COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sildenafil Interdos 50 mg and 100 mg film-coated tablets

(sildenafil citrate)

NL/H/4791/001-002/MR

Date: 13 August 2019

This module reflects the scientific discussion for the approval of Sildenafil Interdos 50 mg and 100 mg film-coated tablets. The procedure was finalised on 24 May 2019. 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 Interdos 50 mg and 100 mg film-coated tablets from Interdos Pharma BV.

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 Interdos to be effective, sexual stimulation is required.

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

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Viagra 50 and 100 mg tablets. Viagra has been registered in the EEA through a centralised procedure by Pfizer Ltd. The date of authorisation was on 14 September 1998.

The concerned member state (CMS) involved in this procedure was the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Sildenafil Interdos 50 mg is a pale blue to blue, capsule-shaped tablet, debossed with "SL50" on one side and plain on other side. Each tablet contains sildenafil citrate equivalent to 50 mg sildenafil.

Sildenafil Interdos 100 mg is a pale blue to blue, capsule-shaped tablets, debossed with "SL100" on one side and plain on other side. Each tablet contains sildenafil citrate equivalent to 100 mg sildenafil.

The film-coated tablets are packed in PVC/aluminum blisters.

The excipients are:
Tablet core - calcium hydrogen phosphate, microcrystalline cellulose, croscarmellose sodium, colloidal silica, magnesium stearate

*Film coat*ing - hypromellose (E464), indigo carmine (E132), lactose monohydrate, titanium dioxide (E171), triacetin (E1518)

The two 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.). The active substance is a white or almost white, slightly hygroscopic, crystalline powder, which is slightly soluble in water and slightly hygroscopic. It does not show polymorphism or enantiomerism.

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 drug substance specification complies with the requirements of the current Ph. Eur. monograph for sildenafil citrate, with in-house requirements for polymorphic form, particle size and the microbiological quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. The analytical methods have been adequately described and validated. Batch analytical data demonstrating compliance with the requirements of the proposed specification have been provided for three full-scale batches.

Stability of drug substance
The CEP does not include a re-test period nor covers a storage condition. Stability data on the active substance have been provided three pilot-scale validation batches and three validation batches at 30°C ± 2°C / 75% ± 5% RH (up to 60 months) and 40°C ± 2°C / 75% ± 5% RH (6 months). Based on the provided stability data, the claimed re-test period of 60 months has been granted, with the storage condition “Store in the original package to protect against moisture”.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and

their functions explained. All excipients used are well known. The choice of packaging material and manufacturing process is justified.
The test product batch used in the bioequivalence study has the same composition as the intended commercial batches. Comparative dissolution studies show similar dissolution profiles for the 100 mg tablet, supporting the bioequivalence studies. The biowaiver of strength can be accepted, as comparative dissolution has been shown at pH 1.2, 4.5 and 6.8.
The discriminatory power of the QC dissolution method, adopted from the USP monograph for sildenafil citrate tablets, is demonstrated.

Manufacturing process
The manufacturing process consists of sifting, dry mixing and blending, dry granulation, milling and sifting and final blending with the extra granular material. These steps are followed by compression, film-coating and packing. The manufacturing process is considered a standard process, and is described in sufficient detail.
Acceptable process validation data were presented for the three full-scale batches of common blend, and pilot scale batches of each strength manufactured from this blend. All predefined acceptance criteria were met and all batches complied with the proposed release specification.

Control of excipients
The excipients comply with Ph.Eur. monographs and in-house requirements. The proposed specifications include the relevant functionality-related characteristics of their respective Ph. Eur. monograph. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, tablet size, water content, uniformity of dosage units by content uniformity, dissolution, assay, related substances and microbiological limits. The release and shelf-life limits for all parameters are identical for all parameters. The dissolution criteria are set in accordance with the 'Reflection paper on the Dissolution specification for generic oral immediate release products'. The specifications for the drug product are acceptable.
The analytical methods have been adequately described and validated. Batch analytical data of three pilot scale batches for each strength show compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for three pilot-scale batches of each strength stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). In addition, stability data for the 100 mg biobatch stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months) is available. The conditions used in the stability studies are in accordance with the ICH stability guideline. The batches were stored in PVC – Alu blisters. Under accelerated and long-term conditions no out-of-specification results or significant changes have been observed in any of the parameters tested. No specific up or downward trends are seen.
Photostability studies are conducted in line with the requirements of ICH Q1C and showed that the tablets stored outside the packaging were not sensitive to light.

