COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Sildenafil Amarox 25 mg, 50 mg and 100 mg, film-coated tablets

# (sildenafil citrate)

# NL/H/4924/001-003/DC

# Date: 1 September 2020

**This module reflects the scientific discussion for the approval of Sildenafil Amarox 25 mg, 50 mg and 100 mg, film-coated tablets. The procedure was finalised on 28 May 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.**

# List of abbreviations

| | |
|---|---|
| ASMF | Active Substance Master File |
| 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 Sildenafil Amarox 25 mg, 50 mg and 100 mg, film-coated tablets from Amarox Pharma B.V.

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 Amarox 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 25 mg, 50 mg and 100 mg, film-coated tablets which has been registered in the EU through centralised procedure EMEA/H/C/000202 by Pfizer Ltd. The date of authorisation was on 14 September 1998.

The concerned member state (CMS) involved in this procedure was Spain.

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

# II. QUALITY ASPECTS

## II.1 Introduction

Sildenafil Amarox 25 mg is a blue colored round, biconvex, film-coated tablet, debossed with 124 on one side and J on the other side. Each tablet contains 35.12 mg of sildenafil citrate equivalent to 25 mg of sildenafil.
Sildenafil Amarox 50 mg is a blue colored, round, biconvex, scored film-coated tablets debossed with 50 on one side and H and J on the other side both letters are separated by the score line. Each tablet contains 70.24 mg of sildenafil citrate equivalent to 50 mg of sildenafil.
Sildenafil Amarox 100 mg is a Blue colored round, biconvex, scored film-coated tablets, debossed with 126 on one side and J on the other side with score line. Each tablet contains 140.48 mg of sildenafil citrate equivalent to 100 mg of sildenafil.

The film-coated tablets are packed in Clear PVC-Aluminium and Clear PVC/PVdc Aluminium foil blisters packs.

The excipients are:
*Tablet core* - cellulose microcrystalline (E460), calcium hydrogen phosphate anhydrous (E341), croscarmellose sodium (E468), magnesium stearate (E470b)
*Tablet coat* - lactose monohydrate, hypromellose 15cp (E464), hypromellose 5cp (E464), titanium dioxide (E171), triacetin (E1518), Indigo Carmine Aluminium Lake (E132)

The three tablet strengths are dose proportional.

## II.2 Drug Substance

The active substance is sildenafil citrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). This is a BCS class IV substance, which is highly hygroscopic, slightly soluble in water and in methanol and practically insoluble in hexane. It contains no chiral carbon. Different polymorphic forms are known, namely Form-I, Form-II, Form-III, anhydrous form, hydrated form and hydrated forms of sildenafil citrate hemicitrate. The drug substance used in the drug product corresponds to the anhydrous form.

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 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 in line with the Ph. Eur. and with the additional requirements indicated on the CEP. In addition, four related compounds have been specified and a limit for the sum of unspecified impurities has been included. Furthermore, tests for particle size distribution and microbial quality have been added. Batch data demonstrating compliance with the drug substance specification have been provided for five batches. The drug substance is tested with methods previously approved by EDQM.

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 has been justified and their functions explained. Several development studies have been performed related to the characterization of the reference product, choice and quantity of the excipients, choice of the manufacturing formula and in vitro comparative study with the reference product. Breakability of the 50 mg and 100 mg tablets is tested in line with the current Ph. Eur. requirements. A bioequivalence study versus the EU reference product Viagra tablets 100 mg has been performed. A biowaiver was proposed for the lower strengths (25 mg and 50 mg). In general, the pharmaceutical development of the product has been adequately performed.

Manufacturing process

Sildenafil citrate film-coated tablets are manufactured with a wet granulation method. This is a standard process which consists of blending, slugging, milling, lubrication, compression and film-coating. The process has been properly described. Process validation data have been presented for three batches per strength.

