European Medicines Agency
Evaluation of Medicines for Human Use

Doc. Ref: EMEA/564519/2009

CHMP ASSESSMENT REPORT

FOR

Vizarsin

International Nonproprietary Name**: sildenafil**

Procedure No. EMEA/H/C/001076

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Krka, d.d., Novo mesto submitted on 2 October 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Vizarsin, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

The legal basis for this application refers to Article 10(1) of Directive 2001/83/EC.

The chosen reference product is:

■ *Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:*

- Product name, strength, pharmaceutical form: Viagra 25/50/100 mg film-coated tablets
- Marketing authorisation holder: Pfizer Limited
- Date of authorisation: 14 September 1998
- Marketing authorisation granted by:
  - Community
- (Community) Marketing authorisation numbers: EU/1/98/077/002-004, EU/1/98/077/006-008, EU/1/98/077/010-019

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Viagra 100 mg film-coated tablets
- Marketing authorisation holder: Pfizer Pharma, GmbH
- Date of authorisation: 14 September 1998
- Marketing authorisation granted by:
  - Community
- (Community) Marketing authorisation numbers: EU/1/98/077/010-012, EU/1/98/077/015
- Bioavailability study numbers: 08-208

The Rapporteur appointed by the CHMP was:Dr P. Demolis

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

The product was not licensed in any country at the time of submission of the application.

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 2 October 2008.
- The procedure started on 22 October 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 January 2009. .
- During the meeting on 16–19 February 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 February 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 26 March 2009.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 18 May 2009.
- During the CHMP meeting on 26 -29 May 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 3 June 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Oustanding Issues to all CHMP members on 15 June 2009.
- During the meeting on 22 – 25 June 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Vizarsin on 25 June 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 22 June 2009. .

2. SCIENTIFIC DISCUSSION

2.1 Introduction

The product is a generic medicinal product containing sildenafil as sildenafil citrate as active substance.

The reference medicinal product is Viagra 25, 50 and 100 mg film-coated tablets.

Sildenafil is an inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase (PDE5). During natural erection, nitric oxide (NO) is released and this triggers the synthesis of cGMP which, in turn, relaxes the corpora cavernosa (a key point in the erection process). PDE5 present in the corpus cavernosum breaks down cGMP, sildenafil prevents the breakdown of cGMP and, thus enhances the induced erectile response.

The safety and efficacy profile of sildenafil has been demonstrated in several clinical trials details of which can be found in the EPAR for Viagra. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this product. Since this application is a generic application referring to the reference medicinal product Viagra, summary of the clinical data of sildenafil citrate is available and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted with sildenafil citrate.

The indication proposed for Vizarsin is the same as the reference medicinal product.

2.2 Quality aspects

Introduction

The product is presented as film coated tablets containing 25, 50 and 100 mg of sildenafil citrate as active substance.
Other ingredients are:
Tablet core: microcrystalline cellulose, anhydrous calcium hydrogen phosphate, croscarmellose sodium, hypromellose (E464), magnesium stearate
Film coating: lactose monohydrate, hypromellose (E464), titanium dioxide (E171), triacetin

The film coated tablets are packed in blisters of PVC/ Al foil blisters.

Active Substance

Sildenafil is a white to off-white, crystalline powder that is slightly soluble in water. It is also insoluble in ethanol, chloroform, acetone,but soluble in dimethyl formamide, DMSO and in methanol. Sildenafil has the chemical name 5-[2-ethoxy-5-(4-methylpiperazin-1-yl)sulfonylphenyl]-1-methyl-3-propyl-4H-pyrazolo[5,4-e]pyrimidin-7-one; 2-hydroxypropane-1,2,3-tricarboxylic acid. It does not show polymorphism or enantiomerism.

- Manufacture

The manufacturing of sildenafil consists of synthesis and crystallization. Sildenafil is manufactured by two manufacturing sites. The complete scientific documentation from the first manufacturer is included in the dossier. Two alternative routes are described leading to the same impurity profile. The information on the manufacturing site from the second active substance manufacturer is provided in an ASMF.

