CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Sildenafil STADA 25/50/100 mg film-coated tablets
STADA Arzneimittel AG, Germany

sildenafil (as 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/1926/002- 004/DC
Registration number in the Netherlands: RVG 106423,106428-9

11 May 2011

Pharmacotherapeutic group:	drugs used in erectile dysfunction
ATC code:	G04BE03
Route of administration:	oral
Therapeutic indication:	treatment of men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.
Prescription status:	prescription only
Date of authorisation in NL:	1 March 2011
Concerned Member States:	Decentralised procedure with AT, BG, DE, ES, HU, IT, PT, RO, and PL (not for 25 mg)
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 Sildenafil STADA 25/50/100 mg film-coated tablets, from STADA Arzneimittel AG. The date of authorisation was on 4 February 2011 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 STADA 25/50/100 mg film-coated tablets to be effective, sexual stimulation is required.

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

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 Viagra 25, 50 mg, and 100 mg film-coated tablets (EU License EU/1/98/077) which have been registered through a centralised procedure by Pfizer EU since 1998.)

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 Germany. 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 generic medicinal products.

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, a known active substance but not described in any of the 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 by both suppliers. 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/EMEA 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.

One of the proposed DMF's can not be accepted yet due to the use of a class 1 solvent. Commitments have been made for the replacement of the solvent and appropriate variation procedures will be followed to resolve the issue.

Manufacture
The manufacturing process has been adequately described. No heavy metal catalysts or class 1 solvents are/will be used by any of the two DMF-holders. The active substance has been adequately characterised and in general acceptable specifications have been adopted for the starting materials, solvents and reagents..

Quality control of drug substance
One supplier conducted most tests in accordance with the EP (European pharmacopoiea) and in-house methods are considered adequately validated. The other supplier uses in-house and EP methods that are considered adequately validated. The tests performed by the MAH are performed in accordance with the EP. 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 by both DMF-holders.

Stability of drug substance
Sufficient stability data on the active substance have been provided to grant retest periods of 18 months. For the substance from one specific supplier an expiry date of 36 months is additionally justified.

** Pharmacopoeia are official handbooks in which methods of analysis with specifications for substances are laid down by the authorities.*

Medicinal Product

Composition
Sildenafil STADA 25 mg – are light blue pearlescent film-coated tablets, round and biconvex in shape with approx. diameter of 8 mm.
Sildenafil STADA 50 mg – are light blue pearlescent film-coated tablets, round and biconvex in shape with approx. diameter of 10 mm.
Sildenafil STADA 25 mg – are light blue pearlescent film-coated tablets, round and biconvex in shape with approx. diameter of 12 mm.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, sodium stearyl fumarate, colloidal anhydrous silica.
Film coating - indigo carmine aluminium lake, medium-chainhypromellose triglycerides, maltodextrin, polydextrose, ponceau 4r aluminum lake, talc, titanium dioxide, dextrose monohydrate, lecithin (soya), maltodextrin, aluminium silicate potassium / titanium dioxide pigment, carboxymethylcellulose sodium.

The tablets are packed into PVC/ PVDC-Aluminium foil blisters. The excipients and packaging are usual for this type of dosage form.
The different strengths of the drug product are manufactured fully dose-proportionally.

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. The provided *in vitro* data show pharmaceutical equivalence of test and reference formulations. The choice of manufacturing process and packaging material is justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for six production-scale batches of each strength. The product is manufactured using conventional manufacturing techniques. Batch sizes in tablets are indicated as several batches may be manufactured from a common blend.

Container closure system
Clear transparent blisters of PVC/PVdC (total 304µm, PVC 250µm, PVdC 90g/m2) – Alu foil (20µm) are chosen as primary packaging material. Specifications, certificates of analysis and compliance with EU Directive 2002/72/EC have been provided for all parts of the container closure system. For the plastic materials, IR spectra and compliance with EP monograph 3.1.11 (non-plasticized PVC) have been provided as well. This is acceptable.
The bulk product (final mixture, core tablets and coated tablets) is packed in double polyethylene bags. Specifications, certificates of analysis, IR spectra and compliance with EU Directive 2002/72/EC and EP monograph 3.1.4 (Polyethylene without additives) have been provided. The bulk packaging material supplier refers in their declaration to monograph EP 3.1.4 ("*Polyethylene without additives for containers for preparations for parenteral use and for ophthalmic preparations*"), as this is the specific polyethylene grade used in the supplied packaging material.

Excipients
The excipients comply with the EP, USP-NF (United States Pharmacopoeia, National Formulary) and Directive EEC/95/45. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, average mass, disintegration, uniformity of dosage units, identification (Sildenafil (HPLC and IR) and colouring agents), dissolution, related substances, assay and microbiological quality. The release and shelf-life specifications are identical.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on six production-scale batches of each strength as used for process validation, demonstrating compliance with the release specification.

