15 March 2012
EMA/351597/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vizarsin

International non-proprietary name: **sildenafil**

Procedure No. **EMEA/H/C/001076/X/06**

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

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List of abbreviations

AEs	adverse events
ANOVA	analysis of variation
ASMF	active substance master file
AUC_{0-t}	area under the curve from time 0 to time t
$AUC_{0-\infty}$	area under the curve from time 0 to infinity
BSE	bovine spongiform encephalopathy
CHMP	Committee for Medicinal Products for Human Use
C_{max}	maximum concentration
EC	European Commission
EP or Ph. Eur.	European Pharmacopoeia
HPLC	high pressure liquid chromatography
GC	gas chromatography
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
IR	infra-red
LC/MS/MS	liquid chromatography followed by two rounds of mass spectrometry
LLOQ	lower level of quantification
ODT	orodispersible tablets
OPA/alu/PVC/PET/alu	orientated polyamide/aluninum/ polyvinyl chloride/polyester/aluninum
PE	polyethylene
PK	pharmacokinetics
RH	relative humidity
PSUR	periodic safety update reports
SAEs	serious adverse events
t½	half life
t_{max}	time to maximum (plasma) concentration
TSE	transmissible spongiform encephalopathy
USP	US Pharmacopeia

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Krka, d.d., Novo mesto submitted on 2 June 2011 an extension application for Marketing Authorisation to the European Medicines Agency (EMA) for Vizarsin 25, 50 and 100 mg orodispersible tablets through the centralised procedure falling within the Article 19 (1) and Annex I point 1 intend a, and point 2, intend d of the Commission Regulation (EC) No 1234/2008.

Krka, d.d., Novo mesto is already the Marketing Authorisation Holder for Vizarsin 25 mg, 50 mg and 100 mg film coated tablets (EU/1/09/551/001-012).

The applicant applied for the following indication: 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 Vizarsin to be effective, sexual stimulation is required.

The application submitted is composed of administrative information, complete quality data and at least a bioequivalent study with the reference medicinal product Viagra instead of non-clinical and clinical unless justified otherwise

Information on Paediatric requirements

Not applicable

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Vizarsin orodispersible tablets were not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: **Pierre Demolis**

- The application was received by the EMA on 2 June 2011.
- The procedure started on 22 June 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 September 2011.
- During the meeting on 17 – 20 October 2011, 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 20 October 2011.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 December 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 January 2012.
- During the CHMP meeting on 13-16 February 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 February 2012.
- During the meeting on 12-15 March 2012 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 orodispersible tablets on 15 March 2012.

2. Scientific discussion

2.1. Introduction

This application for an extension of marketing authorisation is to introduce orodispersible tablets (ODT) as new pharmaceutical form for Vizarsin, which is currently licensed as film coated tablets.

Vizarsin is a generic medicinal product. The reference medicinal product is Viagra film-coated tablets. Vizarsin film-coated tablets contain sildenafil as sildenafil citrate as active substance. For the orodispersible tables sildenafil free base is used as active substance instead of the salt sildenafil citrate, because it is less bitter than the latter. The indication for Vizarsin is the same as the reference medicinal product.

The new ODT formulation can be taken with or without liquid. It may be used as an alternative to film coated tablets.

2.2. Quality aspects

2.2.1. Introduction

Vizarsin ordispersible tablets contain sildenafil as the active ingredient. It is presented in the form of 25 mg, 50 mg, 100 mg orodispersible tablets.

Other ingredients include hydroxypropylcellulose, mannitol, aspartame, neohesperidin-dihydrochalcone, spearmint oil, peppermint oil, sorbitol, poly(vinyl pyrrolidone), calcium silicate, and magnesium stearate.

Vizarsin ordispersible tablets are packaged in OPA/Al/PVC/Al perforated unit dose blisters.

2.2.2. Active Substance

Sildenafil occurs as white to almost white powder. Sildenafil base does not contain any chiral centre and therefore it does not exhibit isomerism. The active substance does not exhibit polymorphism.

Sildenafil base is not hygroscopic; however it shows pH dependent solubility. Solubility decreases with increasing pH. Sildenafil free base is less bitter than the salt sildenafil citrate used in the film coated tablets. Therefore free base was used in the orodispersible tablet formulation.

Manufacture

The route of synthesis of Sildenafil base is similar to the route approved for sildenafil citrate in the film-coated application, except that the citrate formation step is not performed.

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 sildenafil free base include appearance, solubility, identification of sildenafil (IR), water, sulphated ash, heavy metals, related substances, assay of sildenafil, 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 packed in the package intended for marketing 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 one batch. The following parameters were tested: appearance, water, related substances, and sildenafil content. The stability results justify the proposed retest period.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The primary goal of the development was to formulate an essentially similar product to the reference medicinal product Viagra tablets.

Sildenafil citrate has extensive bitter taste, the first trials thus aimed at successfully mask the taste. Despite different approaches implemented, bitter taste of sildenafil citrate could not be masked to a desired level. Since sildenafil free base is less bitter than sildenafil citrate, the development was continued with sildenafil base. Dissolution studies showed that similar in-vivo performance can be expected with a formulation containing sildenafil free base compared to a formulation with sildenafil citrate. In addition stress stability studies were performed showing that stability of tablets prepared with sildenafil base was adequate and comparable to stability of the reference medicinal product.

The selection of excipients was the most critical step to achieve suitable characteristics of the finished product in the form of orodispersible tablets, especially fast and spontaneous disintegration in the mouth, pleasant taste and mouth feel. The chosen excipients are well known for the manufacture of solid dosage forms.

The excipients used in the formulation are hydroxypropylcellulose (binder), mannitol (diluent), aspartame (sweetening agent), neohesperidin-dihydrochalcone (sweetening agent), spearmint oil

(flavouring agent), peppermint oil (flavouring agent), sorbitol, poly(vinyl pyrrolidone) (disintegrant), calcium silicate (disintegrant), and magnesium stearate (lubricant).

Compatibility of active substance and excipients was confirmed with stability studies. No incompatibilities were observed during development work.

All excipients used are in compliance with the Ph Eur. with the exception of the flavouring agents which both meet in-house requirements.

In vitro drug release studies were conducted with Sildenafil 25 mg, 50 mg and 100 mg orodispersible tablets as well as with reference product Viagra. Comparative dissolution profiles were performed in four different dissolution media. The selected dissolution method was proved to be selective and able to identify differences in dissolution properties of different products in regard to different composition of tablets. There was no effect of active ingredient's particle size on the dissolution rate of finished product within the evaluating range.

Different manufacturing processes for preparation of granulate were considered based on the dosage form selection and final dosage form properties. High shear granulation was selected for the granulate preparation as no sticking of the compression mixture was observed. Standard rotary tablet press was used to compress the orodispersible tablets.

OPA/Alu/PVC/Alu was selected as primary packaging. Stability results showed that packing material was suitable.

Adventitious agents

No materials of animal origin are used in the production of Sildenafil orodispersible tablets.

Manufacture of the product

The manufacturing process is standard wet granulation process. All strengths are proportional by weight in composition. Both the manufacturing process and the in process controls have been adequately described. The process validation has been performed at seven batches at pilot scale covering all strengths and supports the proposed batch sizes.

Product specification

The release and shelf-life specifications for the sildenafil 25/50/100 mg orodispersible tablet include tests and limits for: appearance (visually), average mass of tablets (gravimetry), identification (HPLC, UV), related substances (HPLC), Dissolution (Ph.Eur.), assay (HPLC), uniformity of dosage units – content uniformity (Ph.Eur.) and microbiological purity (Ph.Eur.-not routinely).

Batch analysis results for three batches per strength comply with the proposed specifications.

Stability of the product

Stability studies have been performed on three batches per strength packaged in the proposed packaging material under normal (25°C/60%RH), intermediate (30°C/65%RH) and accelerated conditions (40°C/75%RH). Results have been reported for up to 12 months in normal and for six months accelerated conditions and remained within the proposed specifications.

In addition stability results on one batch of bulk 25 mg tablets packed in PE bag / alutriplex bag stored at temperature 20-25°C and relative humidity 25-65%RH for six months were presented. The lowest tablet strength was chosen for this study because it was considered as the most critical since the

surface area of the tablets per mass is the highest. After six months storage, the results remained within the proposed specification.

Based on the above the proposed shelf-life and storage recommendations for the bulk tablets as well as the finished product are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of Vizarsin active substance and orodispersible tablets has been presented in a satisfactory manner. The results of tests carried out indicate 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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

2.3.2. Pharmacology, Pharmacokinetics and Toxicology

The active ingredient in Virzasin ODT is sildenafil base whereas the reference medicinal product Viagra contains sildenafil citrate.

On the basis of the EMA Procedural advice for users of the centralised procedure for generic/hybrid application (EMEA/CHMP/225411/2006), when different salts of the active substance of the reference medicinal product are used, additional information providing proof that their safety and/or efficacy profile is not different from the one of the reference medicinal product should be submitted.

To be absorbed after oral administration the drug substance first has to dissolve. Only the dissolved portion can be transported through enterocites into the blood and distributed. When drugs with similar solubility and dissolution rates are compared, the same safety profiles may be expected.

The test and the referrence formulation dissolve in the acidic environment of the gastrointestinal tract to the same component, sidenafil base. Comparison of the results of preclinical studies cited in the dossier performed with sildenafil base and sildenafil citrate did not reveal any significant differences in findings. Furthermore, neither the impurity profiles nor the available clinical data comparing formulations using the two different forms (base and citrate) did raise any concerns.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.3. Ecotoxicity/environmental risk assessment

No ERA was submitted. The CHMP agrees with the applicant that introduction of Vizarsin ODT is unlikely to result in any significant increase in the combined sales volumes for all sildenafil containing products. Thus, no modification of the ERA is necessary.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for an orodispersible tablet containing sildenafil. To support the marketing authorisation application the applicant conducted one single-dose, two-way crossover bioequivalence study in fasting state comparing the test product sildenafil 100 mg ODT and the reference product Viagra 100 mg film-coated tablets. This study was the pivotal study for the assessment.

For the other two strengths, a biowaiver to conduct a bioequivalence study was requested.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) in its current version is of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that the clinical trial conducted outside the community was carried out in accordance with the ethical standards of Directive 2001/20/ECETHICS

Exemption

According to the Note for Guidance on the Investigation of Bioavailability CPMP/EWP/QWP/1401/98 Rev.1, it may be sufficient to establish bioequivalence at only one or two strengths depending on product characteristics as well as the pharmacokinetics of the active substance (linearity).

The applicant applied for a biowaiver for the 25 mg and the 50 mg ODT formulations. A single bioequivalence study was done with sildenafil 100 mg orodispersible tablets. The use of the highest strength is generally recommended in case of linear kinetics also considering analytical and safety/tolerability aspects. For sildenafil the drug input is deemed to be linear over the therapeutic range.

For the 50 mg and 25 mg strengths it was demonstrated that:

- the pharmaceutical products are manufactured by the same process;
- the quantitative composition in the table core is proportional;
- the qualitative compositions of the different strengths is the same;
- the dissolution profiles were found to be very similar in various media tested.The comparison of dissolution profiles was performed in three dissolution media 0.1M HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. Additionally, the comparison was performed in quality control dissolution medium 0.01M HCl.

Therefore the CHMP considered a biowaiver for the formulations of lower strengths (50 and 25 mg) to be acceptable.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study.

Type of Study	**Study Identifier**	**Location of Study Report**	**Objective of the Study**	**Study Design; Type of Control**	**Test Product(s); Dosage Regimen; Rout of Administration**	**No. of Subjects**	**Healthy Subjects/ Diagnosis Of Patients**	**Duration of Treatment**	**Study Status; Type of report**
BE	11-312	Section 5.3.1.2.	Assessment of single-dose relative bioavailability of two oral formulations after administration under fasting conditions	Crossover; Fasting state with a 1-week washout period	**Test** Sildenafil 100 mg orodispersible tablets (B.No.: 1243 07 P019 1010) **Reference** Viagra 100 mg film coated tablets: (B.No.: 7050504D)	41	Healthy subjects	Single Dose	Complete; Full

2.4.2. Pharmacokinetics

Study 11-312: Single Centre, Randomized, Single-Dose, Laboratory-blinded, Two-way Crossover Comparative Bioavailability Study of Sildenafil 100 mg Orodispersible Tablets and Viagra 100 mg Film-Coated Tablets in Healthy Male Volunteers under Fasting State

Methods

Study design

This was a single-dose, randomized, open-label, two-way crossover, comparative bioavailability study comparing sildenafil 100 mg orodispersible tablets (test product) and Viagra 100 mg film-coated tablets (reference product) in normal, healthy male subjects under fasting conditions. The washout period was 7 days between each dosing.

Both, clinical part as well as analiytical part of the study were conducted outside the Community.The protocol and the informed consent forms were approved by an institutional review board **Drug intake procedure:**

The order of investigational product administration was sequentially assigned from a computer-generated randomization scheme.

The orodispersible tablet (test product) was administered without water. Prior to administration of test product, subjects were asked to rinse their mouth with approximately 20 mL of water and then swallow the water. No water was provided with the administration of the drug until about 2 hours post-dose.

The reference product was administered with about 180 mL of water at ambient temperature. The tablet was to be swallowed whole and was not to be chewed or broken.

Test and reference products

Test Product:

Sildenafil 100 mg orodispersible tablets, manufactured by Krka, d.d., Novo mesto, SloveniaBatch size: 100,000 tablets.

Reference Product:

Viagra 100 mg film-coated tablets, manufactured by Pfizer (marketed in France). Date of authorisation in EU 14.09.1998.

Population studied

A total 48 male subjects were planned for inclusion, 43 subjects (subjects #001-042 and 044) were included and received at least one of the investigational under study. They were 2 drop-outs. Forty-two (42) were analyzed, 41 were considered in the pharmacokinetic and statistical analysis and 43 in the safety analysis.

The basic demographic data such as gender, age, weight, height, race and body mass index of all subjects enrolled into the study are presented in below table.

		Overall
Age (years)	N	43
	Mean (SD)	31 (7)
	Median	32
	Min, Max	18, 45
Gender [n(%)]	Male	43 (100.0)
Race [n(%)]	White	40 (93.0)
	Black	2 (4.7)
	Other	1 (2.3)
Weight (kg) [1]	N	43
	Mean (SD)	74.1 (9.0)
	Median	75.2
	Min, Max	58.0, 100.3
Height (cm)	N	43
	Mean (SD)	174.7 (6.2)
	Median	175.0
	Min, Max	155.5, 185.0
Body Mass Index (kg/m^2)	N	43
	Mean (SD)	24.29 (2.55)
	Median	24.48
	Min, Max	19.28, 29.31

Protocol Deviations

There were no serious deviations in the development of the experimental phase. Certain delays occurred during the process of collecting subject's blood samples. Protocol deviations were documented. None of these are assumed to have introduced any bias in the results.

Analytical methods

Sample pre-treatment involved the solid-phase extraction of Sildenafil and N-Desmethyl Sildenafil from human plasma. The compounds were identified and quantified using a reverse-phase chromatography HPLC with MS/MS detection

Data on stability, in-study validation, as well as sample analysis details were provided.

Overall the bioanalytical method was considered adequately validated.

Pharmacokinetic variables

The main standard pharmacokinetic variables (AUC0-t, AUC0-∞, Cmax) were determined through non-compartmental analysis by the linear log trapezoidal rule. As a second pharmacokinetic variable, tmax, Kel, t1/2 and % extrapolated area were assessed.

Statistical methods

The pharmacokinetic and statistical analysis was performed usingKinetic, version 9.01, and SAS version 9.1 (GLM procedure). Descriptive statistics were performed for all parameters, tabulating descriptive arithmetic means for direct data and for logarithmic data, as well as the corresponding standard deviations.

The comparative study of the bioequivalence parameters Ln (AUC0-t), Ln (AUC0-∞) and Ln Cmax was performed by means of ANOVA, controlling for the sequence, subjects nested in the sequence, the period and the formulation; in order to obtain an estimation of the residual variance and determine the role of these factors.

Bioequivalence was concluded if the 90% confidence interval of the relative mean AUC0-t and Cmax are included within 80.00-125.00% limits. Tmax was analysed with the non-parametric method.

Results

Table 1. Pharmacokinetic parameters of sildenafil for both formulations

PARAMETER	TEST		REFERENCE	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	448.48	42.0	507.90	46.5
ln (C_{max})	6.0131	7.5	6.1179	8.1
T_{max} (hours) §	1.08	66.7	1.08	59.6
AUC_T (ng·h/mL)	1634.07	43.5	1654.83	39.1
ln (AUC_T)	7.3046	6.2	7.3283	5.8
AUC_∞ (ng·h/mL)	1655.82	43.4	1672.71	39.3
ln (AUC_∞)	7.3181	6.1	7.3385	5.8
$AUC_{T/\infty}$ (%)	98.70	2.4	98.99	1.0
K_{el} ($hours^{-1}$)	0.2023	37.1	0.2099	38.5
$T_{½el}$ (hours)	3.97	44.2	3.78	35.3

§ For T_{max}, the median is presented.

Table 2. Statistical analysis for sildenafil (ln-transformed values)

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	29.3	409.14	453.49	90.22	81.07	100.40
AUC_T	12.6	1488.22	1521.63	97.80	93.33	102.49

* units are ng/mL for C_{max} and ng·h/mL for AUC_T

All pre-dose samples were found to be below the LLOQ. There was no subject with extrapolated area > 20%.

Safety data

In this study a total 34 adverse events were reported by 21 subjects out of 43. No serious adverse events or deaths were reported during this study. (not related) In both groups the most common

adverse events related to treatment were headache and somnolence, wich are expected adverse event from the known safety profile of the sildenafil.

Conclusions

Based on the data of the bioequivalence study, the test product Vizarsin 100 mg orodispersible tablet is considered bioequivalent with the reference product Viagra 100 mg film-coated tablet.

The results of the study with the 100 mg formulation can be extrapolated to other strengths 50 mg and 25 mg in accordance with the conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

2.4.3. Pharmacodynamics

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

2.4.4. Post marketing experience

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

2.4.5. Discussion on clinical aspects

The pivotal basis for the clinical assessment is study, a single-dose, randomized, open-label, two-way crossover, comparative bioavailability study comparing sildenafil 100 mg orodispersible tablets (test product) and Viagra 100 mg film-coated tablets (reference product) in normal, healthy male subjects under fasting conditions. The design of this study is overall acceptable for the CHMP.

The CHMP noted that sildenafil could be taken independently of food intake, therefore a 2x2 cross-over single dose study in fasting state is considered the most adequate study design to investigate the pharmacokinetic bioequivalence of Sildenafil. The CHMP considered the wash-out period of 7 days adequate since the drug has a terminal half-life of 3-5 hours and pre-dose levels were not detected. Moreover, 5% levels of the lowest Cmax for sildenafil could be detected with this LLOQ.

The CHMP notes that sildenafil exhibits linear and dose proportional pharmacokinetics over the dose range of 25 to 100 mg. The choice of the 100 mg strength and dose for the conduct of the bioequivalence study is appropriate.

