COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sildenafil Umedica 20 mg film-coated tablets

(sildenafil citrate)

NL/H/4997/001/DC

Date: 8 April 2021

This module reflects the scientific discussion for the approval of Sildenafil Umedica 20 mg film-coated tablets. The procedure was finalised at 19 January 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 Member States have granted a marketing authorisation for Sildenafil Umedica 20 mg film-coated tablets from Umedica Netherlands B.V.

The product is indicated for:

Adults
Treatment of adult patients with pulmonary arterial hypertension classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease.

Paediatric population
Treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. Efficacy in terms of improvement of exercise capacity or pulmonary haemodynamics has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Revatio 20 mg, film-coated tablets (EU/1/05/318) which has been registered in the EEA by Pfizer Limited since 28 October 2005.

The concerned member state (CMS) involved in this procedure was Germany.

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 white, round shaped film-coated tablet, debossed with "1A4" on one side and plain on other side. Each contains 20 mg of sildenafil as 28 mg of sildenafil citrate.

The film-coated tablets are packed in PVC/aluminium blister packs.

The excipients are

Tablet core: calcium hydrogen phosphate, microcrystalline cellulose, croscarmellose sodium, colloidal silica, and magnesium stearate.
Film-coating: hypromellose (E464), 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. It is slightly soluble in water and contains no chiral centre. Polymorph Form 1 is consistently produced.

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 active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur.. Batch analytical data demonstrating compliance with this specification have been provided for three full scale 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.

II.3 Medicinal Product

Pharmaceutical development
The product 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 explained. All excipients used are well known. The choice of packaging material and manufacturing process is justified.
In support of this application a bioequivalence study was performed against Viagra 100 mg film-coated tablets sourced from the UK. The MAH applied for a biowaiver of the proposed 20 mg strength. The 100 mg test product used in the bioequivalence study is fully dose proportional to the proposed 20 mg product. Submitted dissolution profiles show that the

dissolution profiles are similar. From chemical-pharmaceutical point of view, extrapolation from the 100 mg to the 20 mg tablet strength is acceptable. The discriminatory power of the dissolution method, adopted from the United States Pharmacopoeia (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. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for four full scale batches of the common blend and one pilot scale batch (20 mg strength) in accordance with the relevant European guidelines. Process validation for full-scale batches of the 20 mg strength will be performed post authorisation.

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 includes tests for appearance, identification, tablet size, water content, uniformity of dosage units, dissolution, assay, related substances and microbiological limits. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three pilot scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for the 100 mg product strength and three production scale batches of the proposed strength of 20 mg stored at 25°C/60% RH (36 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 the proposed packaging.

On basis of the data submitted, a shelf life was granted of 36 months. Since accelerated stability data showing compliance with the current specification limit for dissolution could not be provided, a temperature storage restriction ‘Store below 25°C’ was set. Photostability studies are conducted and showed no effect of UV exposure on sildenafil citrate tablets. The drug substance is known to be hygroscopic, therefore the storage condition “Store in the original package in order to protect from moisture” is acceptable.

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

Lactose monohydrate, as component of the coating, is the only material of animal and/or human origin contained or used in the manufacturing of the drug product. Scientific data and/or certificates of suitability issued by the EDQM 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 member states consider that <product name> 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 20 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

This product is a generic formulation of Revatio 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 citrate 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 one bioequivalence study with a 100 mg strength tablet and a justification for a biowaiver of the proposed 20 mg strength. Both are discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product sildenafil Umedica 100 mg film-coated tablets (Umedica Netherlands B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Viagra 100 mg film-coated tablets (Pfizer Limited, United Kingdom).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The following prerequisites for requesting a biowaiver for the 20 mg strength based on the bioequivalence study with the 100 mg strength are met:

- the strengths have been manufactured by the same manufacturing process;
- the compositions are qualitatively similar and quantitatively dose proportional
- sufficient information about the dose linearity for sildenafil over the requested dose range for the biowaiver was submitted.

Dissolution tests were performed at the three pH conditions of 1.2, 4.5 and 6.8. Similar dissolution was shown at pH 0.1 N HCl or SGF and pH 4.5 as dissolution was over 85% within 15 minutes. At pH 6.8 dissolution was shown to be comparable when 5 tablets of the 20 mg strength were compared to the 100 mg strength.

Bioequivalence study

Design

An open label, balanced, randomized, three treatment, three-period, three-sequence, single-dose and 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 ten hours. There were three dosing periods, separated by a washout period of seven days. In this study bioequivalence was tested both against an EU reference product and a US reference product. Only the results of bioequivalence testing against the EU reference product are relevant and will be presented in this report.

Blood samples were collected at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5.00, 6, 8, 10, 12, 16, and 24 hours after administration of the products.

The design of the study 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 should be 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. Therefore, 38 subjects were eligible for pharmacokinetic analysis.

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

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 Umedica.

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

Important identified risks	• Organic nitrate interaction, interaction with bosentan (and other CYP3A4 inducers) • Vaso-occlusive crisis in patients with sickle cell disease • Increased relative mortality in the paediatric population • Epistaxis/ bleeding events
Important potential risks	• Hypotension • Non-arteritic anterior ischaemic optic neuropathy (NAION) • Hearing loss • Pulmonary haemorrhage in paediatric patients • Interactions: epoprostenol, iloprost, guanylate cyclase stimulator and PDE5 inhibitors
Missing information	• Long-term ocular safety • Safety in pregnancy • Safety in patients with renal impairment • Safety in patients with cardiovascular diseases • Long-term mortality

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 Revatio. 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 test consisted of: a pilot test with five participants, followed by two rounds with ten participants each. 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 PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sildenafil Umedica 20 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Revatio 20 mg, film-coated tablets. Revatio 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.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, 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. The decentralised procedure was finalised with a positive outcome on 19 January 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