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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Sildenamed 25 mg, 50 mg and 100 mg film-coated tablets
S. MED. Pharmavertriebsgesellschaft mbH, Germany

sildenafil citrate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1716/001-003/DC
Registration number in the Netherlands: RVG 104914-104916

30 January 2013

Pharmacotherapeutic group:	drugs used in erectile dysfunction
ATC code:	G04BE03
Route of administration:	oral
Therapeutic indication:	treatment of men with erectile dysfunction.
Prescription status:	prescription only
Date of authorisation in NL:	21 December 2012
Concerned Member States:	Decentralised procedure with DE
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Sildenamed 25 mg, 50 mg and 100 mg film-coated tablets from S. MED. Pharmavertriebsgesellschaft mbH. The date of authorisation was on 21 December 2012 in the Netherlands.

The product is indicated for treatment of 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 SPC.

Sildenafil is an oral therapy for erectile dysfunction. In the natural setting, i.e. with sexual stimulation, it restores impaired erectile function by increasing blood flow to the penis.
The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood.

Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum, where PDE5 is responsible for degradation of cGMP. Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP. Therefore sexual stimulation is required in order for sildenafil to produce its intended beneficial pharmacological effects.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Viagra 25 mg, 50 mg and 100 mg which has been registered in the EU through a centralised procedure by Pfizer Ltd. The date of authorisation was on 14 September 1998. Further information can be found in the EPAR of Viagra (http://www.ema.europa.eu/htms/human/epar/).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

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' authorised 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. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Viagra 100 mg tablets, registered in the EU. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is sildenafil citrate, an established active substance however not described in the European Pharmacopoeia (Ph.Eur.*) or any other pharmacopoeia. The active substance is a white to off-white crystalline powder and is soluble in dimethylformamide, sparingly soluble in acetic acid and slightly soluble in methanol. No polymorph forms have been detected and sildenafil citrate has no chiral centers.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process has been adequately described. No class 1 solvents or heavy metal catalysts are used. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The tests performed by the MAH are performed in accordance with the Ph.Eur. In general the specifications are acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches.

Stability of drug substance
Stability data have been provided on the drug substance stored at 25°C/60% RH, 40°C/75% RH and 30°C/65% RH. Based on the results, a retest period of 3 years was granted. Although not sensitive to light, the storage conditions are "Store in tight, original, light-resistant containers".

* *Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Sildenamed 25 mg, 50 mg and 100 mg are blue oval, biconvex shaped film-coated tablets. The 50 mg and 100 mg tablets bear break-marks and can be divided into equal halves.

The film-coated tablets are packed are packed in PVC/PE/PVdC-Aluminium foil blisters.

The excipients are:
Tablet core
cellulose, microcrystalline
calcium hydrogen phosphate, anhydrous
croscarmellose sodium

magnesium stearate
povidone

Film coat
hypromellose
cellulose, microcrystalline
titanium dioxide (E 171)
brilliant blue FCF aluminium lake (E 133)
macrogol stearate/polyoxyl 40 stearate
macrogol 6000

The tablets are fully dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation and manufacturing process development have been described adequately. Comparative dissolution testing was performed with pilot-scale batches against the corresponding strength of the innovator product and against the 100 mg strength used in the BE study at pH 1.0, 4.5 and in deionized water (pH 5.4-5.8). The bioequivalence study was performed with the 100 mg strength only. Information on the development of the manufacturing process has been provided. The choice of packaging material is justified. Breakability of the 50 mg and 100 mg tablets has been demonstrated. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The drug product is manufactured by sieving and dry mixing, followed by wet granulation, drying, milling and sieving of the granules. Finally, the blend is pressed into tablets. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot-scale batches of the 25 mg and 100 mg strengths batches. A justification for the omission of the 50mg tablets from process validation has been presented. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with the Ph.Eur. and Directive EEC/95/45. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, average mass and uniformity of mass of single dose, average mass and uniformity of mass of subdivided parts (50 mg and 100 mg only), disintegration, hardness (shelf-life only), content of water, uniformity of dosage units, identification, dissolution after 15 min, related substances, assay, hardness (shelf-life only) and microbiological quality. The release and shelf-life specifications are identical with the exception of related substances. The analytical methods have been adequately described. Batch analytical data from the proposed production site have been provided on 7 pilot-scale batches, demonstrating compliance with the release specification

