Amsterdam, 25 March 2021
EMA/409352/2021
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Sildenafil citrate FGK

International non-proprietary name: sildenafil

Procedure No. EMEA/H/C/005439/0000

Note

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

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List of abbreviations

AAS	Atomic Absorption Spectrometry
ANDA	Abbreviated New Drug Application (ANDA) is an application for a U.S. generic drug approval
API	Active Pharmaceutical Ingredient
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AE	Adverse Event
AUC_{0-14}	area under the plasma concentration time curve from zero to 14 hours
AUC	area under the plasma concentration versus time curve
AUC_{inf}	area under the plasma concentration versus time curve from zero to infinity
AR	Assessment Report
BEQ	Bioequivalence
BMI	Body Mass Index
CoA	Certificate of Analysis
CEP	Certificate of Suitability of the EP
CV	coefficient of variation
CFU	Colony Forming Units
CHMP	Committee for Human Medicinal Products
CMS	Concerned Member State
cGMP	cyclic guanosine monophosphate
CYP3A4, CYP2C9	cytochrome P3A4, cytochrome P2C9
DSC	Differential Scanning Calorimetry
DPM	Drug Product Manufacturer
ECG	Electrocardiogram
ERA	Environmental Risk Assessment
EDQM	European Directorate for the Quality of Medicines
Ph. Eur.	European Pharmacopoeia
FPM	Finished Product Manufacturer
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HDPE	High Density Polyethylene
HT	Holding time
HCT	Hydrochlorothiazide
CRS	Chemical Reference Substance (official standard)
ISR	Incurred Sample Reanalysis
IR	Infrared
IPC	In-process control
IS	internal standard
IU	International Units
LT	Less than
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantitation
LC/MS/MS	liquid chromatography coupled with tandem mass spectrometry

LoQ	List of Questions
LDPE	Low Density Polyethylene
MO	Major Objection
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MS	Mass Spectrometry
Cmax	maximum observed plasma concentration
NA	non applicable
ND	Not detected
NLT	Not less than
NMT	Not more than
NMR	Nuclear Magnetic Resonance
OC	Other Concerns
OOS	Out of Specifications
PL	Package Leaflet
PDE	Permitted Daily Exposure
PDE5	phosphodiesterase type 5
PVC	Poly(vinyl chloride)
PE	Polyethylene
PP	Polypropylene
PI	principal investigator
QC	quality control
QOS	Quality Overall Summary
RMS	Reference Member State
RH	Relative Humidity
RRT	Relative retention time
RSD	Relative standard deviation
RPM	rotation per minute
SD	standard deviation
SmPC	Summary of Product Characteristics
Λz	terminal elimination rate constant
TGA	Thermo-Gravimetric Analysis
UV	Ultraviolet
USP/NF	United States Pharmacopoeia/National Formulary
XRD	X-Ray Diffraction

1. Recommendation

Based on the CHMP review of the data and the Applicant's response to the CHMP LoOIs on quality, safety, clinical, the hybrid application for Sildenafil FGK in the *treatment of adult men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. In order for Sildenafil FGK to be effective, sexual stimulation is required,*

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Regulatory/Legal Question:

Applications for marketing authorisation are validated and assessed by the CHMP on the basis of the claims made by the Applicant and chosen type of application. Accordingly, the data submitted as part of a marketing authorisation application shall support the claims made within the application type, as chosen by the Applicant.

The present hybrid application was submitted on the basis of claims of a different pharmaceutical form ('oral lyophilisate') and a different route of administration ('oromucosal use') compared to the identified reference medicinal product while the PK data submitted referred to a sublingual use. To date the clinical data submitted have not supported the proposed different route of administration. In the responses to the list of outstanding issues, the Applicant requested to convert the type of application from hybrid to generic and to change the route of administration to 'oral use'; the pharmaceutical form would remain 'oral lyophilisate'. It is recalled that the CHMP may only consider changes that are compatible with the application type chosen by the Applicant at the start of the procedure. It is highlighted that, according to Article 10(2)(b) of Directive 2001/83/EC, the various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form, therefore should the pharmaceutical form be maintained as 'oral lyophilisate', there would be no difference in pharmaceutical form in relation to the reference medicinal product. In addition, the route of administration is now claimed to be the same as the reference product (i.e. oral use). The revised claims of the Applicant do not include any differences versus the reference product that would qualify for a hybrid application. Furthermore, they appear to be in contradiction with the development conducted and PK data intended to support a sublingual use (in this regard, see PK MO).

The Applicant is therefore requested to justify how the data submitted supports the submitted hybrid marketing authorisation application.

Pharmacokinetic MO

In line with the legal basis of this application (article 10.3 of Directive 2001/83/EC), the applicant has claimed a different pharmaceutical form *vis a vis* the reference medicinal product. However, the pivotal comparative PK study submitted by the applicant does not support a substantial sublingual absorption of the test product. In addition, the test product failed to completely dissolve under the tongue (even after ten minutes) in a significant proportion of subjects. The results suggest that the product applied for is unsuitable for sublingual use and may lead to variable exposure with unknown consequences regarding safety and efficacy of the medicinal product in the context of its proposed use.

The Applicant is asked to justify that the product is suitable for its intended use.

Questions to be posed to additional experts

Not applicable

Inspection issues

GMP inspection(s)

No further inspections are required.

GCP inspection(s)

No further inspections are required.

2. Executive summary

2.1. Problem statement

Erectile dysfunction (ED) is a condition that affects an estimated 10% of the adult male population. Treatment options for men with ED have advanced significantly during the past years and include intracavernous prostaglandin injections, vacuum constriction therapy and transurethral alprostadil pellets. However, efficacy and/or long-term satisfaction with these treatment options have been suboptimal. Sildenafil, the first oral therapeutic agent for the treatment of ED, is a potent and selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5, the predominant isoenzyme metabolising cGMP in the *corpus cavernosum*. Penile erection depends on relaxation of *corpora cavernosa* smooth muscle. In response to sexual stimuli, cavernous nerves and endothelial cells release nitric oxide (NO), which stimulates formation of cGMP via guanylate cyclase. By selectively inhibiting cGMP catabolism in cavernosal smooth muscle cells, sildenafil restores the erectile response to sexual stimulation without causing erections in the absence of such stimulation.

