COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sildenafil Aurobindo
25 mg, film-coated tablets
(sildenafil citrate)

NL/H/5488/003/DC

Date: 20 March 2024

This module reflects the scientific discussion for the approval of Sildenafil Aurobindo 25 mg, film-coated tablets. The procedure was finalised at 9 November 2016 in Portugal (PT/H/0886/003/DC). After a transfer on 25 January 2023, the current RMS is the Netherlands. 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
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
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 agreed in granting a marketing authorisation for Sildenafil Aurobindo 25 mg, film-coated tablets, from Aurobindo Pharma B.V., The Netherlands.

Sildenafil Aurobindo 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 Aurobindo to be effective, sexual stimulation is required.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

This decentralised application concerns a generic version of Sildenafil citrate, under the trade name Sildenafil Aurobindo. The originator product is Viagra® (film-coated tablets), which is registered in European Union by Pfizer, since September 14, 1998.

The marketing authorization was granted on 2 May 2017 based on Directive 2001/83/EC article 10.1 (a) (iii) first paragraph.

The Concerned Member states (CMS) involved for this procedure were: France, Germany, Italy, Malta and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Sildenafil Aurobindo 25 mg, film-coated tablets. White to off-white, round (7.1 mm diameter), biconvex film-coated tablets debossed with “SL” on one side and 25 on the other side.

The other excipients are:
Tablet core: Calcium hydrogen phosphate anhydrous, cellulose microcrystalline, croscarmellose sodium, silica colloidal anhydrous, magnesium stearate.

Tablet coat: Lactose monohydrate, hypromellose 15cP, titanium dioxide (E171), triacetin.

Sildenafil Aurobindo 25 mg film-coated tablets are available in clear PVC/PVdC- Aluminium foil blisters.

Pack sizes:
Blister pack: 2, 4, 8, 12 and 24 film-coated tablets.

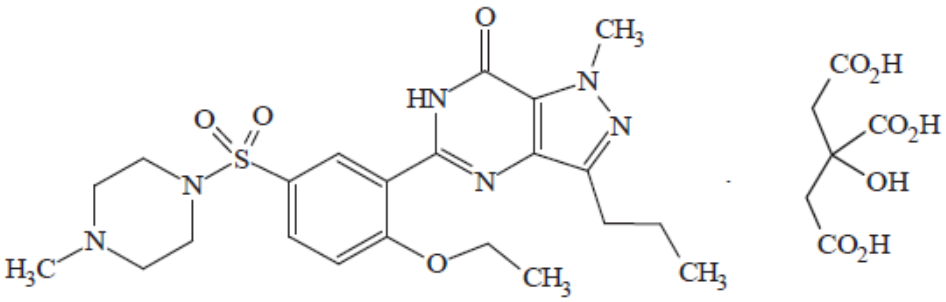
Not all pack sizes may be marketed.

II.2 Drug Substance

General Information

Nomenclature
INN: Sildenafil Citrate.
Chemical Name: 5-[2-Ethoxy-5-[(4-methylpiperazin-1-yl) sulfonyl] phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate).
CAS number: 171599-83-0

Structure



Molecular formula: C22H30N6O4S.C6H8O7
Molecular weight: 666.70

General properties
Appearance: White to off-white crystalline powder. Slightly Hygroscopic.

Solubility: Slightly soluble in Water and in Methanol, Practically insoluble in n-Hexane
Melting range: 183°C to 190°C.

Polymorphism: The manufacturer consistently produces an identical Crystalline Sildenafil Citrate drug substance.

Isomerism: Sildenafil citrate contains no chiral center, and so it does not exhibit isomerism.

Quality control of drug substance
The chemical-pharmaceutical documentation and Quality Overall Summary in relation to Sildenafil Aurobindo are of sufficient quality in view of the present European regulatory requirements. The control tests and specifications for drug substance product are adequately drawn up.

Stability of drug substance
Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of 48 months is justified.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained.

Quality control of drug product
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 3 batches. The batch analysis results show that the finished products meet the specifications proposed.