Adequate In-Process Controls are applied during the manufacture of the active substance. The specifications and control methods for intermediate products, starting materials and reagents, have been presented and are satisfactory.

- Specification

The specifications of the drug substance include identification of sildenafil citrate, identification of citrates, water content, heavy metals, sulphated ash, related substances determination, assay of sildenafil citrate and of citric acid, and residual solvent.

Batch analysis data of the active substance are provided. The results are within the specifications and consistent from batch to batch.

- Stability

Three production scale batches of the active substance from the first manufacturer were put on long-term (25°C/60%RH) for up 12 months, and accelerated (40°C/75%RH) for up 6 months stability testing ICH conditions. Photostability test following ICH guidelines Q1B was performed on two batches. The following parameters were tested: appearance, water, content and related substances of sildenafil and content of citric acid. The stability results justify the proposed retest period.

Four production scale batches of the active substance from the second manufacturer were put on long-term (25°C/60%RH) for up 60 months, and accelerated (40°C/75%RH) for up 6 months stability testing ICH conditions. Photostability test following ICH guidelines Q1B was performed on two batches. The following parameters were tested: appearance, water, content and related substances of sildenafil and content of citric acid. The stability results justify the proposed retest period.

Medicinal Product

- Pharmaceutical Development

Vizarsin has been developed with the objective of developing a stable formulation and to match dissolution profile of the reference product, and being essentially similar product to the reference medicinal product Viagra.

A direct compression process was firstly tested. This approach was not successful due to the static nature of the drug. A wet granulation has then been chosen.
A lot of trials have been conducted in order to obtain suitable compression characteristics, flow properties of compression mixture, optimal physical characteristics of cores and amount of coating layer, but also dissolution and stability properties.

A number of studies were also carried out to define the compatibility of the active substance with the pharmaceutical excipients used. A wet granulation has been selected as manufacturing process especially in view of the static nature of the active substance.

The excipients used in the formulation are tablet core: microcrystalline cellulose, anhydrous calcium hydrogen phosphate, croscarmellose sodium, hypromellose (E464), magnesium stearate
film coating: lactose monohydrate, hypromellose (E464), titanium dioxide (E171), triacetin
All excipients used are in compliance with the Ph Eur. with the exception of the colouring agent.

The lactose anhydrous is derived from milk, it is declared that it satisfy the requirements outlined in the TSE Guideline.

Blister PVC with aluminium foil have been selected in order to provide a good protection of the tablets.

- Manufacture of the Product

The finished product is manufactured by two manufacturers. The manufacturing process includes blending, granulation, tabletting, drying, and film-coating.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process.
The batch analysis data show that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

- Product Specification

The finished product specifications include appropriate tests for appearance, water content (Ph Eur), hardness (Ph Eur), disintegration (Ph Eur), identification of sildenafil (HPLC), identification of citrate, identification of titanium dioxide, related substances (HPLC), dissolution of sildenafil (Ph Eur), assay (HPLC), microbiological quality (Ph Eur)

Batch analysis results confirm consistency and uniformity of manufacture and indicate that the process is under control. Impurity limits in the specification are justified by toxicology studies

- Stability of the Product

Three production scale batches of the finished product (25 mg and 100 mg) from the two manufacturers were put on long-term (25°C/60%RH) for up 12 months, and accelerated (40°C/75%RH) for up 6 months stability testing ICH conditions. Photostability test following ICH guidelines Q1B was also performed. The following parameters were tested: appearance, water content, hardness, disintegration, assay, related substances, dissolution, and microbial quality.

The results support the shelf life and storage conditions as defined in the SPC.

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

2.3 Non-Clinical aspects

This application is made in accordance with Article 10(1) of Directive 2001/83/EC, as amended by Directive 2004/27/EC. The applicant is not required to provide the results of pre-clinical tests. Non-clinical testing strategy did not therefore include any toxicological or pharmacological studies performed by the applicant.

The non-clinical overview on the pharmacology, pharmacokinetics and toxicology is based on literature searches and adequate scientific literature has been provided. The overview justifies why there is no need to generate new non-clinical pharmacology, pharmacokinetics and toxicology data. There is thus no need for conducting tests on animals.

No Environmental Risk Assessment was submitted. The introduction of sildenafil film-coated tablets manufactured by Krka is unlikely to result in any significant increase in the combined sales volumes for all sildenafil containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.4 Clinical Aspects

Introduction

This application concerns a marketing authorization under the centralised procedure. The subject of this application is sildenafil citrate film-coated tablets manufactured by Krka, in three strengths 25mg, 50mg, 100mg.

This application is made in accordance with Art 3(3) of Regulation (EC) No 726/2004 "A generic medicinal product of a reference medicinal product authorised by the Community" and Art 10(1) "generic application" of Directive 2001/83/EC. The reference medicinal product is Viagra 25mg, 50mg, 100mg film-coated tablets from Pfizer Pharma (EU/1/98/077/002-004; EU/1/98/077/006-008; EU/1/98/077/010-019).

Scientific advice was not sought for the development programme. For the clinical assessment the Note for Guidance on Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) in its current version as well as the Questions & Answers on the Bioavailability and Bioequivalence Guidelines (EMEA/CHMP/EWP/40326/2006) are of particular relevance.

The applicant submitted a bioequivalence (BE) study with the highest strength of 100mg film-coated tablets and a biowaiver for the lower 50 and 25mg strengths was accepted in line with the Note for Guidance (CPMP/EWP/QWP/1401/98).

The SmPC is in line with that of the reference product Viagra.

GCP aspects

The bioequivalence study provided in support of the application was performed by a Clinical Research Organisation (CRO) in Canada. The clinical part of the study was conducted in compliance with Good Clinical Practice (GCP), as claimed by the sponsor.

In accordance to Art 8(3)(ib) of the amended Directive, and Art 6.1 of the Regulation EC/726/2004, the applicant has provided a statement to the effect that clinical trials that were conducted outside the EU were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Clinical studies

To support the application, the applicant has submitted 1 bioequivalence study with the highest strength of 100mg. This bioequivalence study was performed with healthy male volunteers under fasting conditions.

Since this is a generic application no further clinical trials were required and the applicant performed none. Concerning clinical pharmacology, clinical efficacy and clinical safety, the applicant performed an adequate review of relevant literature.

Pharmacokinetics

- **Methods**

STUDY DESIGN:

The study was designed according to a randomised, single-dose, laboratory-blinded, two-period, two-sequence crossover classical scheme.

In each period, subjects were housed from at least 10 hours before dosing until after the 24-hour post-dose events. Subjects were instructed to avoid alcohol, and food or beverages containing xanthine for 58 hours prior to dosing and during each study protocol. Subjects were also instructed to avoid food or beverages containing grapefruit for 7 days prior to dosing and during each study protocol.

In each period, subjects received a single oral 100mg dose of sildenafil with 240ml of water on the morning of Day 1. The bioequivalence study was performed under fasting conditions (after a supervised overnight fast), since the concomitant food intake reduces the rate of absorption of sildenafil with T_{max} being delayed by approximately 60 minutes and C_{max} reduced by 29% according to the SmPC of the reference product. Subjects were allowed to leave the clinical site after 24-hour blood draw.

A 7 day wash-out was used in the study. The terminal half-life of sildenafil is 3 to 5 hours, hence the washout period length is acceptable.

A total of 18 blood samples were collected in each period at pre-dose and at 0.25, 0.42, 0.58, 0.75, 0.92, 1.08, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose. Blood samples were processed at 4°C afterwards and plasma samples were collected and stored at (-) 20°C and shipped for analysis.

The clinical part of the study was conducted in Canada between 1st April 2008 and 11th April 2008. The bioanalytical facilities were in Canada and the statistical analysis was performed in Canada.

The protocol and the informed consent form were approved by an institutional review board on 2008/02/14 and the revision 01 of the informed consent forms was approved on 2008/03/11. The final study report was signed in July 2008.

TEST AND REFERENCE PRODUCTS:
Test and reference product used in the study were as follows:

***Test product*:**
Sildenafil 100mg Film-Coated tablets manufactured by Krka, d.d. Novo Mesto, Slovenia; batch n° H8718, expiry date 05/2008.

REFERENCE PRODUCT:
VIAGRA 100mg film-coated tablets manufactured by Pfizer Pharma, Germany; batch n° 7050504D, expiry date 05/2012.

POPULATION(S) STUDIED

34 male non-smoking healthy subjects were enrolled in the study. The main age was 35 (20-45), BMI ranged from 18.5 to below 29 kg/m^2. All subjects were White. Subjects were in good health as determined by medical history, physical examination, ECG, laboratory tests (haematology, biochemistry, urinalysis). Subjects were instructed not to take any OTC medication for the 7 days prior to dosing, any prescription medication for 14 days prior to dosing, enzyme modifying drugs for 28 days prior to Day 1 and nitrates for 30 days prior to dosing and during the study. All the subjects

met inclusion criteria including negative HIV, Hepatitis B and C tests as well as negative screening of ethyl alcohol cotinine test and drug of abuse in urine.

Of the total of 34 volunteers included in the study 32 received the two treatments and were included in the statistical analysis. Of the 2 drop-outs one subject withdrew his consent for personal reasons and second one was withdrawn due to positive drug test (cannabinoids).

ANALYTICAL METHODS:

The analytical part of the study was conducted at Bioanalytical Facility of Algorithme Pharma Inc. (Laval, Quebec, Canada). The analysis of plasma samples of sildenafil and N-desmethyl-sildenafil was performed using the HPLC equipment with MS-MS tandem detection.

A detailed description of the operative procedures was provided. The validation of the method and extended stability evaluation was performed and a detailed description of the validation process was provided.

The main characteristics of the analytical methods are summarised below:

Sildenafil	N-Desmethyl-Sildenafil
Quantification limit (LLOQ): 1 ng/ml. Calibration range: 1.0 ng/ml – 600 ng/ml. Precision (Within-run %CV): 1.5-1.9 Precision (between-run %CV): 1.6-2.4 Accuracy (Within-run %Nominal): 95.5-102.9 Accuracy (between-run %Nominal):96.4-101.2 Linearity: r^2=0.9987 Extraction yield: 85.4-92.6%	Quantification limit (LLOQ): 1 ng/ml. Calibration range: 1.0 ng/ml – 300 ng/ml. Precision (Within-run %CV): 1.8-4.3 Precision (between-run %CV): 1.4-3 Accuracy (Within-run %Nominal): 94.6-100.4 Accuracy (between-run %Nominal): 95.1-101.1 Linearity: r^2=0.9991 Extraction yield: 60-67.4%

In conclusion, the analytical method allowed a suitable investigation of the bioavailability of sildenafil after oral administration.

PHARMACOKINETIC VARIABLES

Relevant PK parameters of sildenafil and its N-desmethyl metabolite were estimated using a non compartmental analysis (NCA).

The pharmacokinetic parameters AUC0-t, AUC0-inf, Cmax and Tmax were either observed or calculated. AUC was calculated using the trapezoidal rule. Cmax and Tmax were directly estimated from the individual concentrations versus time profiles. Additional PK parameters assessed included Kel, T1/2el and intra-subject coefficient of variation (CV).

STATISTICAL METHODS

The pharmacokinetic analysis was performed at the Department of biometry and statistics of Algorithme Pharma Inc. Laval, Quebec, Canada. Parametric ANOVA on ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} was carried out for both analytes: *Sildenafil and its N-desmethyl metabolite*. The statistical model included sequence, period and treatment factors as fixed effects and subject within sequence as random effect. According to the protocol the bioequivalence could be concluded if the least square means ratio with corresponding 90% CI between the test and reference product for ln-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} lied within 80-125% range. A non parametric test (Wilcoxon's rank sum test) was carried out to compare T_{max}.

