CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Sildrem 25 mg, 50 mg and 100 mg film-coated tablets Sigilata Ltd., United Kingdom

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/1694/001-003/DC
Registration number in the Netherlands: RVG 104556-7, 104559

9 November 2010

Pharmacotherapeutic group:	drugs used in erectile dysfunction
ATC code:	G04BE03
Route of administration:	oral
Therapeutic indication:	erectile dysfunction
Prescription status:	prescription only
Date of authorisation in NL:	29 October 2010
Concerned Member State:	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 Sildrem 25 mg, 50 mg and 100 mg film-coated tablets, from Sigilata Ltd. The date of authorisation was on 29 October 2010 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 Sildrem to be effective, sexual stimulation is required.

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

In the natural setting, i.e. with sexual stimulation, sildenafil 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 film-coated tablets (EU license EU/1/98/077), which have been registered through a centralised procedure by Pfizer 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 one 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 UK. 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 which is 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. 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.

Manufacture
The manufacturing process of sildenafil citrate differs between the two active substance manufacturers. In general the manufacturing process has been adequately described. No class 1 solvents are used by any of the 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 of the manufacturers performs most of the tests based on the USP. Another manufacturer performs the tests based on the Ph.Eur. In-house methods have been adequately validated. 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 each manufacturer.

Stability of drug substance
Sufficient stability data on the active substance have been provided for both drug substance manufacturers. The retest period is 24 months or 18 months, depending on the manufacturer.

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

Medicinal Product

Composition
Sildrem 25 mg are blue elliptical, biconvex film-coated tablets marked “SL25” on one side.
Sildrem 50 mg are blue elliptical, biconvex film-coated tablets marked “SL50” on one side.
Sildrem 100 mg are blue elliptical, biconvex film-coated tablets marked “SL100” on one side.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose (E460), povidone K29-32 (E1201), croscarmellose sodium (E468), magnesium stearate (E572).
Film coating - hypromellose (E464), titanium dioxide (E171), macrogol 6000, indigo carmine aluminium lake (E132).

The excipients and packaging are usual for this type of dosage form. The three strengths are fully dose proportional. The film-coated tablets are packed in PVC-PVDC/Aluminium blisters.

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 at different pH was performed with pilot scale batches of all three strengths against the 100 mg strength of the innovator product. All dissolution profiles showed more than 85% dissolved after 15 minutes and can therefore be considered essentially similar. The dissolution medium with pH 6.8 has not been tested as no sink conditions could be achieved. Dissolution data at pH 5.5 and pH 6.0 have been provided, supporting the biowaiver applied. The bioequivalence study was performed with the 100 mg strength only. The choice of packaging material is justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The drug product is manufactured by dry mixing of lactose monohydrate, povidone, sildenafil and part of the croscarmellose sodium, sieving and blending of the powder blend, followed by wet granulation with purified water and sieving and drying of the granules. The granules are compressed, film-coated and packed. The holding times for the intermediates and the bulk product are supported by stability data. The manufacturing process has been adequately validated.
Process validation data on the product has been presented for five pilot-scale batches of each strength. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Excipients
The excipients comply with Ph.Eur, except for the film-coating material. The ingredients of the film-coating material comply with the Ph.Eur, except colouring agent indigo carmine aluminium lake (E132). This colouring agent is in line with EC Directive 95/45/EC and is therefore acceptable. The specifications are acceptable.

Quality control of drug product
The drug product specification includes tests for appearance, identity of active and colourant, average mass, hardness, dissolution, assay, uniformity of dosage units, related substances and microbial purity. The release and shelf-life specification are identical, except for the limit for dissolution. For hardness, bottom limits should be included to cover outliers of too low hardness. The analytical methods have been adequately described and validated. Batch analytical data have been provided on pilot scaled batches of all strengths, demonstrating compliance with the release specification. The MAH has committed to revise the shelf-life limit for dissolution at the end of shelf-life.