Microbiological attributes
The test for microbial contamination is included as a part of finished product specification to check the microbiological quality of the drug product, since some excipients may tend to support microbial growth. Microbiological specifications for the drug product have been set based on the EP.

Stability tests on the finished product
Stability data on the product has been provided for six production scale batches of each strength as used for process validation stored at 25°C/60%RH (36 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 transparent PVC/PVdC-Alu blisters. An increase in average tablet mass and a decrease in assay were observed under all conditions. All results remain within limits. The proposed shelf-life of 36 months can be granted. The claimed storage condition "*No special storage conditions*" is justified.
The bulk product in PE bags was stored at 25°C/60%RH (6 months). All parameters remain within limits and no significant changes could be observed.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Only lactose monohydrate is obtained from animal origin, but a TSE certificate has been provided. Sodium stearyl fumarate is of vegetable origin and lecithin is manufactured from soya.

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

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Sildenafil STADA 100 mg film-coated tablets (STADA Arzneimittel AG, Germany) is compared with the pharmacokinetic profile of the reference product Viagra 100 mg tablets (Pfizer, Germany).

Viagra tablets are registered via the centralised procedure and hence are presumed to be identical in all member states of the EEA.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study
A single-dose, 2-way cross-over bioequivalence study was carried out under fasted conditions in 24 healthy male volunteers, aged 18-43 years. Each subject received a single dose (100 mg) of one of the 2 sildenafil citrate formulations. The tablet was orally administered with 240 ml water after an overnight fast. Fasting was continued for 4 hrs after dosing. There were 2 dosing periods, separated by a washout period of 8 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 analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

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.

Results
There were no dropouts. All 24 subjects completed the study and were included in the analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sildenafil 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	0.91 ± 0.48	3.9 ± 1.9
Reference	1985 ± 738	2115 ± 812	593 ± 190	0.99 ± 0.56	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

**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 Sildenafil STADA 50 mg film-coated tablets and the Viagra 100 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results
The formulations are dose-proportional and are manufactured by the same manufacturer and manufacturing process. In addition, sildenafil shows linear pharmacokinetics over the therapeutic dose range of 25 – 100 mg. Dissolution data showed comparable dissolution of the 25, 50 and 100 mg strength and Viagra 25, 50 and 100 mg tablets at a pH of 1.2, 4.5 and 6.8 at each dose strength. The results of the bioequivalence study performed with the 100 mg strength therefore apply to the 25 mg and 50 mg strengths.

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 postauthorisation 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

Readability test
The package leaflet 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.

Recruitment
Medical recruiters pre-qualified and obtained test participants who are available for the test. The medical recruiters are chosen on the basis of their training and work, and are qualified to select suitable participants. Participants are compensated for their time and effort. This initial selection was checked for the purposes of quality assurance and participants were finally selected so as to obtain a group that represented the general population. To achieve this, the group was complemented with participants chosen because of various demographic reasons like age or education.

Methodology
Personal data of the subjects were recorded at the beginning of testing and include gender, age and a statement on the quality of the subject's vision. Of the twenty subjects under test, fifteen subjects needed and wore glasses and five subjects did not wear glasses. All subjects tested had never before participated in a readability test.
Twenty-three subjects, including three persons in pilot fase, (all males; age 19-80 years) were interviewed by means of an in depth interview (face-to-face.). There were three rounds of testing, including the pilot test. Nineteen questions were asked to the respond to test the findability and readability of the leaflet. The qualitative method was used.

Improvements introduced after the pilot test
Layout
- Section 2, subsection "Taking other medicines": To ease finding of information for particular medicines , e.g. "nitrates" or "medicines used to treat chest pain", those expressions were printed bold.

- Section 3 "How to take Sildenafil STADA": A blank line was introduced between the phrases "You should not take Sildenafil STADA more than once a day." and "You should take Sildenafil STADA about one hour before you plan to have sex." in order to help to distinguish both information visually.

Questionnaire
- The wording of two questions was changed during the first round.

Improvements Between the First and Second Test Cycles
The mock-up of the leaflet was used unchanged for both test cycles.

The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Sildenafil STADA 25/50/100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Viagra 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, 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Sildenafil STADA 25/50/100 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 16 December 2010. Sildenafil STADA 25/50/100 mg film-coated tablets is authorised in the Netherlands on 1 March 2011.

The MAH is expected to follow the PSUR cycle of Viagra, which is in a 3-yearly schedule. Therefore, the first PSUR for Sildenafil STADA is expected to cover three years with DLP 16 December 2013.

The date for the first renewal will be: 16 August 2014

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