Control of excipients

The excipients are tested according to the corresponding Ph. Eur. Additional tests have been included in the specifications of cellulose microcrystalline, croscarmellose sodium and magnesium stearate. The coating agents are tested according to in-house methods, which are similar to the suppliers methods. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identity, average weight, water content, uniformity of dosage units, dissolution, related substances, assay, microbial quality, identification of colourants, resistance to crushing and breakability. The release and shelf life specifications are aligned. The proposed dissolution limit (NLT 85 % (Q) in 15 min) is acceptable. The specified impurities have been characterised, and the risk of elemental impurities in the drug product properly assessed. Analytical data from the proposed production site have been provided for three full-scale batches of drug product, demonstrating compliance with the release specification. The absence of nitrosamine impurities in the drug product has been demonstrated.

Stability of drug product

Stability data on the product have been provided for three pilot batches for each strength stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The stability studies are performed according to the ICH guideline. The batches were stored in PVC/Alu (blisters). Under long-term and accelerated conditions the product remained stable; no specific trends or out-of-specifications were observed. Photostability data are available for the drug product outside the primary packaging. The claimed shelf life of 24 months has been granted without special storage conditions.

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 Sildenafil Amarox 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 Sildenafil Amarox 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 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 Sildenafil Amarox 100 mg (Amarox Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Viagra 100 mg tablets (Pfizer Ltd, UK).

The choice of the reference product in the bioequivalence study is justified as the reference product has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver has been granted for the 25 mg and 50 mg strengths, as the following conditions were met:

- The tablets have been manufactured by the same manufacturing process.
- The tablets are dose proportional.
- Sildenafil shows linear pharmacokinetics and the bioequivalence study is carried out with the highest strength.
- Comparable dissolution was demonstrated at pH 1.2, 4.5 and 6.8; the data show limited dissolution at pH 6.8. It was however demonstrated that the limited dissolution is drug related and not formulation related.

Bioequivalence studies

*Design*

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 21-49 years. Each subject received a single dose (100 mg) of one of the 2 sildenafil 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 8 days.

Blood samples were collected pre-dose and at 0.16, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

The design of the study is acceptable. According to the SmPC, the tablets can be taken with or without food. As such, the fasting condition applied in the study is considered adequate..

*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*

One subject was withdrawn in Period I due to an adverse event. Thirty-nine subjects completed the study and the data of these 39 subjects were included in the statistical analysis.

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

| Treatment N=39 | $AUC_{0-t}$ (ng.h/ml) | $AUC_{0-\infty}$ (ng.h/ml) | $C_{max}$ (ng/ml) | $t_{max}$ (h) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|
| **Test** | 2505 ± 982 | 2550 ± 1000 | 845 ± 442 | 1.1 ± 0.8 | 4.5 ± 1.0 |
| **Reference** | 2524 ± 956 | 2569 ± 982 | 839 ± 451 | 1.0 ± 0.7 | 4.5 ± 0.9 |
| ***Ratio (90% CI)** | 1.00 (0.94 – 1.05) | -- | 1.03 (0.92 - 1.15) | -- | -- |
| **CV (%)** | 14.8 | -- | 29.6 | -- | -- |

**$AUC_{0-\infty}$** 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*

Conclusion on bioequivalence study

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 Sildenafil Amarox 100 mg is considered bioequivalent with Viagra 100 mg.

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 Sildenafil Amarox.

**Table 2. Summary table of safety concerns as approved in RMP**

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|---|---|
| Important identified risks | • Hypotension/increased hypotensive effect (especially in patients taking nitric oxide donors)<br>• Non-arteric anterior ischaemic optic neuropathy (NAION)/eye haemorrhage<br>• Sudden hearing loss<br>• 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. Based upon similarities in the textual content, format, design, layout and wording of the PLs, along with an analysis of the key safety messages, the PL for Sildenafil Amarox meets the necessary guidance for being bridged to Sildenafil Hetero 25 mg, 50 mg & 100 mg film-coated tablets. The Parent PL, Sildenafil Hetero, was successfully tested and the testing report is provided.

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

Sildenafil Amarox 25 mg, 50 mg and 100 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Viagra 25 mg, 50 mg and 100 mg, film-coated 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 Sildenafil Amarox with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 May 2020.

## 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 |
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