- **Results**

The pharmacokinetic variables of sildenafil and N-desmethyl sildenafil, the test and reference product, are shown in the tables below.

Sildenafil: Pharmacokinetic parameters (AUC and C_{max}: arithmetic mean ± SD, t_{max}: median, range): Single 100 mg oral dose (n=32).

Treatment	**AUC_{0-t}** pg*h/ml	**$AUC_{0-\infty}$** pg*h/ml	**C_{max}** pg/ml	**t_{max}** h
Test	1329.7	1342.1	375	1.08
(S.D.)	(577)	(581.4)	(190)	(0.42-4)
Reference	1353	1365	378.4	1.08
(S.D.)	(669.8)	(671.9)	(182.4)	(0.58-8)
***Ratio (90% CI)**	[91; 109]%	[91; 109]%	[86; 113]%	ns
Point estimate	99.9 %	99.8 %	98.4 %	
Intra-subject CV (%)	21.4 %	20.9 %	32.9 %	

$AUC_{0-\infty}$ 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 : mediane, min and max

**log-transformed values*

For sildenafil, the mean K_{el} was 0.2222 $hours^{-1}$ for the test formulation and 0.2369 $hours^{-1}$ for the reference product. The mean $T_{1/2el}$ value for the test and reference product was 3.42 hours and 3.19 hours, respectively. The intra-subject coefficient of variation was 32.9%, 21.4% and 20.9% for C_{max}, AUC_{0-t} and AUC_{0-inf}, respectively.

N-desmethyl sildenafil: Pharmacokinetic parameters (AUC and C_{max}: arithmetic mean ± SD, t_{max}: median, range): Single 100 mg oral dose (n=32).

Treatment	**AUC_{0-t}** ng*h/ml	**$AUC_{0-\infty}$** ng*h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	458.2	471.8	137.2	0.92
(S.D.)	(212.3)	(216.7)	(72.1)	(0.75-3)
Reference	473	486	145.9	0.92
(S.D.)	(218.3)	(221.2)	(80.2)	(0.0.58-2.5)
***Ratio (90% CI)**	[92;106]%	[93; 106]%	[85;111]%	
Point estimate	99.2 %	99 %	97.2 %	
Intra-subject CV (%)	16.7 %	15.8 %	31.3 %	

$AUC_{0-\infty}$ 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 : mediane, min and max

**log-transformed values*

For N-desmethyl sildenafil, the mean K_{el} was 0.1530 $hours^{-1}$ for the test formulation and 0.1574 $hours^{-1}$ for the reference product. The mean $T_{1/2el}$ value for the test and reference product was 4.70 hours and 4.68 hours, respectively. The intra-subject coefficient of variation was 31.3%, 16.7% and 15.8% for C_{max}, AUC_{0-t} and AUC_{0-inf}, respectively.

- **Conclusions**

In conclusion, the conventional CI for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} for sildenafil and N-desmethyl sildenafil were within the acceptance range. No significant difference in T_{max} was evidenced by the non-parametric test. Therefore, this study was considered to have met the

bioequivalence criteria as defined by the study protocol since all 90% confidence intervals were within the acceptance range for both, sildenafil and its major metabolite.

Protocol deviations (blood sampling time deviation and concomitant medication) were judged to have no significant influence on bioequivalence assessment.

Transferability of study results to other strengths

The applicant submitted a Bioequivalence study with the highest strength (100mg tablets) and requested biowaiver for the lower 50 and 25mg strengths. This request was found acceptable since all criteria for a biowaiver listed in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) were fulfilled, namely:
1. The pharmaceutical products are manufactured by the same manufacturer and process;
2. The drug input has been shown to be linear over the therapeutic dose range;
3. The qualitative composition of the different strengths is the same;
4. The ratio between amounts of the active substance and excipients is the same;
5. The dissolution profiles are similar under identical conditions for the additional strength and the strength of the batch used in the bioequivalence study.