2.2. About the product

This centralised application for marketing authorisation concerns a hybrid application according to article 10(3) of Directive 2001/83/EC for Sildenafil FGK 50 mg, lyophilisate. Initially, the application was submitted also for 25 mg strength of sildenafil, but the applicant withdrew a MAA for this strength within the Day 121 responses. The reference product is Viagra 50 mg film-coated tablets (MAA No: EU/1/98/077/006, Pfizer Europe MA EEIG, Belgium). Marketing authorisation for Viagra film-coated tablets was granted in the European Union on 14 September 1998 on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

A hybrid application has been submitted claiming a different route of administration and pharmaceutical form of Sildenafil FGK 50 mg compared to that of the reference product Viagra at the beginning of the centralised procedure. The Applicant claimed that the pharmaceutical form of Sildenafil FGK 50 mg was "oral lyophilisate" and it was for "oromucosal use".

The Applicant was requested to submit scientifically supported justification concerning the absorption of sildenafil from the proposed product and to define the proper route of administration and pharmaceutical form.

Definitions according to EDQM Standard Terms database

Oromucosal use

Administration of a medicinal product to the oral cavity to obtain either a systemic or a local effect. The term oromucosal is only for use when a more specific term (e.g. buccal, gingival, sublingual...) does not apply. Oral use is excluded.

Sublingual use

Administration of a medicinal product under the tongue to obtain a systemic effect.

Oral use

Taking a medicinal product by means of swallowing.

Oral lyophilisate

Solid single-dose preparation made by freeze-drying of a liquid or semi-solid preparation. This fast-releasing preparation is intended to be placed in the mouth where its contents are released in saliva and swallowed or, alternatively, to be dissolved in water before oral administration.

Sublingual lyophilisate

Solid single-dose preparation made by freeze-drying of a liquid or semi-solid preparation, intended for sublingual use.

In response to the MO 11 (D180 LoOI) the Applicant has concluded the majority of absorption takes place after ingestion of sildenafil dispersed in saliva, following the disintegration of the lyophilisate in the oral cavity and a smaller proportion is absorbed sublingually. Consequently, the SmPC and related documents have been amended to specify the pharmaceutical form as "oral lyophilisate" and the route of administration as "oral". In addition, the Applicant changed the type of application to generic application based on Article 10(1) of Directive 2001/83/EC which is not acceptable during an MAA review.

Applications for marketing authorisation are validated and assessed by the CHMP on the basis of the claims made by the Applicant and chosen type of application. Accordingly, the data submitted as part of a marketing authorisation application shall support the claims made within the application type, as chosen by the Applicant.

The present hybrid application was submitted on the basis of claims of a different pharmaceutical form ('oral lyophilisate') and a different route of administration ('oromucosal use') compared to the identified reference medicinal product while the PK data submitted referred to a sublingual use. To date the clinical data submitted have not supported the proposed different route of administration. In the responses to the list of outstanding issues, the Applicant requested to convert the type of application from hybrid to generic and to change the route of administration to 'oral use'; the pharmaceutical form would remain 'oral lyophilisate'. It is recalled that the CHMP may only consider changes that are compatible with the application type chosen by the Applicant at the start of the procedure. It is highlighted that, according to Article 10(2)(b) of Directive 2001/83/EC, the various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form, therefore should the pharmaceutical form be maintained as 'oral lyophilisate', there would be no difference in pharmaceutical form in relation to the reference medicinal product. In addition, the route of administration is now claimed to be the same as the reference product (i.e. oral use). The revised claims of the Applicant do not include any differences versus the reference product that would qualify for a hybrid application. Furthermore, they appear to be in contradiction with the development conducted and PK data intended to support a sublingual use.

In line with the legal basis of this application (article 10.3 of Directive 2001/83/EC), the applicant has claimed a different pharmaceutical form *vis a vis* the reference medicinal product. However, the pivotal comparative PK study submitted by the applicant does not support a substantial sublingual absorption of the test product. In addition, the test product failed to completely dissolve under the tongue (even after ten minutes) in a significant proportion of subjects. The results suggest that the product applied for is unsuitable for sublingual use and may lead to variable exposure with unknown consequences regarding safety and efficacy of the medicinal product in the context of its proposed use. The Applicant is asked to justify that the product is suitable for its intended use.

Proposed indication

Sildenafil FGK is indicated in adult men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. In order for Sildenafil FGK to be effective, sexual stimulation is required.

Pharmacokinetic data for the reference product referred to in the clinical overview

Sildenafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. Concomitant administration with food reduces the rate of absorption (C_{max} mean reduction is 29% and T_{max} is delayed 60 minutes). After oral dosing of sildenafil AUC and C_{max} increase in proportion with dose over the recommended dose range (25-100 mg).

The mean steady state volume of distribution for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-demethylation of sildenafil. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50% that of the parent drug. The total body clearance of sildenafil is 41 L/h with a resultant terminal phase half-life of 3-5 h. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faeces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of administered oral dose).

2.3. The development programme/Compliance with CHMP Guidance/Scientific Advice

The applicant did not receive CHMP Scientific Advice pertinent to this product.

Relevant for the assessment is the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 rev. 1) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

2.4. General comments on compliance with GMP, GLP, GCP

GMP

Active substance

The active substance is sildenafil citrate. A valid QP declaration covering the manufacturing process of API has been provided

Finished medicinal product

A list of manufacturing and control sites involved in the manufacturing process and the process flow charts has been submitted.