Stability of drug product
Stability data on the product has been provided for 7 pilot-scale batches stored at 25°C/60%RH (48 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 transparent PVC/PE/PVdC-Alu blisters. Some trends were observed, but all results remained within limits. Photostability studies showed that the drug product is sensitive to light. The proposed shelf-life of 48 months can be granted. The storage condition “store in the outer carton to protect from light” is justified. The bulk product in PE bags was stored at 25°C/60%RH (12 months). All parameters remain within limits and stability of the bulk product has been demonstrated for 12 months.

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.

II.2 Non-clinical aspects

This product is a generic formulation of Viagra, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of sildenafil released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Sildenafil is a well-known active substance with established efficacy and tolerability.

During the procedure concerns were raised regarding GLP/GCP issues at the clinical site used during the initially submitted bioequivalence study. A previous inspection for a different application showed critical systemic findings at the site.
In response, the MAH submitted a new bioequivalence study, which was carried out at the same site. A new inspection at the site showed that the observed deficiencies were adequately covered and therefore the submitted study was accepted. Only the new study will be reported hereafter.

In the bioequivalence study the pharmacokinetic profile of the test product Sildenamed 100 mg (S. MED. Pharmavertriebsgesellschaft mbH, Germany) is compared with the pharmacokinetic profile of the reference product Viagra 100 mg film-coated tablets (Pfizer, United Kingdom).

The choice of the reference product
As the reference product has been registered through a centralised procedure, it is considered to be uniform across the EU. Therefore, the tablet obtained from the UK is considered acceptable.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 18-53 years. Each subject received a single dose (100 mg) of one of the 2 sildenafil formulations. The tablet was orally administered with 200 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.17, 1.33, 1.67, 2, 2.5, 3.5, 6, 10, 14, 18 and 24 hours after administration of the products.
A single dose, crossover study to assess bioequivalence is considered adequate.

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
One subject withdrew before Period II. Results of forty-seven subjects were included in the pharmacokinetic and statistical analysis.

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

Treatment N=47	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1397 ± 608	1418 ± 617	434 ± 251	0.85 (0.33 – 2.5)	3.9 ± 1.6
Reference	1380 ± 514	1400 ± 526	428 ± 172	0.85 (0.33 – 2.5)	4.0 ± 1.3
***Ratio (90% CI)**	0.99 (0.93-1.06)	1.00 (0.93-1.06)	0.95 (0.85-1.07)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. Based on the pharmacokinetic parameters of sildenafil under fasted conditions, it can be concluded that Sildenamed 100 mg and Viagra 100 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

When sildenafil is taken with food, the rate of absorption is reduced with a mean delay in t_{max} of 60 minutes and a mean reduction in C_{max} of 29% after administration. Therefore the tablet may be taken with or without food, but if taken with food the onset of activity may be delayed. The bioequivalence study under fasting conditions is therefore appropriate and in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to different strengths
The results obtained for the 100 mg tablets were extrapolated to the 25 and 50 mg tablet based upon:
- dose-proportional formulations
- manufactured by the same manufacturer and manufacturing process
- sildenafil shows linear pharmacokinetics over the therapeutic dose range of 25 – 100 mg
- comparative dissolution profiles have been presented in different media.

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).

Risk management plan
Sildenafil was first approved in 1998, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of sildenafil can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Viagra.

Readability test
The package leaflet has not been evaluated via a user consultation study. A bridging report for user testing was submitted. This bridging report is accepted. Layout and in-house style from already user tested PILs have been used and the PIL text is harmonised with Viagra. It is noted that the 25, 50 and 100 mg leaflets will be marketed as separated leaflets in compliance with the innovator.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Sildenamed 25 mg, 50 mg and 100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Viagra 25, 50 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 Sildenamed 25 mg, 50 mg and 100 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 13 March 2012. Sildenamed 25 mg, 50 mg and 100 mg film-coated tablets were authorised in the Netherlands on 21 December 2012.

The date for the first renewal will be: 13 March 2017.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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