Based on the results provided, a shelf life of 24 months has been granted, with the following storage conditions: “Store in the original package in order to protect from moisture” and “This medicinal product does not require any special temperature 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. Magnesium stearate is of vegetable origin (derived from palm oil).

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Sildenafil Interdos 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 Interdos 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 Interdos 100 mg (Interdos Pharma BV, the Netherlands) is compared with the pharmacokinetic profile of the reference product Viagra 100 mg tablets (Pfizer Ltd, UK) and Viagra 100 mg (Pfizer Inc, USA).

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing. The choice of the reference product in the bioequivalence study has been justified, as it has been authorised through a centralised procedure. As only the UK reference product is representative for the European market, the data on the US reference product have not been assessed.

Biowaiver

The following prerequisites for requesting a biowaiver for the 50 mg strength based on the bioequivalence study with the highest strength of 100 mg are met:

- the strengths are manufactured by the same manufacturing process.
- the compositions are qualitatively similar and quantitatively dose proportional.
- plasma pharmacokinetics of sildenafil can be considered dose linear in the dose range of 50-100 mg.
- comparative dissolution data for both strengths of the test formulation show similar dissolution at three pH conditions.

Bioequivalence studies

Design

A single-dose, randomised, three-period, three-treatment, three-sequence, crossover bioequivalence study was carried out under fasted conditions in 42 healthy male subjects, aged 19-38 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 of at least 10 hours. There were 3 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-does and at 0.25, 0.50, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

The design, including the blood sampling scheme, is acceptable. As sildenafil citrate may be taken with or without food, a study under fasted conditions is required. The mean half-life of sildenafil is about 3-5 hours. Therefore plasma sampling until 24 hours after dosing and a wash-out period of 7 days are considered sufficient.

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
Two subjects did not report to the clinical facility for period 2 check-in and another two subjects did not report to the clinical facility for period 3 check-in and hence were considered as dropouts. Statistical analysis was performed on the data obtained from subjects completing both treatments with test and EU reference product (N=38).

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

Treatment N=38	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	3214 ± 1347	3347 ± 1644	979 ± 366	1.25 (0.25 – 2.5)	4.8 ± 2.1
Reference	3021 ± 1344	3151 ± 1646	985 ± 464	1.13 (0.25 – 3.5)	4.9 ± 2.2
***Ratio (90% CI)**	1.07 1.02 - 1.13	--	1.03 (0.94 – 1.14)	--	--

$AUC_{0-\infty}$ 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} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Sildenafil Interdos 100 mg is considered bioequivalent with Viagra 100 mg tablets.

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).

Safety
A total of sixteen adverse events were reported by thirteen subjects in the study; five adverse events during period 1, one adverse event during period 2, three adverse events during period 3 and seven adverse events during post study clinical laboratory safety evaluation (clinically significant changes in laboratory parameters). All adverse events were mild in intensity. Out of the observed sixteen adverse events, the relationship of eleven adverse events in the test (T) and reference (R1 and R2) group was judged as possibly

related to the study drug and the relationship of five adverse events in the test (T) and reference (R1 and R2) was judged as unlikely related to the study drug. Eleven subjects having adverse events were followed up till resolution. Two subjects, having adverse events during post study safety evaluation, did not report to the clinical facility in spite of repeated follow up and hence were considered as lost to follow up.
No severe, serious or life-threatening adverse events were reported during the course of the study. The test and reference products were comparable in their safety and tolerability. Hence the test product was found to be safe and well tolerated upon single dose administration in healthy, adult, males under fasting conditions.

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 Interdos.

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

Important identified risks	• Nitrate interaction
Important potential risks	• Non-arteritic anterior ischaemic optic neuropathy (NAION) • 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. 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

The package leaflet (PL) 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 questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL 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

Sildenafil Interdos 50 mg and 100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Viagra 50 mg and 100 mg 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. Sildenafil Interdos was registered in the Netherlands on 15 August 2018.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Sildenafil Interdos with the reference product, and has therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 24 May 2019.

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