All relevant sites have valid manufacturing authorizations or valid GMP certificates as appropriate. Hence, no GMP inspections are deemed necessary at this stage within the scope of this MAA evaluation procedure.

GLP

As applicant did not submit new non-clinical studies, this chapter is considered non-applicable.

GCP

Applicant submitted statement that clinical study was carried out according to the principles of GCP No inspection has been conducted by the EU/EEA competent authorities at the clinical or analytical study sites involved in the pivotal study. Presently, no GCP inspection for the following clinical study SIL-003, clinical study site Linear Clinical Research and bioanalytical study site CPR Pharma Services Pty Ltd is requested.

2.5. Type of application and other comments on the submitted dossier

- Article 10(3) of Directive 2001/83/EC.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Viagra, 25 mg, 50 mg, 100 mg, film–coated tablet
- Marketing authorisation holder: Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgium
- Date of authorisation: 14-09-1998
- Marketing authorisation granted by:
  - Union
- Marketing authorisation numbers: 25 mg: EU/1/98/077/002, 50 mg: EU/1/98/077/006, 100 mg: EU/1/98/077/010

Medicinal product authorised in the Union /Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Viagra 50 mg, film-coated tablet
- Marketing authorisation holder: Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgium
- Date of authorisation: 14-09-1998
- Marketing authorisation granted by:
  - Union
- Marketing authorisation numbers: 50 mg: EU/1/98/077/006

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

- Product name, strength, pharmaceutical form: Viagra, 50 mg, film-coated tablet
- Marketing authorisation holder: Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgium
- Date of authorisation: 14-09-1998
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number(s): EU/1/98/077/006
- Bioavailability study number: SIL-003

Orphan designation

Not applicable

Similarity with orphan medicinal products

The application did not contain a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

Information on paediatric requirements

Not applicable

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as oral lyophilisate containing 50 mg of sildenafil as active substance.

Of note, the EDQM term "sublingual lyophilisate" was approved just after the submission of this dossier but was never used by the Applicant who referred to "oral lyophilisate" during the MAA review.

Other ingredients are: microcrystalline cellulose, carmellose sodium, mannitol, lactose monohydrate, potato starch, glycine, macrogol 1500, citric acid, peppermint flavour, Quinoline yellow (E104).

The product is available in PVC/PCTFE blisters with aluminium laminate peel/push lidding foil, in packs of 4, 8, 12 and 24 lyophilisates.

3.1.2. Active Substance

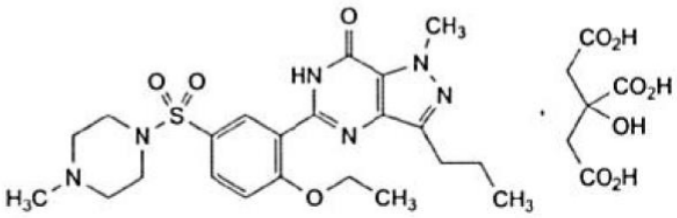
The sildenafil citrate active substance is of compendial standard, Ph. Eur. Information about the active substance is covered by a valid Certificate of Suitability.

General Information

Nomenclature

International non-proprietary name (INN):	sildenafil citrate
Compendial name:	sildenafil citrate
Chemical name:	(S)-5-chloro-N-((2-oxo-3-(4-(3-oxomorpholino)phenyl) oxazolidin-5-yl)methyl)thiophene-2-carboxamide
Other name (IUPAC):	5-[2-Ethoxy-5-[(4-methylpiperazin-1-yl) sulfonyl] phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate.
CAS registry number:	171599-83-0
Molecular formula:	$C_{28}H_{38}N_6O_{11}S$
Relative molecular mass:	667

Structural formula



General properties

The sildenafil citrate active substance used for the finished product is of compendial standard, Ph. Eur.

Manufacture, process controls and characterisation

Manufacture and micronisation as part of the active substance manufacturing process are performed by one manufacturer.

Specification, analytical procedures, reference standards, batch analysis, and container closure

No.	Test	Reference
1.	**Appearance**	Current Ph.Eur Sildenafil Citrate
2.	**Identification (IR)**	Current Ph.Eur Sildenafil Citrate
3.	**Water content (KF)**	Current Ph.Eur Sildenafil Citrate
4.	**Sulfated ash**	Current Ph.Eur Sildenafil Citrate
5.	**Assay**	Current Ph.Eur Sildenafil Citrate
6.	**Related Substances**	Current Ph.Eur Sildenafil Citrate
7.	**Impurity E**	Current Ph.Eur Sildenafil Citrate
8.	**Residual solvents**	In-house
9.	**Particle size**	In-house
10.	**Microbiological**	Current Ph.Eur

Specification of sildenafil citrate is in line with current version of Ph. Eur. monograph. Additional tests not included in monograph are residual solvents, particle size and microbiological purity. The specifications applied by DPM are identical to the CEP holder (the test methods for testing Residual Solvents and Particle Size Distribution are different to that of the drug substance manufacturer).

Analytical method and reference standards

Description and validation of in-house analytical method for residual solvent and particle size were provided.

Data for the reference standards (for sildenafil citrate and impurities) including CoAs, IR spectra were provided.

Batch analysis

Batch analytical data for several commercial scale batches of the active substance tested by both, ASM and FPM, were submitted. Batch details, manufacturing dates and batch sizes were provided. In 2017 (Ph.Eur. version 9.2), new LC method for control of additional impurities has been introduced and control of impurity D has been added. Batch results are within the specification in force of the time of analysis.

Container closure system and stability

Re-test period is 60 months, if stored in double polyethylene bag (outer black) in a triple laminated bag placed in a polyethylene container, as stated in the CEP.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description of the product

Sildenafil 50 mg oral lyophilisate –light yellow to yellow oval disc.

Composition of finished product:

Ingredient
Sildenafil citrate
Carmellose sodium
Mannitol
Lactose monohydrate
Potato starch
Glycine
Macrogol 1500
Citric acid
Peppermint flavour
Quinoline Yellow
Microcrystalline Cellulose
Sodium Hydroxide

Pharmaceutical development

New formulation of sildenafil citrate, a lyophilisate, has been developed. Of note, the EDQM term sublingual lyophilisate was approved just after the submission of this dossier but was never used by the Applicant who referred to "oral lyophilisate" during the MAA review.

Sildenafil citrate is a BCS Class II drug, applied in a micronized form since particle size proved to be a critical parameter influencing the dispensing and removing the lyophilisate (referred to also as "wafers") from the blister after lyophilisation. The choice of the excipients aimed to maintain the API embedded within a crystalline, porous, rapidly water-soluble matrix that has a suitable mechanical strength for handling, storage and stability over the required storage conditions.

Sildenafil 50 mg was developed as a lyophilisate which disintegrates rapidly. Therefore, product is manufactured by lyophilisation (freeze drying) by which the water in the porous structure of the matrix is frozen and is followed by sublimation and desorption. The temperature and pressure have been identified as critical parameters of the lyophilisation process and have been validated.

No overages are used in formulation.

Because no USP or Ph. Eur. monograph is available for Sildenafil lyophilisates, development of suitable dissolution testing method was performed. The results from initial dissolution testing showed an immediate release in both dissolution media (0.1 N HCL and buffer with pH 4.5). Due to the solubility of the API the development of a discriminatory dissolution method cannot be reasonably expected. Thus, inclusion of a dissolution test in the product specification is not warranted; instead the proposed disintegration test is considered sufficient.

The pivotal PK study was performed under fasting conditions to compare the pharmacokinetic data of Sildenafil 50 mg lyophilisates with reference product Viagra 50 mg film-coated tablets sourced from the EU market.

Final product is packaged in PVC/PCTFE blisters with a peel/push CR (child resistant) aluminium lidding foil. The PVC thermoforming blister foil provides a barrier for light moisture and gases. The lidding foil consists of aluminium and paper, lyophilisates are in contact with aluminium.

Microbiological purity of the product is routinely tested according to Ph. Eur. 5.1.4 Microbiological quality of non-sterile pharmaceutical preparations and substances.

Manufacture of the product and process controls

Sildenafil citrate lyophilisates are manufactured. Testing of finished product is performed. Manufacturers with their responsibilities were presented.

A flow chart and description of manufacturing process have been provided. The non-standard process of manufacture of lyophilisates comprises compounding, mixing, dispensing, lyophilisation and blister sealing.

Control of the critical steps includes a combination of process parameters and in-process control tests.

The process validation report of several commercial batches has been submitted. Parameters tested during process validation are those corresponding to the IPC tests. All samples collected from each batch in each stage of manufacture were in compliance with set acceptance criteria. The proposed duration of single steps of the non-standard process is confirmed by reproducible results of IPC control tests in the validation report.

Product specification, analytical procedures, batch analysis

Specifications

Test
Appearance
Dimensions
Identification (by HPLC)
Identification (FTIR)
Disintegration
Water Content
Uniformity of Dosage Units – Content Uniformity
Assay
Related Substances
Microbial

The proposed specification for the finished product is in line with ICH Q6A, where relevant, and it is generally acceptable for this type of dosage form.

The test methods and the specification limits for the following tests are referenced to the Ph.Eur. monographs: identification by FTIR, disintegration, water content, uniformity of dosage units – content uniformity and microbiological testing.

Provided specifications are acceptable.

Analytical methods

All analytical methods were described in detail in 3.2.P.5.2. Appearance is performed visually, methods for identification by FTIR, water content, disintegration, and uniformity of dosage units – content uniformity and for microbiological purity are referred to appropriate Ph. Eur. and USP monographs. In-house HPLC methods were developed for identification, dimensions, assay and for related substances.

Batch analysis

Satisfactory data for several batches have been provided.

Reference standards

Working standard of API and API impurity reference standards are characterised. The provided chapter P.6 is identical to the chapter S.5 of the quality documentation.

Container closure

The finished product is packed in PVC/PCTFE blisters with a peel/push CR (child resistant) aluminium lidding foil contained in a cardboard secondary package. Specification, analytical methods and certificates of analysis were presented for all component of the primary packaging. Technical drawings were presented for each strength of the product for the printed laminate and the thermoformed blister.

Compliance with Commission Regulation (EU) No. 10/2011 and (EU) No. 2016/1416 on plastic materials and articles intended to come into contact with food was declared for each of the primary container closure materials, i.e. foil laminate and blister material.

Stability of the product

Long-term and intermediate stability data covering 36 month and accelerated data covering 6 months were presented for several batches of product packed in the proposed container. Long-term results (for both strengths) are in line with proposed shelf-life specification.

Significant colour changes were observed at intermediate and accelerated stability study. It is considered to be a minor cosmetic defect which has no impact on the safety or efficacy of the product.

At long-term stability study, appearance of lyophilisates is well within shelf-life specification.

Performed photostability studies demonstrated that drug product is stable when subjected to photodegradation.

Based on results from stability study, the proposed shelf life of 36 months with storage condition of "Store below 25°C" and "Protect from moisture" is acceptable.

Adventitious agents

BSE statement for lactose are provided.

GMO

Not applicable

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Sildenafil FGK 50 mg lyophilisate is intended for treatment of adult men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

Active substance

The manufacture of API is covered by CEP procedure. The specification of the API is in line with Ph. Eur. monograph 2270 and this is adequate to ensure the quality of the substance to be used in the proposed finished product.

Finished product

The formulation of finished product Sildenafil 50 mg lyophilisate was developed as an alternative to reference product Viagra film-coated tablet.

Sildenafil 50 mg was developed in the form of lyophilisate which disintegrates rapidly. Therefore, product is manufactured by lyophilisation. A detailed description of the process has been provided in the dossier. Process validation was performed.

The proposed specification for the finished product is in line with ICH Q6A, where relevant, and is generally acceptable.

Stability data were provided for several batches under long-term, intermediate and accelerated conditions which were packed in the proposed container (PVC/PCTFE blisters with a peel/push CR (child resistant) aluminium lidding foil). Long-term and intermediate stability data cover 36 months and accelerated data cover 6 months. The proposed shelf life of 36 months with storage condition of "Store below 25°C" and "Protect from moisture" is acceptable.

Conclusion

The quality dossier is generally well presented and all manufacturing processes with regards to the finished product are well controlled. The application is considered approvable from the quality perspective.

3.2. Non clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of sildenafil are well known. As sildenafil is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

3.2.1. Ecotoxicity/environmental risk assessment

No new Environmental Risk Assessment studies were submitted. Thus, the applicant claims that their product would not bring any increased risks to the environment. This justification is not accepted given the consumption data provided by the Applicant which showed increasing volumes of sildenafil marketed over the last 4 years. Therefore a signed environmental risk assessment in line with the guideline EMEA/CHMP/SWP/4447/00 corr 2 is required, with the CV of the expert who authored the report.

3.2.2. Discussion on non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is considered adequate.

Justification for not providing ERA based on hybrid nature of this application has been provided by the applicant. However, this justification is not acceptable. Applicant submitted consumption data over the last 4 years. However, applicant´s claim that the consumption of sildenafil is stable cannot be supported. Thus, an Environmental risk assessment in line with the guideline EMEA/CHMP/SWP/4447/00 corr 2 would be required.

3.2.3. Conclusion on non-clinical aspects

As stated above, there are issues that need to be clarified.

3.3. Clinical aspects

This is a centralised procedure according to regulation (EC) No 726/2004 for Sildenafil FGK, submitted as a hybrid of a centrally authorised medicinal product according to Article 10(3), with the following indication:

Sildenafil FGK is indicated in adult men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. In order for Sildenafil FGK to be effective, sexual stimulation is required.

Reference medicinal product is Viagra, film-coated tablet (Pfizer Europe MA EEIG) registered since 1998 in EU. Compared to the reference medicinal product, the Applicant claimed for Sildenafil FGK a different pharmaceutical form (oral lyophilisate) and a different route of administration (oromucosal use was claimed by applicant at the beginninng of the procedure, then sublingual and since D180 "oral use" is used which is the same route of administration as the reference product).

Relevant for the assessment is the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 rev. 1) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

The applicant did not receive CHMP Scientific Advice pertinent to the clinical investigation.

3.3.1. Exemption

Applicant submitted a pivotal PK study with Sildenafil FGK 50 mg lyophilisate and requested biowaiver for additional 25 mg strength. During the procedure in the responses to the Day 120 LoQ, marketing authorisation application for 25 mg strength has been withdrawn and with it the request for a biowaiver.

3.3.2. Pharmacokinetics

To support the application, the applicant has submitted 1 pivotal PK study:

A pivotal study of the bioequivalence of oral Viagra and a test sublingual sildenafil wafer.

Methods

Study design

Study is designed as single-centre, randomised, two-treatment, two period, open label, two-way crossover pivotal PK study in healthy male volunteers with single dose administration under fasting conditions. In each study period, subjects received a single 50 mg dose of sildenafil, either as a test sublingual sildenafil wafer or as reference Viagra film-coated tablet. Subjects fasted for 10 hours prior to receiving study medication and continued fasting until 4 hours post-dose on Day 1. Immediately prior to administration of the test sildenafil 50 mg sublingual wafer, the sublingual area was moistened with approximately 1 mL of water, and the subject was then instructed to swallow. There was to be no standing water in the sublingual space. One study medication wafer was placed in the sublingual space and was required to be allowed to dissolve under the tongue and was not to be crushed, chewed, or swallowed while waiting for its disintegration for 10 minutes. After the administration of test product, sublingual check was performed to determine, if the test product was dissolved. In approximately 50% of cases, the test product was not dissolved completely during the 10 minutes interval after the administration (according to the protocol, expected time for test product to dissolve was 1-5 min). In case that test product was not dissolved after 10 minutes, the sublingual area was rinsed with a small amount of water to remove any remaining material and the participant was instructed to swallow. Viagra 50 mg oral film-coated tablet was administered with 250 mL of water. Water and other clear non-caffeinated beverages were allowed as desired except 1 hour either side of dosing. Blood samples were collected pre-dose (0.0) and at 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 8.00, 10.00, 12.00 and 14.00 hours post-dose. Wash-out period was minimum 7 days. Sildenafil in human plasma was analysed by LC/MS/MS.

Population(s) studied

Forty-eight subjects were planned for Period 1 and Period 2. Study started with 48 subjects, two subjects terminated study in/after Period I. As the dosing was done in four groups, it was possible to enrol 2 new subjects as the replacement for 2 withdrawn subjects. Forty-eight subjects completed both periods in the study as per protocol (pharmacokinetic population). As a safety population, all 50 subjects (including 2 withdrawn) were assessed.

Screening procedures to determine subjects' eligibility for participation in the study were to be performed no more than 21 days before the first scheduled dosing date. Screening included details of demography, medical and surgical history, prior and concomitant medications, physical examination (including an oral cavity and sublingual space assessment), height and weight, vital signs, 12-lead ECG and clinical laboratory testing for haematology, clinical chemistry, urinalysis, serology and drugs of abuse.

The inclusion criteria were: healthy male subjects aged 18-50 years, BMI ≥ 19 to ≤ 30 kg/m^2, ability to provide signed informed consent form, being in good general health without clinically significant haematological, cardiac, respiratory, renal, endocrine, gastrointestinal, psychiatric, hepatic, or malignant disease, ability to refrain from smoking while at the research unit.

