CBG MEB

Public Assessment Report

Scientific discussion

Sildenafil CF 20 mg, film-coated tablets

(sildenafil citrate)

NL/H/3630/001/DC

Date: 12 December 2017

This module reflects the scientific discussion for the approval of Sildenafil CF 20 mg, film-coated tablets. The procedure was finalised on 17 September 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
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 CF 20 mg, film-coated tablets from Centrafarm 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 (>20 kg) 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 (see SmPC section 5.1).

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 which has been registered by Pfizer Limited since 28 October 2005 through a centralised procedure (EU/1/05/318).

The concerned member states (CMS) involved in this procedure were France, Germany, Ireland and Slovenia.

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

II. QUALITY ASPECTS

II.1 Introduction

Sildenafil CF is a round, biconvex, white film-coated tablet containing 20 mg of sildenafil, as 28 mg of sildenafil citrate.

The tablets are packed in PVC/PVDC-Aluminium foil blisters.

The excipients are:
Tablet core: lactose monohydrate, microcrystalline cellulose (E460), hydroxypropylcellulose (E463), croscarmellose sodium (E468), colloidal anhydrous silica (E551) and sodium stearyl fumarate (E485).
Film coating: Opadry II white (consisting of hypromellose 2910 (E464), titanium dioxide (E171), polydextrose FCC (E1200), talc (E553b), maltodextrin and medium chain triglycerides).

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 contains no chiral centre and is consistently produced as the anhydrous form. It is slightly soluble in water and in methanol, practically insoluble in hexane. Sildenafil citrate belongs to BCS class I. The solubility of sildenafil in aqueous solution is pH dependent.

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. and additional requirements as mentioned on the CEP. 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. The tablet cores of the current 20 mg strength were developed based on the dose proportional tablet cores of the, already approved Sildenafil CF 100 mg, film-coated tablets; and to be pharmaceutically equivalent to the originator product.

One pivotal and one supportive bioequivalence study with the 100 mg strength was submitted. Comparable dissolution was observed between the 20 mg strength and the 100 mg strength. At the lower pH's of 1.2, 4.5, and 6.0 dissolution was fast (>85% within 15 minutes). At the higher pH of 6.8 it was shown that sink conditions are not achievable for the 100 mg strength. Similar dissolution was shown by using the same dose, five tablets of 20 mg versus one 100 mg tablet. This is accepted.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is a three step process consisting of production of the final mixture, compression of the tablet cores and film coating of the tablet cores. The manufacturing process has been adequately validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation data on the product have been presented for seven batches.

Control of excipients
The excipients comply with the Ph.Eur., except for the coating system. For the coating system in house requirements have been set. Additional functionality-related characteristics have been set for particle size distribution of the excipients lactose monohydrate, cellulose, microcrystalline, and hydroxypropylcellulose. 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, average mass, uniformity of dosage units, identification, dissolution, assay, degradation products, and microbial quality. 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 four full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided on four full scaled batches stored at 25°C/60% RH (60 months), 30°C/65% RH (12 months), and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVDC-Aluminium blisters. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. All results, under all conditions, and for

all batches, remain within the specifications up to the six months under accelerated conditions, twelve months under intermediate conditions and five years under long term conditions. Therefore, the proposed shelf-life of five years, without any special temperature storage condition, is acceptable. As the product is slightly sensitive to moisture the storage condition “Store in the original package in order to protect from moisture” is required.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is used originating from animal sources. 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 Sildenafil CF 20 mg, film-coated tablets 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 CF 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 two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

Bioequivalence studies
The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Sildenafil CF 100 mg, film-coated tablets (Centrafarm B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Viagra 100 mg, film-coated tablets (Pfizer, Germany). The studies have been submitted and assessed for procedure NL/H/1925/002-004/DC. As

the batch size of the test product in the first study was lower than required according to the Note for guidance on Bioequivalence, the study was repeated with a second study employing a different batch of the same formulation with sufficient batch size. The first study will be regarded as supportive and only the results will be reported. The second study is addressed as pivotal and completely assessed.

The choice of the reference product
The choice of the reference product in the bioequivalence studies is accepted. The use of Viagra as a reference product is acceptable as it is part of the same global marketing authorisation as Revatio. Viagra 100 mg is homologous to Revatio 20 mg. The formula and preparation of the bioequivalence batch is identical to the formula that is used for marketing.

Biowaiver
The results obtained for the Sildenafil CF 100 mg tablets can be extrapolated to the 20 mg tablet as the following accounts:

- Dose-proportional formulations
- Manufactured by the same manufacturer and manufacturing process
- Sildenafil shows linear pharmacokinetics over the therapeutic dose range of 20 mg - 100 mg
- Comparable dissolution data

The biowaiver for the Sildenafil CF 20 mg tablet is acceptable.

Pivotal second bioequivalence study
Design
A single-dose, two-way, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 18-43 years. Each subject received a single dose (100 mg) of one of the two sildenafil citrate formulations. The tablet was orally administered with 240 ml water after an overnight fast. Fasting was continued for four hours after dosing. There were two dosing periods, separated by a washout period of eight days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14 and 24 hours after administration of the products.

The study design is acceptable, the wash-out long enough, sampling period long enough and sampling scheme adequate. Sildenafil may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of sildenafil. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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
There were no dropouts. All 24 subjects completed the study and 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=24	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	1870 ± 566	1961 ± 587	611 ± 200	0.75 (0.50 - 2.50)	3.9 ± 1.9
Reference	1985 ± 738	2115 ± 812	593 ± 190	0.75 (0.50 - 2.50)	4.3 ± 2.2
***Ratio (90% CI)**	0.96 (0.90 - 1.01)	0.95 (0.88 - 1.01)	1.02 (0.89 - 1.17)	--	--
CV (%)	11.8	13.9	27.6	--	--

$AUC_{0-\infty}$ 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*

Supportive data from first bioequivalence study

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sildenafil citrate under fasted conditions.

Treatment N=24	AUC_{0-t} ng.h/ml	C_{max} ng/ml	t_{max} h
Test	1705 ± 826	530 ± 199	1.26 (0.50 – 4.00)
Reference	1682 ± 749	520 ± 211	1.09 (0.50 – 4.0)
***Ratio (90% CI)**	1.00 (0.93 - 1.07)	1.02 (0.92 - 1.14)	--
CV (%)	14.6	21.9	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies
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 studies Sildenafil CF 100 mg is considered bioequivalent with Viagra 100 mg.

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).

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 CF 20 mg, film-coated tablets.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Nitrate interaction • Vaso-occlusive crisis in patients with sickle cell disease • Increase relative mortality in the paediatric population • Epistaxis/bleeding events
Important potential risks	• Hypotension • Pulmonary haemorrhage in off label paediatric use • Non-arteritic anterior ischaemic optic neuropathy • Hearing loss
Identified and potential drug interactions	• Identified Interaction: bosentan • Potential interactions: epoprostenol, iloprost
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 3 participants, followed by two rounds with 10 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 CF 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 CF with the reference product, and have therefore

granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 September 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached