CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Sildenafil Lek 25 mg, 50 mg, and 100 mg tablets
Lek Pharmaceuticals d.d., Slovenia

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/1471/001-003/DC
Registration number in the Netherlands: RVG 103559,103561,103562

6 May 2010

Pharmacotherapeutic group:	drugs used in erectile dysfunction
ATC code:	G04BE03
Route of administration:	oral
Therapeutic indication:	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:	6 May 2010
Concerned Member States:	Decentralised procedure with SI.
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 Lek 25 mg, 50 mg, and 100 mg tablets, from Lek Pharmaceutical d.d., Slovenia. The date of authorisation was on 6 May 2010 in the Netherlands. The product is indicated for treatment of erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. In order for Sildenafil LEK 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 licenses EU/1/98/077002-4, EU/1/98/077007-8, and EU/1/98/077010-2 respectively), 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 a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Viagra 100 mg film-coated tablets, registered in the United Kingdom. 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, an established active substance which is not described in any Pharmacopoeia*. The active substance is a white to off-white crystalline powder which 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 centres.

The Active Substance Master File (ASMF) procedure is used for the active substance by both manufacturers. 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 for the two manufacturers. For both manufacturers the manufacturing process has been adequately described. No class 1 solvents or heavy metal catalysts are 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
Most of the tests from one of the manufacturers are based on the USP*. In-house methods have been adequately validated. One manufacturer conducts most tests in accordance with the Ph.Eur. and in-house methods are also considered 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 both manufacturers.

Stability of drug substance
Sufficient stability data on the active substance have been provided for both drug substance manufacturers. The applicant has adopted the DMF-holders respective re-test periods.

* *Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and USA respectively.*

Medicinal Product

Composition
The drug product is an uncoated immediate release tablet presented in three different strengths. All three strengths are light-blue, round and slightly dotted tablets. (The colouring was changed from blue into light-blue by a post-approval type IA variation, see table “steps taken after finalisation of the initial procedure” on page 11) The 25 mg tablets have a breaking notch and embossment “25”, whilst the 50mg tablets have a cross breaking notch and embossment “50” and the 100mg tablets have a cross breaking notch and embossment “100”. The breaking notch on the 25 mg tablet is present in order to facilitate the ease of swallowing, the other three strengths can be broken in a reproducible way. The tablets are packed in aclar/aluminium blister packs.
The excipients are: microcrystalline cellulose, anhydrous calcium hydrogen phosphate, copovidone, croscarmellose sodium, magnesium stearate, indigo carmine aluminium lake (E132) and saccharin sodium. 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 main development studies performed were in respect to the manufacturing process development and comparison of dissolution profiles with the originator product.
The choices of the packaging and manufacturing process are justified. The pharmaceutical development of the product has been adequately performed.

Dissolution
Dissolution profiles of all three strengths have been included for tablets manufactured with the active substance obtained from active substance manufacturers respectively, and all tablets dissolved more than 85% in 15 minutes following the routine method. The tablets obtained from the respective active substance manufacturers therefore have similar dissolution profiles.

Manufacturing process
For the manufacturing of Sildenafil LEK tablets, the production steps include wet granulation, followed by sieving and drying. Process validation data on the product has been presented for pilot scaled batches only, from both of the manufacturing sites. The manufacturing process is considered to be a standard process.

Excipients
The excipients comply with the Ph.Eur. All specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, dimensions, average mass, dissolution, identity of active and colorant, assay, uniformity of dosage units, related substances and microbial purity. The limit for dissolution was set sufficiently tight in relation to the biobatch. An identical assay limit is included for release and shelf-life
The analytical methods have been adequately described and validated. The stability indicating nature of the assay and related substances method has been adequately demonstrated. Batch analytical data from the proposed production sites have been provided on pilot-scale batches of all strengths, demonstrating compliance with the release specification.

Breakability:
Sildenafil LEK tablets are divisible in several parts:
25 mg: divisible in 2 parts theoretical weight of subdivided parts: 75.0 mg
50 mg: divisible in 4 parts theoretical weight of subdivided parts: 75.0 mg
*100 mg:*divisible in 4 parts theoretical weight of subdivided parts: 150.0 mg
During validation of the manufacturing process it has been proven that the subdivided parts comply with the test as described in the Ph.Eur. monograph *‘Tablets’* under *‘Subdivision of Tablets’.*

Tablets compressed with low and high hardness were analysed for breakability according to the Ph.Eur. All results are well within the Ph.Eur. acceptance criteria.
It was demonstrated that differences in hardness do not influence the breakability of the tablets.

