandoz BV, The Netherlands) is compared with the pharmacokinetic profile of the reference product Viagra 100 mg tablets (Pfizer, Germany).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 26-54 years. Each subject received a single dose (100 mg) of one of the two sildenafil formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours after administration of the products.

A single dose, crossover study to assess bioequivalence is considered adequate. The design of the study is acceptable.

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

All subjects completed the study. Therefore, 36 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=36	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	1207 ± 436	1221 ± 443	356 ± 163	1.2 ± 0.7	4.4 ± 1.0
Reference	1220 ± 481	1235 ± 488	338 ± 147	1.5 ± 1.0	4.4 ± 0.9
***Ratio (90% CI)**	1.00 (0.93 – 1.06)	1.00 (0.93 – 1.06)	1.04 (0.93 – 1.17)	--	--

CV (%)	16.9	16.8	29.1	--	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of N-desmethyl-sildenafil under fasted conditions.

Treatment N=36	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	542 ± 242	554 ± 246	148 ± 58	1.2 ± 0.7	4.2 ± 0.8
Reference	526 ± 223	539 ± 228	141 ± 58	1.4 ± 0.9	4.3 ± 1.2
***Ratio (90% CI)**	1.02 (0.97 – 1.08)	1.02 (0.96 – 1.07)	1.06 (0.96 – 1.17)	--	--
CV (%)	13.5	13.2	25.1	--	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

<u>Conclusion on bioequivalence study</u>
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Sempavox 100 mg tablets is considered bioequivalent with Viagra 100 mg 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 Sempavox.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Hypotension/increased hypotensive effect (especially in patients taking nitric oxide donors) • Non-arteric anterior ischemic optic neuropathy (NAION/eye haemorrhage) • Sudden hearing loss • Priapism
Important potential risks	None
Missing information	• Severe hepatic impairment

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 Viagra. 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 a bridging report making reference to several successfully user tested PL's. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sempavox 100 mg tablets has a proven chemical-pharmaceutical quality and is a generic form of Viagra 100 mg tablets. Viagra 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 Sempavox with the reference product, and have therefore granted a marketing authorisation. The decentralized procedure was finalised with a positive outcome on 24 September 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse