21 February 2013
EMA/CHMP/633051/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Viagra

International non-proprietary name: **sildenafil**

Procedure No. EMEA/H/C/000202/X/0070

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8545
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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List of abbreviations

AAS	Atomic Absorption Spectrometry
AP	Applicant's Part (or Open Part) of a DMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CMS	Concerned Member State
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
DMF	Drug Master File = Active Substance Master File
DP	Decentralised (Application) Procedure
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
GC	Gas Chromatography
GSM	Grams per square meter
HDPE	High Density Polyethylene
HPLC	High Performance Liquid Chromatography
IPC	In-process control
IR	Infrared
IU	International Units
KF	Karl Fischer
LDPE	Low Density Polyethylene
LOA	Letter of Access
LOD	Limit of Detection
LOQ	(1) Limit of Quantification, (2) List of Questions
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board
MS	Mass Spectrometry
ND	Not detected
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NT	Not tested
OOS	Out of Specifications
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PP	Polypropylene
PVC	Poly vinyl chloride
QOS	Quality Overall Summary
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of a DMF
RRT	Relative retention time
RSD	Relative standard deviation
RVG #	Marketing Authorisation number in NL
SPC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis
TLC	Thin Layer Chromatography
TLR	Theoretic Logarithmic Reduction Factor
UV	Ultraviolet
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Ltd submitted on 28 February 2012 an application for an extension of the Marketing Authorisation to the European Medicines Agency (EMA) for Viagra, 50 mg, orodispersible tablets, through the centralised procedure falling within the Article 19 (1) and Annex I (point 2 intend d) of the Commission Regulation (EC) No 1234/2008.

Pfizer Ltd. is already the Marketing Authorisation Holder for Viagra, 25, 50, 100, film-coated tablets (EU/1/98/077/002-004, 006-008, 010-012, 013-019).

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

The application submitted is composed of administrative information, complete quality data, and a clinical bioequivalence study.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/17/2008 for the following condition: Treatment of Erectile dysfunction on the granting of a class waiver.

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Information relating to Orphan Market Exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Licensing status

Viagra has been given a Marketing Authorisation in European Union since 14 September 1998.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Pieter de Graeff

- The application was received by the EMA on 28 February 2012.
- The procedure started on 21 March 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 6 June 2012.
- During the meeting on 16-19 July 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 July 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 10 October 2012.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 November 2012.
- During the CHMP meeting on 10-13 December 2012, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 18 January 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 4 February 2013.
- During the meeting on 18-21 February 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension of the Marketing Authorisation for Viagra, 50 mg, orodispersible tablets on 21 February 2013.

2. Scientific discussion

2.1. Introduction

This application concerns an extension to the existing Viagra marketing authorisation. Viagra is currently authorised as 25mg, 50 mg and 100 mg immediate release film-coated tablets (EU/1/98/077/002-004, 006-008, 010-019). This line extension application concerns the addition of a new pharmaceutical form: an orodispersible tablet (ODT) containing 70.225 mg sildenafil citrate, corresponding with 50 mg sildenafil. The indication remains the same as for the already authorised presentations:

Viagra is indicated in the 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 Viagra to be effective, sexual stimulation is required.

Viagra 50 mg orodispersible tablets are proposed to be available in pack sizes of 2, 4, 8 and 12 orodispersible tablets like the already authorised 50 mg film-coated tablets. This is consistent with the dosage regimen and duration of use.

In this line extension application the entire product information was brought in line with the latest QRD template.

2.2. Quality aspects

2.2.1. Introduction

Viagra 50 mg orodispersible tablets are presented as blue diamond-shaped orodispersible tablets containing 50 mg sildenafil (as citrate) as active substance. The composition is described in section 6.1. of the SmPC. Viagra 50 mg ODT are packaged in aluminium foil blisters in carton of 2, 4, 8 or 12 tablets.

2.2.2. Active Substance

Viagra 50 mg orodispersible tablets contain the same active substance as the authorised film-coated tablets; the substance is sourced from the same commercial drug substance site, is manufactured with the same manufacturing process and is released in accordance with the same approved active substance specifications. The active substance specifications were found to be suitable for use in the sildenafil citrate orodispersible tablets. Hence the applicant referred to the dossier of the already authorised tablet presentations of Viagra for information on the active substance.

2.2.3. Finished medicinal Product

Pharmaceutical development

The aim of the applicant was to develop a more convenient dosage form for the existing 50 mg film-coated tablet. The applicant selected an orodispersible tablet because it allows to be administered without water, after dispersion it can easily be swallowed when placed in the mouth. The formulation development of the ODT was driven by the need to satisfy several criteria for optimal performance: acceptable taste and mouth feel, timely disintegration, acceptable pharmacokinetic profile (i.e. bioequivalent to the commercially available sildenafil citrate immediate release tablet 50 mg), satisfactory chemical and physical stability, and suitable for conventional manufacturing processes and equipment.

The physicochemical characteristics of the active substance that can potentially influence the performance of the finished product have been discussed. Modelling studies (based on the active substance's physicochemical attributes), predict that the content uniformity of the sildenafil citrate 50 mg ODT will not be substantially affected by the particle size of the drug substance should the particle size distribution reach the upper limit of the drug substance specification. No new degradants were observed during development of sildenafil citrate 50 mg ODT. Sildenafil citrate demonstrates high solubility from pH 1 to pH 6. With solubility high across the gastric pH range, tablet disintegration is the rate limiting step for bioavailability. During development both disintegration and dissolution studies have been performed. The discriminatory nature of the disintegration and dissolution tests has been demonstrated. A DOE was performed to study the effect of different ODT compositions and the hardness on the disintegration and dissolution

The excipients in sildenafil citrate 50 mg ODT were selected based upon their suitability for use in a conventional manufacturing process as well as their organoleptic properties, and are different from the excipients used in the Viagra film-coated tablets. The ODT excipients are generally regarded as safe (GRAS) and/or comply with the relevant food flavouring regulations and with the

provisions of Directive 88/388/EEC. The excipients of the ODT are: mannitol, crospovidone, polyvinylacetate, povidone (which are the four ingredients of the diluent), croscarmellose sodium (disintegrant), microcrystalline cellulose (filler), silica colloidal anhydrous (glidant), sucralose (sweetener), indigo carmine aluminium lake E132 (colorant), magnesium stearate (lubricant), maltodextrin, dextrin, propylene glycol, glycerol, alpha-tocopherol and flavouring ingredients. The latter six ingredients are part of commercially available sweeteners and flavours. Adequate specifications were proposed for all excipients and compatibility with all the excipients in the formulation has been demonstrated.

The 50 mg orodispersible tablet contains a commercially available diluent used to provide good mouth feel. The composition of the diluent and its specifications have been adequately justified and assurance was provided that this has no influence on the final drug product specifications No special warnings in the SmPC were considered necessary for any of the excipients. In view of the amount in which mannitol is present, mannitol is not considered to have a relevant effect on the motility of the gastro-intestinal tract.

A bioequivalence study was performed showing bioequivalence between the authorised 50 mg film-coated tablet formulation and the orodispersible tablet proposed for marketing (see clinical part). The products used in the bioequivalence studies are acceptable. The dissolution profiles of the batches of test and reference product that were used in the bioequivalence study at three different buffers (normally pH 1.2, 4.5 and 6.8), are comparable. The primary packaging proposed is aluminium foil blisters. All packaging components comply, where applicable, with the current European Pharmacopoeia. The blisters provide appropriate protection from moisture and light and are adequate to support the stability and use of the product.

Adventitious agents

No excipients derived from animal or human origin have been used. Magnesium stearate is of vegetable origin.

Manufacture of the product

The manufacture of the sildenafil citrate ODT consists of seven steps: three cycles of blending and milling, two blending steps, compression and packaging. It is a standard manufacturing process and there are no intermediates isolated during the manufacturing process. There are no critical steps, and no in-process controls have been proposed. The process has been adequately validated on three commercial scale batches manufactured at the commercial site. It was demonstrated that the process is capable of producing the finished product of the intended quality.

Product specification

The finished product release specifications include appropriate tests for description (visual), identification (HPLC and HPLC-DAD), assay (HPLC), uniformity of dosage units (Ph. Eur.), chromatographic purity (HPLC), disintegration and microbiological purity. Batch analysis results from nine commercial scale batches confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

Stability of the product

Stability data of three commercial scale batches stored under long term conditions (at 25ºC/60%RH) for up to 24 months and under accelerated conditions (at 40ºC/75%RH) for up to 6 months, according to ICH guidelines, have been provided. The batches were manufactured according the proposed commercial process and packed in the packaging as proposed for marketing.

The tablets were evaluated for assay, degradation products (by HPLC), appearance, disintegration and microbiological activity (total aerobic microbial count and total combined yeasts and molds count). The test methods as proposed for release have also been applied in the stability studies and demonstrated to be stability indicating. The samples stored under long term and accelerated conditions meet the predefined acceptance criteria, no significant trends were seen in any of the parameters tested.