Stability tests on the finished product
Stability data on the product has been provided on 4 laboratory-scale and 5 pilot-scale batches of the 25 mg and 100 mg strengths and on 3 laboratory-scale and 5 pilot-scale batches of the 50 mg strength. The lab-scale batches are considered supporting batches only. The pilot-scale is used for commercial

production as well. All pilot-scale batches were manufactured at the proposed sites. All batches were stored at 25°C/60%RH (up to 36 months), 30°C/65%RH (12 months; appearance tested only) and 40°C/75% RH (up to 6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVDC-Alu blisters. For all strengths and storage conditions, an increase in average mass and a decrease in dissolution are observed. The increase in mass is demonstrated to be caused by the hygroscopic nature of several excipients. A shelf-life of 36 months can be granted with the storage condition '*store below 30°C*'.
The MAH has committed to perform stability studies on the first three full-scale batches of each strength and to provide the data upon request. In addition, the MAH has committed to provide 12 month loss on drying results for batches stored at 30°C/65%RH when the total increase will be more than 2.5%.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Only lactose monohydrate is of animal origin. A TSE statement has been provided, stating compliance with the *NfG on Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* (EMEA/410/01 Rev2). Magnesium stearate is of vegetable origin.

II.2 Non clinical aspects

This product is a generic formulation of Vaigra, 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 Sildrem 100 mg film-coated tablets (Sigilata Ltd., UK) is compared with the pharmacokinetic profile of the reference product Viagra 100 mg tablets (Pfizer, UK).

The choice of the reference product
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.

Study design
A randomized, open label, two-treatment, two-period, two sequences, single dose, crossover bioequivalence study was carried out under fasted conditions in 32 healthy male volunteers, aged 18-39 years. Nine subjects were light smokers (less than 10 cigarettes a day). 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. There were 2 dosing periods, separated by a washout period of 5 days.

Blood samples were collected predose and at 0.17, 0.33, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 4, 5, 6, 8, 10, 12, 16, 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 citrate. 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
All 32 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 under fasted conditions.

Treatment N=32	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	2365 ± 971	2402 ± 991	701 ± 264	1.2 ± 0.7	3.7 ± 1.1
Reference	2326 ± 978	2362 ± 989	622 ± 248	1.5 ± 0.9	3.7 ± 0.8
***Ratio (90% CI)**	1.01 (0.96 – 1.07)	1.01 (0.96 – 1.06)	1.13 (1.02 – 1.25)	---	---
CV (%)	12.2	11.9	24.7	---	---

$AUC_{0-\infty}$ 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*

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

Treatment N=32	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	397 ± 131	416 ± 134	84 ± 29	1.2 ± 0.7	3.9 ± 0.8
Reference	403 ± 162	423 ± 166	78 ± 32	1.4 ± 0.8	4.1 ± 1.2
***Ratio (90% CI)**	1.01 (0.95 – 1.06)	1.00 (0.95 – 1.06)	1.10 (1.00 – 1.22)	---	---
CV (%)	12.6	12.3	22.7	---	---

$AUC_{0-\infty}$ 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 Sildrem 100 mg film-coated tablets and 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 to other strenghts
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. Finally, *in vitro*-dissolution data at a pH of 1.2 and 4.5 showed comparable dissolution (>85% < 15 min) for the 25, 50 and 100 mg strengths. The results of the bioequivalence study performed with the 100 mg film-coated tablets therefore also apply to the other strengths.

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.
The subjects were recruited by placing advertisements in the local press, contacts in local community groups and through random approaches to members of the public in the targeted age groups.
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. All subjects tested had never before participated in a readability test.
The qualitative method was used. Twenty-three subjects, including three professionals in pilot-fase, (all males; age 18-64 years) were interviewed by means of an in depth interview (face-to-face.).

The readability and findability were successfully tested. In both rounds all respondents (100%) were able to answer and locate the respective information. The extra "open" questions are endorsed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Sildrem 25 mg, 50 mg and 100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Viagra 25 mg, 50 mg, 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 Sildrem 25 mg, 50 mg and 100 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 14 March 2010. Sildrem 25 mg, 50 mg and 100 mg film-coated tablets are authorised in the Netherlands on 29 October 2010.

The MAH is expected to follow the PSUR cycle of Viagra, which is in a 3-yearly schedule. Therefore, the first PSUR for Sildrem is expected to cover three years with DLP is 31 December 2010.

The date for the first renewal will be: 31 August 2014.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH has committed to perform process validation on the full-scale batch of tablets, for each manufacturing site. The full-scale validation data should be available on request.
- The MAH has committed to revise the shelf-life limit for dissolution at the end of shelf-life.
- The MAH has committed to perform stability studies on the first three full-scale batches of each strength and to provide the data upon request.
- The MAH has committed to provide 12 month loss on drying results for batches stored at 30°C/65%RH when the total increase will be more than 2.5%.

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