Safety assessments of the subjects included monitoring of adverse events (AEs), vital signs (blood pressure, heart rate, respiratory rate and oral temperature), clinical laboratory findings, 12-lead ECGs, physical examination, oral cavity and sublingual space assessments (at baseline, 30 min, 1 hour and at 14 hours after administration of the medicinal product) and oral symptoms questionnaire.

One subject was withdrawn from the study due to an adverse event in Period I, another one was withdrawn from the study as he was unable to complete Period 2 within a reasonable timeframe.

Analytical methods

Bioanalytical report concerning LC/MS/MS method for the determination of sildenafil in human plasma (Li-Heparin) was submitted.

During the study, blood samples were collected into tubes containing lithium heparin as an anticoagulant, then centrifuged. Once spun, plasma samples were shipped to the bioanalytical laboratory and assayed for concentrations of sildenafil.

Samples were analysed. Data was collected and integrated using software, then regression and reporting were performed. The bioanalytical group was blinded to the randomization code to maintain objectivity in the analysis.

Internal standard was d8-sildenafil.

Pharmacokinetic Variables

Pharmacokinetic parameters were determined. Non-compartmental methods were used to determine following pharmacokinetic parameters:

C_{max}: maximum observed plasma concentration obtained directly from the data

AUC_{0-14}: area under the plasma concentration-time curve from zero to 14 hours post-dosing

T_{max}: time to maximum observed concentration, taken directly from the data

λz: terminal elimination rate constant obtained from the slope of the line, fitted by linear least squares regression through the terminal points of the logarithmic concentration-time profiles

AUC_{inf}: area under the plasma concentration versus time curve from zero to infinity, calculated as ($AUC_{0-tlast}$ + C_{last}/λz), where Ct is the last quantifiable concentration.

$t_{½}$: apparent terminal half-life, calculated as $t_{1/2}$ = ln(2)/λz, where ln(2) = 0.693.

Statistical methods

Statistical analysis was performed on the pharmacokinetic parameters. Log-transformed AUC_{0-14}, AUC_{inf} and C_{max} were analysed, using analysis of variance with fixed effects for sequence, period and treatment, with participant as a random effect. The confidence intervals were derived from this model and back-transformed into standard units. The method of evaluation for the primary objective was standard bioequivalence criteria of test product versus reference product for AUC_{0-14}, AUC_{inf} and C_{max}. The secondary objective was evaluated by a descriptive analysis.

Summary statistics for continuous variables included mean, standard deviation, coefficient of variation (CV %), median, minimum, and maximum; T_{max} was summarized using median, minimum, and maximum values.

Results

Table 1: **Arithmetic Means (SD) of plasma pharmacokinetic parameters by treatment**

(n=48)	Median (range)	Arithmetic Mean (± Standard Deviation)			
Treatment	**T_{max} (hr)**	**C_{max} (ng/mL)**	**AUC_{0-14} (hr*ng/mL)**	**AUC_{inf} (hr*ng/mL)**	**$T_{1/2}$ (hr)**
Test sildenafil wafer	1.00 (0.25 – 2.00)	188 (±104)	591 (±309)	605 (±319)	2.56 (±0.51)
Viagra® film-coated tablet	1.00 (0.50 – 4.00)	167 (±98)	512 (±308)	526 (±319)	2.61 (±0.58)

Table 2: **Geometric means (CV) of plasma pharmacokinetic parameters by treatment**

(n=48)	Median (range)	Geometric Mean (Coefficient of Variation)			
Treatment	**T_{max} (hr)**	**C_{max} (ng/mL)**	**AUC_{0-14} (hr*ng/mL)**	**AUC_{inf} (hr*ng/mL)**	**$T_{1/2}$ (hr)**
Test sildenafil wafer	1.00 (0.25 – 2.00)	168 (55%)	536 (52%)	549 (53%)	2.51 (20%)
Viagra® film-coated tablet	1.00 (0.50 – 4.00)	147 (59%)	459 (60%)	470 (61%)	2.55 (22%)

Table 3: **Comparisons of pharmacokinetic parameters between treatments**

		Test Sildenafil Wafer / Reference Viagra® Tablet		
Analyte	**Parameter**	**Ratio of Geometric Means**	**90% Confidence Interval for Ratio**	**Intra-subject CV**
Sildenafil (n=48)	C_{max} (ng/mL)	114.7%	105.4 – 124.7%	24.5%
	AUC_{0-14} (hr*ng/mL)	116.8%	111.2 – 122.6%	14.3%
	AUC_{inf} (hr*ng/mL)	116.6%	111.2 – 122.4%	14.0%

There was zero median change in time to maximal concentration (T_{max}) for the test sildenafil wafer compared with Viagra® (p = 0.156).

There were no pre-dose concentrations of sildenafil in period II. There was one case of C_{max} observed in the first time point after dosing (R4009 in period I after test product). Extrapolated AUC was less than 20% in all the subjects. There were 15 cases of C_{max} being outside of the calibration range.

Safety data

No serious adverse events (AEs) were reported. One subject was withdrawn due to an adverse event (AE) of syncope (immediately following dosing in Period 1 (sublingual wafer)), it was not deemed related to study drug.

There were a total of 60 AEs reported by 28 subjects during the study, 32 and 28 AEs following administration of Sildenafil 50 mg sublingual wafers and Viagra 50 mg film-coated tablets, respectively. Most AEs were classified as mild. 45 AEs were "possibly" related to the study drug. All

subjects who experienced treatment-related AEs during the study recovered completely. No significant safety concerns emerged.

All AEs were mild or moderate with no AE of severe intensity. Most AEs resolved by the end of the study, with the exception of 4 AEs (upper respiratory tract infection [1 AE], phlebitis [1 AE], viral upper respiratory tract infection [2 AEs]. These 4 AEs were of mild severity and considered not related to study drug.

