COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Silandyl 25 mg, 50 mg, 75 mg and 100 mg, orodispersible film (sildenafil citrate)

NL/H/5579/001-004/DC

Date: 15 September 2023

This module reflects the scientific discussion for the approval of Silandyl 25 mg, 50 mg, 75 mg and 100 mg, orodispersible film. The procedure was finalised on 8 June 2016 in Portugal (PT/H/1340/001-004/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 Silandyl 25 mg, 50 mg, 75 mg and 100 mg, orodispersible film, from IBSA Farmaceutici Italia S.r.L.

Silandyl 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 Silandyl to be effective, sexual stimulation is required.

A comprehensive description of the indications and posology is given in the SmPC.

This Decentralized Procedure application concerns a generic version of Sildenafil, 25 mg, 50 mg, 75 mg and 100 mg. The application is an abridged application according to Directive 2001/83/EC:
- Article 10.1 for Silandyl 25, 50 and 100 mg, orodispersible film, as a generic application of Viagra 25, 50 and 100 mg film-coated tablets by Pfizer Limited, registered since 14 Sept 1998 in the RMS;
- Article 10.3 for Silandyl 75 mg, orodispersible film, as hybrid application (this strength is not available for Viagra).

The originator product is Viagra, 25 mg, 50 mg, 100 mg, film-coated tablets, by Pfizer Limited, UK, authorized in the EU in 1998.

The marketing authorization was granted on 26-12-2018 based on Directive 2001/83/EC article 10.1 (a) (iii) first paragraph and the Article 10.3 and Marketing Authorisation Holder is IBSA Farmaceutici Italia S.r.L.

The concerned member states (CMS) involved in this procedure were Poland, Slovakia and United Kingdom (Northern Ireland).

II. QUALITY ASPECTS

II.1 Introduction

Orodispersible film.

25 mg:
Rectangular, flexible, opaque light blue film strip (30 mm x 15 mm).
50 mg:
Square, flexible, opaque light blue film strip (30 mm x 30 mm).
75 mg:
Rectangular, flexible, opaque light blue film strip (30 mm x 45 mm).
100 mg:
Rectangular, flexible, opaque light blue film strip (40 mm x 45 mm).

The other excipients are: Maltodextrin, Glycerol, Polysorbate 20, Propylene glycol monocaprylate, Polyvinyl acetate dispersion 30%, Lemon and Grapefruit flavours (Lemon essential oil, Citral, Linalool, Grapefruit essential oil, Orange essential oil, Nootkaton, Butylated hydroxyanisol E320, Ascorbic acid E300, Maltodextrin, Arabic gum E414), Sucralose, Titanium dioxide, Indigotine.

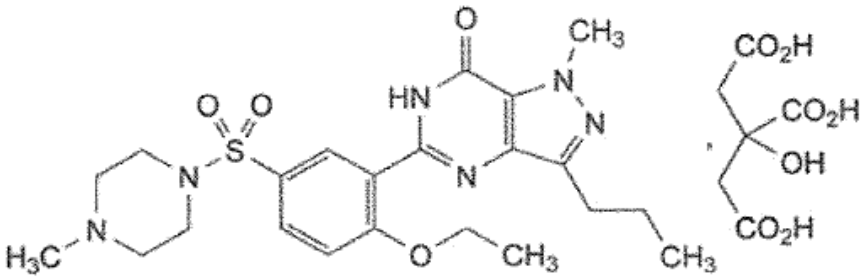
Each orodispersible film is packed in a PET/Foil Extrusion laminate sachet.

Pack size of 2, 4, 8 or 12 orodispersible films.
Not all pack sizes may be marketed.

II.2 Drug Substance

Nomenclature
The drug substance is Sildenafil Citrate (INN) or 1-[[3-(4,7-Dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine or 5-[2-Ethoxy-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl]-1-methyl-3-3propyl-1,6-dihydro-7Hpyrazolo[4,3-d]pyrimidin-7-one dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate and presents the CAS Registry number 171596-29-5.