Stability of drug product
The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. The proposed shelf-life of 24 months and no specific storage conditions are required. Following completion of the procedure, new data were submitted supporting the extension of the shelf life to 3 years (PT/H/0886/001-3/IB/018). This was considered acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of sildenafil are well known. As sildenafil is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Sildenafil Aurobindo 25 mg, film-coated tablets 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

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Bioequivalence study
To support this application, the Applicant has submitted as report a single-dose bioequivalence study conducted in healthy subjects under fasting conditions with the strength of Sildenafil 100 mg tablets (A188-11) entitled:

"An open label, randomized, two-treatment, two-sequence, two-period, crossover, single-dose comparative oral bioavailability study of Sildenafil 100 mg Tablets (Test) of Aurobindo Pharma Limited, India and Viagra 100 mg Tablets (Reference) of Pfizer Limited, UK in 42 healthy adult, male human subjects under fasting conditions."

Both products (Test and Reference) are oral immediate release tablets. Taking into account the recommendations of the SmPC of Reference product, sildenafil film-coated tablets can be administered regardless of meals. Therefore, the basis of the BE study (single-dose BE study under fasting conditions) is acceptable.

Conclusion on bioequivalence study
Based on the submitted bioequivalence study Sildenafil Aurobindo 25 mg, film-coated tablets is considered bioequivalent with Viagra 25 mg film-coated tablets.

Biowaiver
The Bio-equivalence study was carried out on Sildenafil Aurobindo 100 mg film-coated tablets. Based on acceptable Bio-equivalence study for Sildenafil Aurobindo 100 mg film-coated tablets, a bio-waiver is requested for Sildenafil Aurobindo 25 mg film-coated tablets as per following considerations:

1. *Sildenafil 25 mg and 100 mg Tablets are manufactured by the same manufacturer i.e. Aurobindo Pharma Limited (Unit-VII) and using the same manufacturing process.*

2. *After oral dosing of sildenafil AUC and Cmax increase in proportion with dose over the recommended dose range (25-100 mg). [eMC_UK_Viagra tablets (2010)].*

3. *The qualitative composition of Sildenafil 25 mg Tablets is the same as that of Sildenafil 100 mg Tablets.*

4. *Sildenafil 25 mg Tablets are dose proportional with Sildenafil 100 mg Tablets. Thus, the ratio of amount of active substance and the excipients is the same for all the strengths.*

The conditions required for a biowaiver for the additional strength of Sildenafil 25 mg film-coated tablets seem to be fulfilled, based on the demonstration of bioequivalence with the strength of 100 mg film-coated tablets.

IV.2 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 Aurobindo 25 mg, film-coated tablets.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension • Nitrate interaction • Concomitant use with ritonavir • Priapism • Concomitant use with other treatments for erectile dysfunction • Non-arteritic anterior ischaemic optic neuropathy (NAION) • Concomitant use with alpha-blockers • Anti-platelets effect in the presence of sodium nitroprusside • Lactose intolerance • Concomitant use with CYP3A4 inhibitors
Important potential risks	None
Missing information	None

IV.3 Discussion on the clinical aspects

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorized medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. This generic product can be used instead of its reference product.

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.

The proposed PIL text is in line with Viagra 25 mg, 50 mg and 100 mg tablets which was centrally approved by EMEA (Reference no: EMEA/H/C/000202) and the date of issue of marketing authorization valid throughout the European Union is 14.09.1998. EPAR of the Viagra 25 mg, 50 mg and 100 mg tablets, user test shows that the patients/ users are able to act upon the information that it contains

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application for Sildenafil Aurobindo 25 mg, film-coated tablets contains adequate quality, non-clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.

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
894518-20	RMS Transfer PT/H/0886/001-003 to NL/H/5488/001-003	Yes	7 September 2023	Yes	N.A.
NL/H/5488/ IA/024/G	- Deletion of manufacturing sites for an active substance. - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product: Secondary packaging site.	No	7 July 2023	Yes	N.A.
NL/H/5488/ 001-2/IA/025	Submission of a new or updated Ph. Eur. certificate of suitability: For an active substance.	No	7 September 2023	Yes	N.A.