Commonly occurring treatment-related AEs were headache, reported in 21 subjects after administration of test product and 15 subjects after administration of reference product.

Seven subjects used concomitant medication during the study period for treatment-emergent AEs post-dose – paracetamol (6x) and ibuprofen (1x).

Oropharyngeal tolerability was assessed for both the test sublingual sildenafil wafer and Viagra film-coated tablet. There were no abnormal findings of oral cavity tolerability in any subject, with mucosa and inflammation deemed as normal in all post-dose assessments of oral cavity and sublingual space, following both study treatments.

Based on the results of oral symptoms questionnaire, following administration of test sildenafil wafer, bitterness was reported by 21 subjects (13 mild, 8 moderate) at 30 minutes post-dose administration, by 5 subjects (all mild) at 1 hour post-dose, and by no subjects at 14 hours post-dose. One subject reported a burning sensation (mild) following administration of test sildenafil wafer (R4009 at 30 min post-dose on Day 1 of Period 1). This had resolved by 1 hour post-dose. No subjects reported sublingual irritation at pre-dose or following administration of test sildenafil wafer.

3.3.3. Pharmacokinetic conclusion

After the administration of test product, sublingual check was performed to determine if the test product was dissolved. In approximately 50% of cases, the test product was not dissolved completely during the 10 minutes interval after the administration (according to the protocol, expected time for test product to dissolve was 1-5 min). In case that test product was not dissolved after 10 minutes, the sublingual area was rinsed with a small amount of water to remove any remaining material and the participant was instructed to swallow. This alerts to the test product not behaving as intended in 50% of cases. Rinsing of the sublingual area with an unspecified amount of water also means a loss of standardised conditions for administration of the test product which increases the difficulty in concluding on the findings of the study.

While the PK parameter results of the study showed C_{max} and AUC_{inf} were within the acceptance criteria for bioequivalence, both were higher for the test compared to the reference product i.e. C_{max} 114.7% (90%CI 105.4-124.7%) and AUC_{inf} 116.6% (90%CI 111.2 – 122.4%) which may reflect some limited sublingual absorption of sildenafil from the wafer. The higher C_{max} and AUC_{inf} may however also be due to formulation differences between the test and reference products and the study design with the different administration of the two products makes it difficult to conclude. Of note, the upper limit of the 90%CI for the C_{max} of the test product is on the margins of the acceptance criteria for bioequivalence.

Overall, the results of the submitted pivotal PK study lyophilisate do not support a substantial sublingual absorption of the test product. In addition, the test product failed to completely dissolve under the tongue (even after ten minutes) in a significant proportion of subjects. The results suggest that the product applied for is unsuitable for sublingual use and may lead to variable exposure with unknown consequences regarding safety and efficacy of the medicinal product in the context of its proposed use (see PK MO).

3.3.4. Pharmacodynamics

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

3.3.5. Additional data

Not applicable

3.3.6. Post marketing experience

The medicinal product received marketing authorisation in Australia in June 2018. At the time of the preparation of dossier, there were less than 200 cartons of medicinal product supplied to Australian pharmacies. There has been no spontaneous reports of adverse events, errors or defects. No other data were supplied by the applicant.

3.3.7. Discussion on clinical aspects

In the submitted application, the Applicant claimed that sildenafil administration via their test product differs from the reference medicinal product Viagra film-coated tablets in that the product can be administered without water and can be taken by persons who are averse to taking tablets. In addition, the Applicant claimed that sildenafil 50 mg lyophilisate has therefore been developed to allow the drug to be absorbed sublingually, after the product has been placed under the tongue.

To support this application for a hybrid medicinal product containing sildenafil, the Applicant submitted a review of pre-clinical and clinical data as well as one pivotal PK study comparing the test product to the 50 mg strength of the reference medicinal product Viagra.

The submitted PK study is randomised, two-treatment, two period, open label, two-way crossover study comparing two formulations (lyophilisate vs. reference film-coated tablet) of sildenafil 50 mg in healthy male volunteers under fasting conditions. While the statistical analysis demonstrated comparable PK parameters between test product (Sildenafil FGK) and reference product (Viagra), the test and reference products were administered under different conditions. Immediately prior to administration of the test product, the sublingual area was moistened with approximately 1 mL of water, and the subject was then instructed to swallow. There was to be no standing water in the sublingual space. One test product was placed in the sublingual space and was required to be allowed to dissolve under the tongue and was not to be crushed, chewed, or swallowed and to wait for its disintegration for 10 minutes. Viagra 50 mg oral film-coated tablet was administered with 250 mL of water. Therefore, in comparison to the tablet, swallowing of the wafer was not expected to occur. Hence the claim that the product was to be used by persons who are averse to taking tablets. However, during the conduct of the pivotal PK study in approximately 50% of subjects it became apparent that sublingual absorption had not occurred as intended and for those participants in whom the wafer visibly appeared as not fully dissolved, water was administered to help swallow the contents.

The clinical study site as well as bioanalytical study site has not been inspected by any of the EU agencies. In the submitted study, there were uncertainties considering the administration of the test product, as there were recorded several discrepancies considering the dosing and check-up after dosing. These issues have been solved by the Applicant.

Although the results of the study for the two products appear to show PK parameters (C_{max} and AUC_{inf}) which would usually meet the acceptance criteria for bioequivalence (although higher absorption and exposure for the test product), the study conduct and the PK results failed to show sublingual

absorption for the test product as anticipated, although the higher C_{max} and AUC for the wafer may suggest limited sublingual absorption.

According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) Section 4.1.1 '*The study should be designed in such a way that the formulation effect can be distinguished from other effects*'. For a hybrid application with two different formulations, different administration of test and reference products is expected in line with their intended use (posology). However, the conducted study did not show mostly sublingual absorption for the test product and therefore did not confirm the test product behaved as a hybrid formulation different to the reference product.