Structure
The drug substance Sildenafil Citrate, with the molecular formula C22H30N6O4S.C6H8O7 and molecular weight 666.7, presents the following structural formula:



General Properties
The drug substance Sildenafil Citrate is a white or almost white crystalline powder, slightly hygroscopic, slightly soluble in water and in methanol, practically insoluble in hexane. Sildenafil citrate has a melting point of 185-190°C. There is no isomerism in Sildenafil citrate as no asymmetric carbon is observed and thus this drug substance is not optically active. In respect to polymorphism it is stated that Sildenafil citrate produced is an anhydrous form.

Quality control of drug substance
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. As stated in the CEP the retest period for Sildenafil citrate API is 3 years if stored in double polyethylene bags placed in a card board drum.

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 36 months is acceptable for the 75 mg and 100 mg strengths. No special requirements for storage if kept in the original package to protect from moisture.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to Sildenafil IBSA are of sufficient quality in view of the present European regulatory requirements.

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 Silandyl 25 mg, 50 mg, 75 mg and 100 mg, orodispersible film 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 Introduction

The MAA, IBSA, had developed a sildenafil orodispersible film (ODF) containing sildenafil citrate. The film dissolves very rapidly in the oral cavity with no need for drinking or chewing, thus providing an alternative to the marketed solid oral forms (tablets) in the treatment of erectile dysfunction (ED).
Sildenafil ODF IBSA has been developed in four strengths:
- 25 mg, 50 mg, 75 mg and 100 mg sildenafil ODF.
As per discussion with the Portuguese Regulatory Authority – Infarmed -, the legal basis for Decentralized Procedure (DCP) of Sildenafil IBSA is:
- Article 10.1 for Sildenafil IBSA 25, 50 and 100 mg ODF, as a generic application of Viagra® 25, 50 and 100 mg tablets; and
- Article 10.3 for Sildenafil IBSA 75 mg ODF, as hybrid application (this strength is not available for Viagra®, but it has been approved for a generic Sildenafil Sandoz) (Sildenafil Sandoz ODF - EPAR - 03sep13).
Before the clinical development started, it has been agreed with Infarmed on October 2013 that, being the application based on generic/hybrid versions of already authorized immediate release solid oral forms, a bioequivalence (BE) study performed with the highest strength – 100 mg – would have been sufficient to support the application. Additionally, and according to section 4.1.6 of current edition of EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/ 1401/98 Rev. 1/Corr **, 20JAN10), a study comparing the highest 100 mg strength to the originator product would have been adequate.

IV.2 Pharmacokinetics

Bioequivalence studies
The MAA has performed a single dose, randomised, 2-way cross-over bioequivalence (BE) study in order to assess that new Sildenafil 100 mg ODF and marketed Viagra® 100 mg film-coated tablet, are bioequivalent after single dose administration to healthy male volunteers. The clinical development program followed by the MAA for Sildenafil IBSA seems to be appropriate and compliant with the current European guidance on the investigation of BE and the preliminary discussion and agreement with the Portuguese Regulatory Authority.

Biowaiver
The justification for biowaiver of the strengths 25 mg, 75 mg and 50 mg has been provided.

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 Silandyl 25 mg, 50 mg, 75 mg and 100 mg, orodispersible film.

Table 1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Nitrate interaction Severe hepatic impairment
Important potential risks	Non-arteritic anterior ischaemic optic neuropathy (NAION) Sudden hearing loss Eye haemorrhage
Missing information	Severe hepatic impairment

IV.4 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

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application for Silandyl 25 mg, 50 mg, 75 mg and 100 mg, orodispersible film 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
935971, 935973-5	RMS transfer from PT/H/1340/001-004 to NL/H/5579/001-004.	Yes	07-08-2023	Approved	N.A.