COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sildenafil Aurobindo
50 mg and 100 mg, film-coated tablets
(sildenafil citrate)

NL/H/5488/001-002/DC

Date: 20 March 2024

This module reflects the scientific discussion for the approval of Sildenafil Aurobindo 50 mg and 100 mg, film-coated tablets. The procedure was finalised at 12 July 2013 in Portugal (PT/H/0886/001-002/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, 50 mg, 100 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 claiming essential similarity with the reference product Viagra, 50 mg, 100 mg, film-coated tablets, from Pfizer, Ltd., which is registered in European Union by Pfizer, since September 14, 1998.

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 only 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.

The marketing authorization was granted on 28 May 2014 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, contain sildenafil as the active substance.

The core tablets excipients are: calcium hydrogen phosphate anhydrous, cellulose microcrystalline, croscarmellose sodium, silica colloidal anhydrous, and magnesium stearate. Film-coating excipients are: lactose monohydrate, hypromellose 15cP, titanium dioxide (E171) and triacetin.

II.2 Drug Substance

Manufacturing process
The chemical-pharmaceutical documentation and Expert Report in relation to Sildenafil Aurobindo are of sufficient quality in view of the present European regulatory requirements.

Quality control of drug substance
The control tests and specifications for drug substance product are adequately drawn up.

Stability of drug substance
The proposed retest period of 24 months, when stored in a well-closed container, at controlled room temperature for the active substance is justified.

II.3 Medicinal Product

Pharmaceutical development
The documentation provided complies with relevant EU guidelines and directives. The development of the product has been described, the choice of excipients is justified and their functions explained.

Manufacturing process
Manufacture is performed in accordance with cGMP and consistency in quality and homogeneity is demonstrated.

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 for each. 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 2 years, without special storage conditions is considered acceptable. 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.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of sildenafil are well known. As sildenafil is a widely used, well-known active substance, no further studies are required and the applicant provides none. An overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Sildenafil is an oral therapy for erectile dysfunction. In the natural setting, i.e. with sexual stimulation, it restores impaired erectile function by increasing blood flow to the penis.
The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood.

IV.2 Pharmacokinetics

The application concerns 50 mg and 100 mg film-coated tablets proposed for marketing. The bioequivalence study was carried out with the 100 mg strength. The conditions for bio-waivers in sections 5.4 of the Bioequivalence Guideline have been fulfilled: same manufacturer and process, drug input has been shown to be linear over the therapeutic dose range, same qualitative composition, same ratio between active and excipients and similar dissolution profile under identical conditions between the 100 mg and 50 mg strengths.

IV.3 Clinical efficacy & Clinical safety

Sildenafil has a well-recognised efficacy and acceptable level of safety in the indications approved for 50 mg and 100 mg, film-coated tablets, and has been widely used in many countries.

IV.4 Pharmacovigilance System

The applicant submitted a signed Summary of the Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements, it is considered acceptable.

IV.5 Risk Management Plan

The applicant provided a Risk Management Plan RMP for Sildenafil Aurobindo. Due to none additional risk minimization activities have been prescribed for the reference medicinal product, no additional risk minimization activities were proposed for Sildenafil Aurobindo.

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

Important identified risks	None
Important potential risks	None
Missing information	None

V. USER CONSULTATION

The readability of the package leaflet was successfully demonstrated.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application for Sildenafil Aurobindo 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.