In addition, a photostability study was performed; sildenafil citrate ODT stored in the immediate packaging (foil/foil blister) were exposed to photostability conditions outlined in option 2 of the ICH Photostability Guideline Q1B. The tablets were tested for appearance, assay, degradation products and disintegration. No changes were observed.

According to the ICH Guideline on photostability testing, also unpacked tablets should be tested in photostability studies. However, as the tablets are sensitive to moisture and should be stored in the original Aluminium blister packaging to protect from moisture, a photostability test of the unpacked tablets is not considered relevant.

Based on available stability data, the proposed shelf-life as stated in section 6.3 of the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The Viagra 50 mg ODT has been developed to be a more convenient dosage form for the existing 50 mg film-coated tablets because it can be administered without water. The ODT contains different excipients than the film-coated tablets, however none of the excipients is considered a concern. The active substance is identical to the one used in the film-coated tablets. Information on development, manufacture and control of the active substance and finished product 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 clinical performance.

At the time of the CHMP opinion, there were no unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.2.1. 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.

2.2.2. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Sildenafil is an oral therapy for erectile dysfunction (ED). In the natural setting, ie, with sexual stimulation, it restores impaired erectile function by increasing blood flow to the penis. The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood. Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum, where PDE5 is responsible for degradation of cGMP. Therefore, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP and relaxation of penile corpus cavernosal smooth muscle occurs leading to the hemodynamic event of penile erection.

Sildenafil effect is more potent on PDE5 than on other known phosphodiesterases (10-fold for PDE6, >80-fold for PDE1, >700-fold for PDE2, PDE3, PDE4, PDE7, PDE8, PDE9, PDE10, and PDE11). The approximately 4,000-fold selectivity for PDE5 versus PDE3 is important because PDE3 is involved in control of cardiac contractility. Sildenafil is only about 10-fold as potent for PDE5 compared to PDE6, an enzyme found in the retina which is involved in the phototransduction pathway of the retina. This lower selectivity is thought to be the basis for mild and transient differences in colour discrimination (blue/green) reported clinically in some subjects. Sildenafil has no effect on visual acuity or contrast sensitivity.

In animal safety pharmacology studies on the central and peripheral nervous systems, and on cardiovascular, renal, gastrointestinal, and pulmonary function, sildenafil was well-tolerated up to doses of 10 mg/kg IV in the mouse and 300 mg/kg orally in the rat. The only effects of sildenafil noted were consistent with its known vasodilatory action.

2.3.2. Pharmacology

No new pharmacology studies have been conducted on sildenafil to support the ODT line extension application. An extensive range of pharmacology studies was submitted as part of the marketing authorization applications for sildenafil film-coated immediate release (IR) tablet (Viagra EMEA/H/C/202, Revatio EMEA/H/C/638), which are sufficient for the present extension application.

2.3.3. Pharmacokinetics

Sildenafil is currently available as film-coated tablet in 25, 50 and 100 mg. The applicant is now applying for a line extension of an orodispersible tablet which will facilitate administration of the drug. The orodispersible tablet contains 50 mg of sildenafil and the excipients identified in Section 2.2.3. Bioequivalence of the orodispersible tablet with the film-coated tablet was only investigated in humans and not in the non-clinical species, which is considered acceptable.

The applicant submitted kinetic data for a ^{14}C labelled polyvinyl acetate/povidone mixture, similar in composition to components of the orodispersible tablet. Following single oral dose

administration of ^{14}C-mixture of polyvinyl acetate/povidone to rats and dogs, whole blood radioactivity concentrations resulted below the limit of quantification at all time-points analysed. Except for the higher gastrointestinal tract walls concentration, radioactivity measured in kidney and liver of male rats after oral dosing was low (≤0.01% of the administered dose) as it was below the limit of quantification in whole blood, spleen, mesenteric lymph nodes and muscle. Based on the chemical structure it is unlikely that polyvinyl acetate/povidone components will undergo biotransformation. Therefore, it is acceptable that the applicant has not provided metabolism information for polyvinyl acetate/povidone. Radioactivity was rapidly and almost completely eliminated via faeces and elimination via urine accounted for <0.1% dose in both rats and dogs. In bile duct-cannulated rats 0.01% of the administered radioactivity was recovered in bile during 0-48 hours post dose. Overall, the very high proportion of the dose excreted in faeces and the small proportion excreted in bile and urine, together with the whole blood and tissue radioactivity concentrations indicates negligible absorption of ^{14}C-labelled polyvinyl acetate/povidone mixture. Based on the chemical structure it is also unlikely that the mixture of polyvinyl acetate/povidone will be involved in drug-drug interactions and also in this case it is acceptable that the applicant will not provide with drug-drug interaction data for the polyvinyl acetate/povidone components of the orodispersible tablet.

2.3.4. Toxicology

In support of the line extension application, a repeat-dose toxicity study on a closely related mixture of polyvinyl acetate/povidone to that employed in the ODT formulation and a local tolerance study assessing the safety of sildenafil formulated as an ODT on the oral mucosa and upper gastrointestinal tract were submitted.

The purpose of the repeat-dose study (study 8230096) was to evaluate the toxicity of a closely related mixture of polyvinyl acetate/povidone, when administered daily via oral route for a long period of time (6 months followed by 4 weeks recovery) in dogs. No test article-related deaths or clinical signs were noted. No test article-related findings were observed in body weight, food consumption, ophthalmology, or ECGs. No test article-related clinical pathology findings were observed at any dose level at the end of the dosing or recovery phase. No test article-related differences were noted in mean absolute or relative organ weights in any group at the dosing or recovery phase necropsy. No test article-related macroscopic findings were noted in dosing phase or recovery animals, and no test article-related microscopic findings were found in dosing phase animals. Due to the lack of test article-related findings in the dosing phase, microscopic evaluation of recovery animals was limited to macroscopic findings identified at necropsy. All macroscopic and microscopic findings were considered spontaneous or incidental background findings unrelated to the test article. In conclusion, Kollidon is well tolerated at high dose in dogs. A risk for human use is not to be expected.

To study local tolerance a 14-day repeat-dose study in male dogs (study 20017126) was conducted to evaluate the orodispersible formulation on the local oral mucosal tissue and upper gastrointestinal (GI) tract with either one 50 mg of sildenafil ODT or a placebo ODT twice daily. A macroscopic grading system similar to the dermal Draize scale was used when examining the mucosa of the mouth for erythema and edema. Mild signs of erythema were identified in very limited cases and restricted to the first week of administration. However, as erythema was not observed in any animal during the second week of dosing, this finding was considered insignificant. There were no test article-related findings on clinical signs, no effects on body weight, body weight gain, or mean food consumption, and no test article-related macroscopic or microscopic findings in the mucosal/upper GI tissues collected for histopathological evaluation. In

conclusion, no serious findings occurred on the local oral mucosal tissue and upper gastrointestinal tract during the local tolerance test. A risk for human use is not to be expected.

The sildenafil citrate orodispersible tablet (ODT) 50 mg dosage form was evaluated for the formation of new impurities/degradants and no new impurities/degradants have been observed for the ODT formulation either in registration stability testing in line with ICH Q1C and ICH Q1A(R2) or forced degradation experiments. All impurities are specified below the identification threshold of 0.2%.

2.3.5. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of the ODT formulation is considered unlikely to result in any significant increase in the total usage of sildenafil as the new ODT formulation will be an additional formulation available for use in place of the immediate release (IR) tablet currently on the EU market. Therefore, the ERA is expected to be similar and not increased.

2.3.6. Conclusion on the non-clinical aspects

A limited nonclinical programme has been conducted in support of this extension application, which is considered acceptable. The available nonclinical safety data on sildenafil ODT, including existing toxicity data on sildenafil IR, the local tolerance study conducted specifically on the ODT formulation and risk assessment on other components of the formulation, indicate from the nonclinical perspective no difference in the benefit/risk profile compared to the one of the approved film-coated IR tablet.

2.4. Clinical aspects

2.4.1. Introduction

To support the application for the 50 mg orodispersible tablet, two main pharmacokinetic studies were submitted: a pivotal bioequivalence study (A1481289) and a food-effect study (A1481290). These studies with the final proposed ODT formulation were key for the assessment and are described below. In addition, during the development three studies (A1481265, A1481266, A1481273) were conducted investigating the bioavailability of sildenafil following administration of experimental ODT formulations. Using a taste mask approach (A1481265 and A1481266) as well as a modified ODT that used citrate salt and a simple drug substance plus flavourings approach (A1481273).

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 clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

Study A1481289

Methods

Study design

This was a randomized, open-label, 3-treatment, 3-period, crossover, single-dose bioequivalence study in healthy male subjects 45 years or older. Thirty six (36) subjects were planned to be enrolled into the study; dropouts could be replaced at the discretion of the sponsor and investigator. Screening evaluation occurred within 28 days prior to the first dose of Period 1. The randomization of subjects to treatment administration was generated using a Williams design; eligible subjects were assigned to 1 of the 6 treatment sequences to receive the following 3 treatments:

- Treatment A: Viagra 50 mg tablet, administered with approximately 240 mL water under fasted conditions.
- Treatment B: Sildenafil ODT tablet 50 mg, administered without water under fasted conditions. Subjects were required to wet the mouth by swallowing 20 mL of water directly before placing the ODT on the tongue. Subjects were permitted to consume water as desired without restriction 1 hour post dose.
- Treatment C: Sildenafil ODT tablet 50 mg, administered with water under fasted conditions. Subjects were asked to allow the tablet to disintegrate completely in their mouth prior to drinking 240 mL water.

