COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Staxar 50 mg, orodispersible film (sildenafil (citrate))

NL/H/5500/001/DC

Date: 30 January 2023

This module reflects the scientific discussion for the approval of Staxar 50 mg, orodispersible film. The procedure was finalised at 3 November 2022. 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
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PD	Pharmacodynamics
PK	Pharmacokinetics
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of medicinal 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 Staxar 50 mg, orodispersible film, from Farmitalia s.r.l.

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.

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 film-coated tablets (from Upjohn EESV, The Netherlands) which has been registered via centralized procedure in the EEA since 1998 (EU/1/98/077).

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

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

II. QUALITY ASPECTS

II.1 Introduction

Staxar is a blue coloured, rectangular, opaque, non-sticky, orodispersible film and contains as active substance sildenafil citrate equivalent to 50 mg of sildenafil.

Each film is packed in a triple laminate foil sachet and the sachets are packaged in a carton.

The excipients are: hypromellose 50 cps (E464), propylene glycol (E1520), povidone (E1201), anhydrous sodium carbonate (E500), polysorbate 80, poly (vinyl alcohol) (E1203), sucralose, hypromellose 15 cps (E464), sodium lauryl sulphate, neotame, bitterness masker (B.T.M.) NG-410-146-4, raspberry flavour, partly dementholised mint oil and FD & C Blue 1 colour (E133).

II.2 Drug Substance

The active substance is sildenafil citrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Sildenafil citrate is a crystalline powder and is slightly soluble in water and in methanol, and practically insoluble in hexane. It exhibits polymorphism and the same polymorphic form is produced consistently.

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. This information, which has been evaluated by the member states during the procedure, is considered confidential.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. The specification of a substance is the total of quality tests, analytical procedures and acceptance criteria (limits) this substance has to adhere to. The test for identification of polymorphism is performed according to an in-house method which has been adequately validated. Batch analytical data demonstrating compliance with the specification parameters have been provided for two product scale batches.

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) and is therefore considered confidential.

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 aim of the development was to develop a product similar to the reference product.

The MAH discussed the compatibility of the excipients and their effect on the physicochemical characteristics of the finished product (including assay, content uniformity, dissolution and related substances as well as taste, folding endurance and disintegration). The manufacturing process was selected based on the characteristics of the formulation. Bioequivalence of the final formulation with the reference product was demonstrated in a bioequivalence study, discussed in section IV.2 (Pharmacokinetics). Supporting comparative dissolution data showed a rapid and similar dissolution at pH 1.2 and 4.5, and a slower dissolution at pH 6.8, which was acceptable.

Manufacturing process

The process is considered non-standard. First, the excipients are dispensed and then the ingredients including the active substance are mixed into a dispersion. The dispersion is then casted using a casting machine. The solvent casting technique was selected as the manufacturing process because the excipients are soluble in water. The film is then cut, slit and packaged. The manufacturing process has been adequately validated according to

relevant European guidelines. Process validation data for the product have been presented for three full scale batches.

Control of excipients

The excipients comply with the relevant Ph.Eur. and in-house requirements. These specifications were acceptable.

Quality control of drug product

The finished product specifications were adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, identity of colourant, average weight, uniformity of weight, uniformity of dosage units, dissolution, assay, degradation products, microbial content and water content. Limits in the specification have been justified and were considered appropriate for adequate quality control of the product.

Because of the high solubility of the active substance, it was not possible to develop a dissolution method with discriminatory capacity with regard to a quantitative change in content of the excipient hypromellose. Considering the high solubility of the substance and that of the final product (orodispersible film), dissolution was not considered the most critical quality attribute of this drug product and the dissolution method was considered acceptable.

There is a possibility of the formation of nitrosamine impurities from sildenafil citrate. An adequate nitrosamines risk evaluation report was provided by the MAH. Three commercial scale substance batches were tested for these impurities and those were found to be well below the limits. Considering these results and the fact that no nitrites are present in the excipients, further testing was not deemed to be required.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three production scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three product scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline and the batches were stored in the commercial packaging. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. A shelf life of 24 months was granted and, as stated in the SmPC, this medicinal product does not require any special storage condition.