Analyte for the phrmacokinetic evaluation is the parent compound sildenafil, which is in line with the applicable Guideline on Investigation of Bioequivalence.

According to the CHMP the pre-study validation of the analytical method as satisfactory. No (outlier) value was excluded from calculations. The LLOQ is lower than 5% of the minimum Cmax. Therefore, in case of a carry-over effect was present it would have been detected. Furthermore, the CHMP considered that the in-study validation shows acceptable calibration standards (zero) and QC values. It was noted that incurred sample analysis demonstrated that the analysis was robust.

The pharmacokinetic analyses based on the linear trapezoidal rule are appropriate. The statistical analysis performed is parametric, except for Tmax, in accordance with the Guideline on the investigation on bioequivalence. The employed software was considered acceptable by the CHMP.

The CHMP considered that based on the statistical analysis, test and reference product are bioequivalent. The 90% confidence intervals calculated for AUC0-t and Cmax of sildenafil were inside the acceptance range of 80.00 – 125.00.

With regard to the lower strengths of the ODT formulation (25 mg and 50 mg), the CHMP acknowledged that the different tablet strengths are manufactured with the same process, have the same qualitative composition and a proportional quantitative composition in the table core. In vitro dissolution profiles are similar between the different strengths investigated. Therefore, the bioequivalence conclusion can be extrapolated to these lower strengths.

2.4.6. Conclusions on clinical aspects

The application contains an adequate review of published literature concerning aspects of pharmacology, pharmacodynamic, efficacy and safety of sildenafil. The justification that the different salt of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP.

The bioequivalence of the 100 mg orodispersible tablet to the reference product is considered demonstrated. This conclusion can be extrapolated to the lower strengths 50 and 25 mg as all criteria for a biowaiver are fulfilled.

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.

2.5. Pharmacovigilance

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The CHMP did not require the applicant to submit a risk management plan because of the well established safety profile of the reference product and the proven bioequivalence between Vizarsin orodispersible tablets and the reference product.

2.6. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to: a) Vizarsin 25, 50 and 100 mg film-coated tablets, a medicinal product with the same active substance of the same therapeutic group and same route of administration with same key safety messages but different formulation to the orodispersible tablets and b) to Rivastigmine Krka orodispersible tablets 1,5 mg, 3 mg, 4,5 mg, 6 mg, a product with the same formulation, same route of administration and identical pictograms. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

This application concerns a line extension application for Vizarsin 25, 50 and 100 mg orodispersible tablets. The therapeutic indication remain unchanged to the one licensed for the reference product, i.e. treatment of erectile dysfunction in men.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient.

From a clinical perspective, this application does not contain new data on efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The orodispersible tablet contains the sildenafil base rather than sildenafil citrate like the reference product. Based on the available nonclinical and clinical data it is concluded that the different salt of the active substance does not differ significantly in properties with regards to safety and efficacy. This is in accordance with the relevant guideline and additional clinical studies were considered necessary.

The bioequivalence study forms the pivotal basis with a single-dose, randomized, open-label, two-way crossover, comparative design in healthy male subjects under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of sildenafil 100 mg orodispersible tablets met the protocol-defined criteria for bioequivalence when compared with the reference product Viagra 100 mg film-coated tablets. The 90% confidence intervals calculated for AUC0-t and Cmax of sildenafil were inside the acceptance range of acceptability (80.00 – 125.00) hence bioequivalence of the two formulations was demonstrated. This conclusion can be extrapolated to the lower strengths 50 and 25 mg as all criteria for biowaiver are fulfilled.

The benefit/risk ratio of the orodispersible tablet formulation 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.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Vizarsin 25mg, 50 mg and 100 mg orodispersible tablets in the indication:

"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 Vizarsin to be effective, sexual stimulation is required."

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

Risk management system

Not applicable

PSUR cycle

The PSUR cycle for the product will follow PSURs submission schedule for the reference medicinal product.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable