CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Azulsix 25 mg, 50 mg and 100 mg, chewable tablets Farmalider S.A., Spain

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/2244/001-003/DC
Registration number in the Netherlands: RVG 109181-109183

5 July 2012

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:	27 March 2012
Concerned Member States:	Decentralised procedure with ES
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 Azulsix 25 mg, 50 mg and 100 mg, chewable tablets from Farmalider S.A. The date of authorisation was on 27 March 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 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 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. It 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
In general the manufacturing process of sildenafil citrate has been adequately described. No class 1 solvents are used. 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
The tests performed by the MAH are 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.

Stability of drug substance
Sufficient stability data on the active substance has been provided for the drug substance to justify the claimed re-test period of 5 years with no specific storage conditions.

* *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
Azulsix 25 mg contains 25 mg sildenafil formed in situ from 35.12 mg sildenafil citrate. It is a white, triangular, biconvex tablet, embossed with "25" on one side.
Azulsix 50 mg contains 50 mg sildenafil formed in situ from 70.24 mg sildenafil citrate. It is a white, triangular, biconvex tablet, embossed with "50" on one side.
Azulsix 100 mg contains 100 mg sildenafil formed in situ from 140.48 mg sildenafil citrate. It is a white, triangular, biconvex tablet, embossed with "100" on one side.

The chewable tablets are packed in transparent PVC/PCTFE - Aluminium blisters.

The excipients are: polacrilin potassium, silica colloidal anhydrous, lactose monohydrate, povidone K-30, aspartame (E951), croscarmellose sodium, peppermint flavour, magnesium stearate, potassium hydroxide (for pH adjustment) or hydrochloric acid (for pH adjustment).

The formula for all strengths is dose proportional.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The MAH provided a justification for the choice of a deviating pharmaceutical form compared to the reference product, i.e. chewable tablet, even when the drug product is not designed for absorption in the oral cavity. The formulation and manufacturing process development have been described adequately. The main target in the development was to overcome the unpleasant, bitter taste of sildenafil citrate when dispersed in the mouth. Polacrilin potassium is used to form an in-situ complex with sildenafil, eliminating the citrate ions, to mask the bitter taste of the drug substance. This complex is designed to disintegrate at low pH, additional supporting information clarified that the drug substance is present as free base.
Comparative dissolution testing at different pH (pH 2.2 (0.01 N HCl), pH 4.5 acetate buffer and pH 6.8 phosphate buffer) was performed with pilot-scale batches against the 100 mg strength of the innovator product. The bioequivalence study was performed with the 100 mg strength only. This has been adequately justified. The choice of packaging material is justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process has been adequately described and validated according to relevant European guidelines with three pilot-scale batches of each strength. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

Except for polacrilin potassium (USP-NF) and peppermint flavour and Ludipress LCE (both in-house), all excipients meet the specifications of their Ph.Eur. monograph. The components of Ludipress LCE, lactose monohydrate and Povidone K-30, are in line with the Ph.Eur. monographs for these materials. The specifications are acceptable.

Quality control of drug product

The drug product specification includes tests for appearance, diameter and thickness, identification, average weight, water content, dissolution, assay, uniformity of dosage units, related substances and microbiological quality. The release and shelf-life specification are identical, except for the limit for water content. The analytical methods have been adequately described and validated. The stability indicating nature of the assay and related substances methods has been adequately demonstrated. Batch analytical data have been provided on the process validation batches of all strengths, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three batches per strength as used for process validation. All batches were stored at 25°C/60%RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PCTFE-Alu blisters.
For all strengths, an increase in average mass, water content and impurities were observed under accelerated storage conditions. From the long-term stability data of 12 months, only an increasing trend for water content can be observed. All results remain within limits. No degradation occurs after 12 months at 25°C/60%RH.
A photostability study has been performed in line with ICH Q1B on the directly exposed product. The results from the photostability study demonstrate an increase in one impurity when directly exposed.
A shelf-life of 24 months was granted with the storage condition “This medicinal product does not require any special temperature storage conditions; store in the original packaging to protect from light”.

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.

Several commitments have been made with regard to the drug product; these are listed on page 8 of this report.

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.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Azulsix 100 mg chewable tablets (Farmalider S.A., Spain) is compared with the pharmacokinetic profile of the reference product Viagra 100 mg tablets (Pfizer Limited UK).

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 28 healthy male subjects, aged 19-38 years. Each subject received a single dose (100 mg) of one of the 2 sildenafil formulations. The tablet was orally administered after an overnight fast. The reference tablet was taken with 240 ml water. The test tablet was chewed and thereafter swallowed and no water was given. This is considered acceptable and the most sensitive way to assess bioequivalence for such a formulation. 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 0.16, 0.33, 0.5, 0.67, 0.92, 1.08, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

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
All 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=28	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	2274 ± 752	2397 ± 785	540 ± 192	1.5 (0.5 – 3.0)	3.5 ± 1.4
Reference	2294 ± 804	2420 ± 849	590 ± 234	1.2 (0.5 – 3.0)	3.7 ± 1.8
***Ratio (90% CI)**	1.00 (0.92-1.08)	1.00 (0.93-1.07)	0.93 (0.83-1.04)	--	--
CV (%)	17.1	15.9	25.2	--	--

$AUC_{0-\infty}$ 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 Azulsix 100 mg chewable 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.

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 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 tests at a pH 1.0, 4.5 and 6.8 showed that dissolution is comparable for the 25, 50 and 100 mg tablets. The results of the bioequivalence study performed with the 100 mg chewable tablet 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 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 marketed by Pfizer.

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 test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Overall, each and every question met the criterion of 81% correct answers. The readability test has been sufficiently performed. The MAH committed that for the leaflet a minimum font size of 9 point will be used as this is mandatory for new applications as of February 2011.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Azulsix 25 mg, 50 mg and 100 mg, chewable tablets have a proven chemical-pharmaceutical quality and are generic forms of Viagra 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 Azulsix 25 mg, 50 mg and 100 mg, chewable tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 19 January 2012. Azulsix 25 mg, 50 mg and 100 mg, chewable tablets were authorised in the Netherlands on 27 March 2012.

The date for the first renewal will be: 19 December 2015.

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

Quality - medicinal product

- The MAH committed to review the shelf-life limit for water content at the end of shelf-life.
- The MAH committed to continue the stability studies of submitted batches as stated in the stability protocol up to 36 months.
- The MAH committed to carry out a validation study on the stage of blend: the first 2 blend batch sizes will be validated with the first 3 batches.
- The MAH committed to carry out a validation study on the stage of compression: the first 2 batch sizes per strength will be validated with 3 batches each.
- The MAH committed that the first 5 commercial blend batches will also be checked with XRD to confirm absence of sildenafil citrate and resinate and the first 10 blend batches will be checked for % free drug.

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