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 could be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Staxar 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 Staxar is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was 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 was made to the preclinical data obtained with this innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there was no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies were 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 member states agreed that no further clinical studies are required, besides the bioequivalence study discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Staxar 50 mg, orodispersible film (Farmitalia s.r.l., Italy) was compared with the pharmacokinetic profile of the reference product Viagra 50 mg film-coated tablet (Upjohn EESV, The Netherlands). The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Bioequivalence study

Design

An open label, balanced, randomized, two-treatment, two-period, two sequence, single oral dose, crossover bioequivalence study was carried out under fasted conditions in 26 healthy male subjects, aged 22-42 years. Each subject received a single dose (50 mg) of one of the two sildenafil formulations after an overnight fast of at least 10 hours. The Viagra tablet (reference product) was orally administered with 240 mL water, or the Staxar (test product) was administrated without water and the film was allowed to disintegrate on the tongue after which it was swallowed without chewing or crushing. There were two dosing periods, separated by a washout period of 9 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 12, 18 and 24 hours after administration of the products.

The SmPCs of both products recommend administration without food. When sildenafil is taken with food, the rate of absorption is reduced (with a mean delay in the time in which the maximum plasma concentration is reached (t_{max}) of 60 minutes and a mean reduction in the maximum plasma concentration (C_{max}) of 29%). Therefore the fasted condition in this study was deemed appropriate.

The design of the study was acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and was considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation were considered acceptable.

Results

One subject was withdrawn from the study in Period II due to non-compliance with the protocol. This left 25 subjects eligible for pharmacokinetic analysis.

The area under the curve value (AUC), presented in the tables below, is a measure of the concentration of sildenafil or piperazine N-desmethylsildenafil in the plasma of test subjects after oral administration. The new (test) product and the reference product should be comparable in AUC values, as well as in the maximum plasma concentration reached (C_{max}). The time at which this is reached (t_{max}) is also compared. The ratio (90% confidence interval) represents the similarity between the two products, with an acceptance range of 0.80 to 1.25.

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

Treatment N=25	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	1217 ± 429	1236 ± 435	347 ± 136	1.0 (0.5 - 2.5)
Reference	1148 ± 537	1164 ± 545	334 ± 140	1.0 (0.5 - 4.0)
***Ratio (90% CI)**	1.10 (0.99 – 1.21)	1.10 (1.00 – 1.21)	1.03 (0.93 – 1.15)	--

$AUC_{0-\infty}$	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 the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval
*****	Ln-transformed values

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of piperazine N-desmethylsildenafil under fasted conditions.

Treatment N=25	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	343 ± 168	359 ± 177	51.6 ± 22.9	1.0 (0.5 - 2.5)
Reference	322 ± 168	338 ± 181	50.3 ± 20.1	1.0 (0.5 - 6.0)
***Ratio (90% CI)**	1.05 (0.96 – 1.15)	1.06 (0.96 – 1.16)	0.99 (0.89 – 1.09)	--

$AUC_{0-\infty}$	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 the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval
*****	Ln-transformed values

<u>Conclusion on bioequivalence study</u>

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, Staxar is considered bioequivalent with Viagra.

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 Staxar.

Table 3. Summary of safety concerns as approved in RMP

Important identified risks	• Nitrate interaction
Important potential risks	• Non-arteritic anterior ischaemic optic neuropathy (NAION)/ eye haemorrhage • Sudden hearing loss • Eye haemorrhage
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. 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 was 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 Viagra 50 mg film-coated tablets (EU/1/98/077) for content and Sildenafil ZIM 10 mg orodispersible films for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and design of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Staxar 50 mg, orodispersible film has a proven chemical-pharmaceutical quality and is a generic form of Viagra 50 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 Staxar with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 November 2022.

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
N/A	N/A	N/A	N/A	N/A	N/A