During the procedure, the question considering the route of absorption of sildenafil from the lyophilisate was raised. It was indicated by the applicant that this pharmaceutical form was supposed to have sublingual absorption. However, the results of the PK study and dissolution of sildenafil at higher pHs opposed it. At D180, applicant claims that even if there is some sublingual absorption after the administration of proposed product under the tongue, the dominant part of absorption takes place after ingestion of sildenafil dispersed in saliva following the disintegration of the lyophilisate in the oral cavity.

Consequently, applicant proposes the pharmaceutical form as "oral lyophilisate" and the route of administration as "oral", which is the same pharmaceutical form (as it is immediate-release oral pharmaceutical form) and route of administration as the reference product has.

In addition, the Applicant changed the legal basis of this application to generic application, based on Article 10(1) of Directive 2001/83/EC which is not acceptable during an MAA review.

Given the submitted pivotal PK study was designed and conducted for an intended hybrid formulation, and the results demonstrating PK parameters falling within the 80 – 125% acceptance criteria for bioequivalence (C_{max} 114.7% (90%CI 105.4-124.7%) and AUC_{inf} 116.6% (90%CI 111.2 – 122.4%)) were unexpected, it is considered that the design, conduct and results of the submitted pivotal PK study do not support a hybrid Marketing Authorisation.

The Applicant sought a biowaiver for 25 mg strength in the initial application, however, the marketing authorisation application for 25 mg strength was withdrawn along with the request for a biowaiver in the responses to the Day 120 LoQ. A posology for the 25 mg and 100 mg strengths is now reintroduced with a proposal in the SmPC (see Response to Q12), however, the proposed posology for the 25 mg and 100 mg strengths is not supported by neither a biowaiver for the 25 mg lower strength nor appropriate PK studies for the 100 mg strength.

3.3.8. Conclusions on clinical aspects

In line with the intended use of this product in persons who are averse to swallowing and the legal basis of this application (article 10.3 of Directive 2001/83/EC), the Applicant has claimed a different pharmaceutical form *vis a vis* the reference medicinal product. However, the submitted pivotal comparative PK study does not support a substantial sublingual absorption of the test product. In addition, the test product failed to completely dissolve under the tongue (even after ten minutes) in a significant proportion of subjects. The results suggest that the product applied for is unsuitable for sublingual use and may lead to variable exposure with unknown consequences regarding safety and efficacy of the medicinal product in the context of its proposed use.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of the safety concerns

The Safety Specification (Part II, SVIII) from RMP version 0.1, signed 09 January 2020 is assessed below:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Nitrate interaction
Important potential risks	• Non arteritic ischemic optic neuropathy (NAION) • Sudden hearing loss • Eye haemorrhage
Missing information	• Severe hepatic impairment

Discussion on safety specification

According to the GVP Module V (Rev. 2), for new application under Article 10(3) of Directive 2001/83/EC, RMP module SVIII should be based on the safety concerns of the reference medicinal product unless the hybrid product significantly differs in properties which could relate to safety, or unless requested otherwise by the Agency or national competent authority. The summary of safety concerns proposed by the Applicant is fully in line with the last approved version 3.2 of the RMP for the reference medicinal product Viagra signed 26 November 2013. Therefore the PRAC agrees that the safety concerns listed by the Applicant are appropriate.

Conclusion on safety specification

Having considered the data in the safety specification,

- The PRAC agrees that the safety concerns listed by the Applicant are appropriate.

3.4.2. Pharmacovigilance plan

Routine pharmacovigilance activities

The applicant proposed routine pharmacovigilance activities only, which is in line with the reference product, Viagra. No additional pharmacovigilance activities are considered required for the proposed formulation of oral lyophilisate.

Overall conclusions on the PhV Plan

The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

3.4.3. Risk minimisation measures

Routine Risk Minimisation Measures

The safety information in the proposed product information is aligned to the reference medicinal product.

Additional risk minimisation measures

Not applicable. The reference product does not have additional risk minimisation measures.

Overall conclusions on risk minimisation measures

The PRAC having considered the data submitted was of the opinion that:

In line with the reference product, the proposed risk minimisation measures are sufficient to minimise the risks of the product in the approved indication(s).

3.5. Summary of the risk management plan

The public summary of the RMP does not require revision.

3.5.1. Overall Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.1 is acceptable.

3.6. Pharmacovigilance system

The Applicant FGK Representative Service GmbH has submitted an updated Summary of the Pharmacovigilance System signed on 26 August 2020. The updated Summary of the Pharmacovigilance System is signed by EU QPPV. In the summary the Applicant confirms that he has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC.

The PRAC considers that the updated Summary of the Pharmacovigilance System submitted by the Applicant would fulfil the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

4. Benefit/risk assessment

Quality

From a quality point of view the dossier is generally well presented. All quality issues are resolved. The quality of the product is considered acceptable for an oral lyophilisate albeit intended for sublingual use. The EDQM term sublingual lyophilisate was approved just after the submission of this dossier but was never used by the Applicant who referred to "oral lyophilisate" during the MAA review.

Non-clinical

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is considered adequate. However, as the consumption of sildenafil increases over the past 4 years, applicant is expected to submit ERA in line with the guideline EMEA/CHMP/SWP/4447/00 corr 2.

Clinical

With the submitted PK study for 50 mg strength between test product (Sildenafil FGK) and reference product (Viagra) under fasting conditions the Applicant was not able to demonstrate a different (sublingual) route of absorption compared to the reference product. The results suggest that the

product applied for is unsuitable for sublingual use and may lead to variable exposure with unknown consequences regarding safety and efficacy of the medicinal product in the context of its proposed use.

Conclusions

The overall B/R of Sildenafil FGK is considered negative.