COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sildenafil Umedica 25 mg film-coated tablets (sildenafil citrate)

NL License RVG: 125767

Date: 28 October 2021

This module reflects the scientific discussion for the approval of Sildenafil Umedica 25 mg film-coated tablets. The marketing authorisation was granted on 1 July 2021. 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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Sildenafil Umedica 25 mg film-coated tablets, from Umedica Netherlands B.V.

Sildenafil Umedica 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 to be effective, sexual stimulation is required.

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

The submitted dossier concerns a national application in The Netherlands. This national procedure concerns a generic application claiming essential similarity with the innovator product Viagra 25 mg tablets which has been registered in the EEA by Pfizer Limited since 1998 (original product), by the central procedure EU/1/98/077.

The application concerns a line extension to the already approved products Sildenafil Interdos 50 and 100 mg film-coated tablets (RVG 121099 and 121116, respectively). In the Netherlands, Sildenafil 50 and 100 mg film-coated tablets, from Interdos Pharma BV, were authorised through a national procedure in 2018. In 2021, a MAH transfer of Sildenafil 50 and 100 mg tablets has been finalised, from Interdos Pharma BV to Umedica Netherlands B.V.

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

II. QUALITY ASPECTS

II.1 Introduction

Sildenafil Umedica is a film-coated tablet. The tablets are light blue to blue, round and marked “25” on one side and “SL” on the other side. Each tablet contains as active substance sildenafil citrate equivalent to 25 mg of sildenafil.

The tablets are packed in PVC/Aluminium blisters.

The excipients are:
Tablet core – calcium monohydrogen phosphate (E341), microcrystalline cellulose (E460), croscarmellose sodium (E468), colloidal silica (E551) and magnesium stearate (E470b)
Film coating – hypromellose (E464), indigo carmine (E132), lactose monohydrate, titanium dioxide (E171) and triacetin (E1518)

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, slightly soluble in water and 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 European Pharmacopoeia.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

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. In addition to the monograph requirements, the MAH adopted tests and limits for residual solvents, polymorphic form, particle size and the microbiological quality. A description of the methods used and the validation reports of the in-house methods have been provided. Batch analytical data demonstrating compliance with this specification have been provided for seven batches.

Stability of drug substance

The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM. The MAH however claimed a retest period of one year.

II.3 Medicinal Product

Pharmaceutical development

Sildenafil Umedical is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. The proposed dissolution method, adopted from the USP monograph of sildenafil citrate, is acceptable.

The test product batch used in the bioequivalence (BE) study has the same composition as the intended commercial batches. Data on comparative dissolution testing at 3 pHs and the quality control (QC) release medium of the test and reference batches used for BE studies have been provided. The comparative dissolution data in support of the bioequivalence study is generated in conformance with the Guideline on The Investigation of Bioequivalence and is therefore acceptable. An additional biowaiver of strength was requested for the 25 mg

strength based on the bioequivalence study of the highest strength of 100 mg. Since the biobatch was expired, a new drug product batch having a similar dissolution profile was used. Comparative dissolution data at 3 pH's and the QC release medium of the test and reference batches have been provided.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. It 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 whole manufacturing process is considered a standard process, and it is described in sufficient detail. Process validation data on the product have been presented for three full scale batches of common blend, and pilot scale batches of 50 mg and 100 mg strength manufactured from this blend. Additionally, validation data with three pilot scale batches of sildenafil 25 mg strength were provided. 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. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on the monograph for sildenafil in the Ph.Eur. and includes tests for appearance, identification, water content, uniformity of mass, uniformity of dosage unit by content uniformity, dissolution, assay, related substances, residual solvents and microbiological quality. The release and shelf life limits are aligned and acceptable. The analytical methods have been adequately described and validated. Batch analytical data of three pilot scale batches for the 25 mg, 50 mg and 100 mg strengths show compliance with the proposed specifications.