Stability tests on the finished product
Stability data on the product has been provided on 5 pilot-scale batches of the 25 mg and 100 mg strengths respectively and on 4 pilot batches of the 50 mg strength. These data are representative for both proposed manufacturing sites and both proposed active substance manufacturers. All batches were stored at 30°C/75%RH (18 to 24 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 Aclar/Al-blisters. Registration was requested only for the Aclar/Al-blisters. No changes were seen under both conditions. Based on the submitted data, the proposed shelf-life of 36 months in the proposed packaging without further storage conditions is thus justified, as well as the 12 months for the bulk storage.

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.

A non-clinical overview was provided by the MAH. This report gives an adequate overview of the available preclinical data on sildenafil. The pharmacological, toxicological and pharmacokinetic properties of the active substance have been adequately described in the non-clinical overview. The overview gives a good review of the data published in open literature.

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 Lek 100 mg tablets (Lek Pharmaceuticals d.d., Slovenia) is compared with the pharmacokinetic profile of the reference product Viagra 100 mg tablets (Pfizer, Germany).

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

Study design
A single-dose, comparative, randomised, two-way, crossover bioequivalence study was carried out under fasted conditions in 36 healthy, non - smoking male volunteers, aged 26-54 years. Each subject received a single dose (100 mg) of both the test and reference sildenafil formulations. The tablet was orally administered in solid form with 240 ml water after an overnight fast of at least 10 hours. 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 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours after administration of the products.

The analytical method is adequate 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. However, the applicant argued that a wider acceptance range may be applied, as the widening is not clinical relevant. The RMS did not agree. In case it is proven that the drug is subject to a high intra-subject variability, widening may be eventually applied. The submitted bioequivalence study showed that the drug is not subject to a high intra-subject variability, as the ANOVA CV is less than 30%. Moreover, the obtained 90% CI for Cmax is within the normal criteria (80-125%)

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
All 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=36	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1207 ± 436	1221 ± 443	356 ± 163	1.2 ± 0.7	4.4 ± 1.0
Reference	1220 ± 481	1235 ± 488	338 ± 147	1.5 ± 1.0	4.4 ± 0.9
***Ratio (90% CI)**	1.00 0.93 - 1.06	1.00 0.93 - 1.06	1.04 0.93 - 1.17	---	---
CV (%)	16.9	16.8	29.1	---	---

$AUC_{0-\infty}$ 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=36	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	542 ± 242	554 ± 246	148 ± 58	1.2 ± 0.7	4.2 ± 0.8
Reference	526 ± 223	539 ± 228	141 ± 58	1.4 ± 0.9	4.3 ± 1.2
***Ratio (90% CI)**	1.02 (0.97 - 1.08)	1.02 (0.96 - 1.07)	1.06 (0.96 - 1.17)	---	---
CV (%)	13.5	13.2	25.1	---	---

$AUC_{0-\infty}$ 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 Lek 100 mg tablets and Viagra 100 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. The data for metabolite N-desmethyl-sildenafil are considered supportive.

Extrapolation to other strengths
The 100 mg tablets are dose proportional with the 25 mg and 50 mg tablets. In addition, the dissolution profile is similar under identical conditions for the additional strengths and the strength of the biobatch. The tablets are manufactured by the same manufacturer with the manufacturing process, sildenafil shows linear pharmacokinetics over the therapeutic dose range of 25 – 100 mg. The results of the bioequivalence study performed with the 100 mg tablets therefore apply to the other 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

Viagra 25 mg, 50 mg, and 100 mg film-coated tablets were centrally authorized by the EMEA. Therefore a harmonized PIL was accepted throughout the EU.

The MAH submitted a bridging report with respect to the layout of the leaflet. The bridging report refers to several successfully finalised MR and/or DC procedures, in which user tests have been assessed. Furthermore the MAH compared the layout for “Sildenafil LEK” to the common layout of other leaflets as used by the MAH.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Sildenafil Lek 25 mg, 50 mg, and 100 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Viagra 25 mg, 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 Sildenafil Lek tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 10 September 2009. Sildenafil Lek was authorised in the Netherlands on 6 May 2010.

The applicant is expected to follow the PSUR cycle of Viagra, which is in a 3-yearly schedule.
The PSUR submission cycle is 3 years. The first PSUR will cover the period from September 2009 to December 2010.

The date for the first renewal will be: 31 August 2011.

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
Change in the colouring system currently used in the finished product. Reduction or deletion of one or more components of the colouring system.	NL/H/1471/ 001-003/IA/ 001	IA	18-11-2009	2-12-2009	Approval	N