In conclusion, the extrapolation of the results obtained for the 100mg sildenafil film-coated tablets to the 50mg and 25mg film-coated tablets was deemed acceptable.

CLINICAL SAFETY

Twenty seven subjects participating in the trials reported adverse events. The maximal intensity reported for these events ranged from mild to severe. None of the events were considered serious. Four adverse events (2 cases of headache, testicular pain and testicular swelling) required the use of concomitant medication. No subject was withdrawn from the study because of an event.

In conclusion, both formulations were well tolerated with no major adverse events and no relevant differences in safety profile were observed between the preparations.

Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

Discussion on Clinical aspects

To support the application, 1 bioequivalence study with the highest strength of sildenafil, i.e. 100mg was submitted. The study was designed according to a randomised, single-dose, laboratory-blinded, two-period, two-sequence crossover classical scheme.

32 subjects of the 34 enrolled received the two treatments and were included in the statistical analysis.

The bioequivalence study was performed under appropriate conditions and in line with applicable guidelines.

The results of the bioequivalence study showed that the conventional confidence intervals for ln-transformed AUC0-t, AUC0-inf and Cmax for sildenafil and N-desmethyl sildenafil were within the acceptance range of 80-125%. No significant difference in Tmax was evidenced by the non-parametric test. Therefore, based on the available data it was concluded that bioequivalence of the two products had been demonstrated.

The extrapolation of the bioequivalence study results obtained for the 100mg sildenafil film-coated tablets to the 50mg and 25mg film-coated tablets was deemed acceptable since all criteria for a biowaiver listed in the applicable guidance were fulfilled.

The adverse events observed in the study were graded mild to severe and were comparable to the originator. None of the events were considered serious. Four adverse events (2 cases of headache, testicular pain and testicular swelling) required the use of concomitant medication. No subject was withdrawn from the study because of an event.

The safety concerns with the use of sildenafil have been addressed in the SmPC with the inclusion of appropriate warnings, precautions, and contraindications, and are in line with the reference product.

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.5 Pharmacovigilance

- **PSUR**

The PSUR submission schedule for should follow the PSUR schedule for the reference product.

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements. The company must ensure that this system is in place and functioning before the product is placed on the market.

The company should ensure that the pharmacovigilance activities are in line with the current safety measures applied to the reference medicinal product.

- **Risk Management Plan**

The application is based on a reference medicinal product for which no safety concerns requiring additional risk minimization activities have been identified.

- User consultation

The results of user consultation provided indicates that the Package leaflet is well structured and organized, easy to understand and written in a comprehensible manner. The test shows that the leaflet is readable in patients /users are able to act upon the information that it contains.

2.6 Overall conclusions, benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

This application is made in accordance with Art 3(3) of Regulation (EC) No 726/2004 “A generic medicinal product of a reference medicinal product authorised by the Community” and Art 10(1) “generic application” of Directive 2001/83/EC. The reference medicinal product is Viagra 25mg, 50mg, 100mg film-coated tablets. According to the legal basis no non-clinical studies were required. The applicant provided an appropriate non-clinical overview of sildenafil based on scientific literature. Moreover, no additional clinical trials were required except for bioequivalence studies. The clinical overview provided an adequate summary of clinical data for sildenafil. The results of the bioequivalence study demonstrated the bioequivalence of 100mg film-coated tablet of Krka sildenafil and the reference product, Viagra 100mg film-coated tablet. The extrapolation of the study results to lower strengths of sildenafil, i.e. 50mg and 25mg, was deemed acceptable. The adverse events in the bioequivalence study were comparable to the reference product and no serious adverse events were observed.

The application contains adequate quality, non clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the originator can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Recommendation

Based on the CHMP review of available data, the CHMP considered that the benefit/risk ratio of Vizarsin 25mg, 50mg and 100mg film-coated tablets in the treatment of erectile dysfunction was favourable and therefore recommended the granting of the marketing authorisation.