The absence of nitrosamines in the final drug product has been sufficiently demonstrated. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Stability of drug product

Stability data on the product have been provided for three pilot scale batches for each strength stored at 25°C/60% RH (50/100 mg: 36 months; 25 mg: 18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are in accordance with the ICH stability guideline. The batches were stored in PVC/Alu blisters (proposed for commercial supply) 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 ICHQ1C and showed that the tablets stored outside were not sensitive to light. On basis of the data submitted, a shelf life was granted of 24 months. No specific storage conditions need to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The MAH declares that the finished product does not contain any excipients of human or animal origin. Melamine and TSE BSE certificates for the excipients have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Sildenafil Umedica 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 Umedica 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 film-coated tablets 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 MEB 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 MEB agreed that no further clinical studies are required.

For this generic application, the MAH is referring to one bioequivalence study, which is outlined below. In support of the application, a justification is applied for biowaiving for the lower strength of 25 mg.

IV.2 Pharmacokinetics

Based on a bioequivalence study using the 100 mg dose, Sildenafil Umedica (previously Sildenafil Interdos) 100 mg film-coated tablets was previously concluded to be bioequivalent to the innovator, Viagra 100 mg, film-coated tablets (Pfizer Limited, United Kingdom) and Viagra 100 mg (Pfizer Incorporate, United States of America). The MAH has applied for a justification for biowaiving the lower strength of 25 mg based on the bioequivalence study with the highest strength of Sildenafil Umedica, the 100 mg.

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

All strengths are manufactured by the same manufacturing process. The compositions are qualitatively similar and quantitatively dose proportional. The plasma pharmacokinetics of sildenafil can be considered dose linear in the dose range of 25-100 mg. Also, comparative dissolution data for the 25 mg and 100 mg strengths of the test product have shown similar dissolution profiles at three pH conditions. For pH 6.8, this was demonstrated based on comparison of 1x100 mg versus 4x25 mg test tablets as sink conditions were not achievable at this pH for all strengths.

It is noted that the biobatch of Sildenafil 100 mg film-coated tablets was expired. Therefore, the MAH used another batch of Sildenafil 100 mg film-coated tablets for the purpose of dissolution profile comparison between the 100 mg and 25 mg strengths of the test product. The similarity of their dissolution profiles has been demonstrated at pH 4.5 and QC conditions only. The similarity of dissolution profiles of biobatch and reference batch should have also been demonstrated at pH 1.2 and pH 6.8. However, considering that similarity of dissolution profiles of Sildenafil 25 mg film-coated tablets) with the reference product Viagra 25 mg film-coated tablets has been demonstrated in all conditions (pH 1.2, pH 4.5, pH 6.8, QC conditions), this issue was not further pursued.

In conclusion, a biowaiver for the Sildenafil Umedica 25 mg tablet strength, based on the bioequivalence study with the highest strength of 100 mg, is acceptable.

Bioequivalence study

Previously, the MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Sildenafil Umedica 25 mg, film-coated tablets (Umedica Netherlands B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product

Viagra 100 mg, film-coated tablets (Pfizer Limited, United Kingdom). This study was agreed in mutual recognition procedure NL/H/4791/MR and is described below.

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 two sildenafil formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were three dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose 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 citrate 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 Umedica (previously 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).

The results of the bioequivalence study are extrapolated to the lower strength 25 mg. The dissolution requirements in the bioequivalence study guideline (CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, 2010) for granting an biowaiver are fulfilled as well.

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 sixteen adverse events, the relationship of eleven adverse events in the test and reference group was judged as possibly related to the study drug. The relationship of five adverse events in the test and reference 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 (RMP), 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 Umedica film-coated tablets. The products covered by this RMP are Sildenafil 25 mg, 50 mg and 100 mg film-coated tablets.

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 MEB 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. The biowaiver for the lower strength is acceptable. Risk management is 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 Sildenafil Umedica 50 mg and 100 mg film-coated tablets. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sildenafil Umedica 25 mg film-coated tablets have a proven chemical-pharmaceutical quality and are an approvable line extension to Sildenafil Umedica 50 mg and 100 mg film-coated tablets. Sildenafil Umedica (previously Sildenafil Interdos) are well-known medicinal products 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.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Sildenafil Umedica with the reference product, and have therefore granted a marketing authorisation. Sildenafil Umedica was authorised in the Netherlands on 1 July 2021.

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