Day 0 was defined as the day prior to first day of dosing (Day 1) in each Period. Subjects were admitted to the Clinical Research Unit (CRU) on Day 0 of each Period and remained at the CRU until the completion of all study activities on Day 1 for Periods 1 and 2, and Day 2 for Period 3. There was at least a 1-day washout period between successive doses. Subjects could have been accommodated to stay at the CRU between Periods if successive doses were no more than 2 days apart.

Blood samples (6 mL) were collected for each study period to provide a minimum of 2.5 mL plasma for pharmacokinetic (PK) analysis at pre-dose, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 14 hours post-dose in tubes containing sodium heparin anticoagulant. Sildenafil and UK-103,320 PK parameters were calculated for each subject and treatment using non-compartmental analysis of concentration-time data.

Test and reference products

Sildenafil citrate ODT 50 mg and commercial Viagra 50 mg immediate release tablets (Amboise-manufactured) were supplied by Pfizer Global Research & Development to the CRU in bulk labelled blisters. CRU generated labels consistent with protocol for dispensation and administration of drug to subjects.

Population(s) studied

Thirty six (36) subjects were assigned and received study treatment. No subjects were discontinued from the study and all 36 subjects completed the study. All subjects were analysed for PK and safety. Twelve (12) subjects in each of the sildenafil ODT 50 mg (with and without

water) treatments and 14 subjects receiving Viagra 50 mg (with water) were analyzed for laboratory data in Period 3 (collected at Screening, Day 0 of Period 1 and prior to discharge from the CRU in Period 3).

Mean age (standard deviation [SD]) for all subjects was 51.3 (6.1) years. Mean (SD) weight, BMI and height for all subjects were 69.5 (9.3) kg, 24.7 (3.0) kg/m2 and 167.6 (5.9) cm, respectively. All subjects were Asian males.

Analytical methods

For analysis of sildenafil and the active metabolite UK-103,320, validated LC-MS/MS methods were applied, with a lower limit of quantitation of 1 ng/ml. Run performance for the calibration standards as well as for the QC samples during study sample analysis were within the standard criteria, as indicated in the EMA guideline on bioanalytical method validation. Incurred samples reanalysis showed good reproducibility.

Pharmacokinetic variables

The primary PK variables of the study were defined as area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (AUC_{last}) and maximum observed plasma concentration (C_{max}) of sildenafil and secondary PK variables included area under the plasma concentration-time profile from time 0 to infinity (AUC_{inf}), time to achieve maximum plasma concentration (T_{max}) and terminal half-life (t½) of sildenafil.

Statistical methods

Natural log transformed AUC_{last}, AUC_{inf} and C_{max} of sildenafil were analyzed using a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (Test - Reference) and corresponding 90% confidence interval (CI) were obtained from the model. The adjusted mean differences and 90% CI for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. Treatment A was the Reference treatment while Treatments B and C were the 2 Test treatments. Bioequivalence of Test treatment (Treatment B) relative to the Reference treatment (Treatment A) was to be concluded if the 90% CI for the ratio of adjusted geometric means for both AUC_{last} and C_{max} fell wholly within (80%, 125%). Relative bioavailability was to be estimated as the ratio of adjusted geometric means for Test treatment (Treatment C) relative to the Reference treatment for AUC_{last} and C_{max}. The PK parameters AUC_{last}, AUC_{inf}, C_{max}, T_{max} and t½ were summarized descriptively by treatment.

Results

In the pivotal study A1481289, using the proposed final 50 mg ODT formulation and including 36 healthy volunteers, bioequivalence could be proven between the ODT administered without water and the 50 mg Viagra tablet. This was the primary objective of this study. In case the ODT formulation is administered with water, bioequivalence could be proven for AUC but not for C_{max}. For C_{max}, the observed 90% confidence interval of 79.76 – 92.78% was just outside the normal applied 90% confidence interval of 80.00 – 125.00% (see tables below), which is considered not of concern also in light of the overall data.

Table PK 1. Mean pharmacokinetic variables of sildenafil after administration of the final proposed 50 mg ODT formulation with and without water and the 50 mg Viagra tablet with water.

Parameter (Units)	Parameter Summary Statistics by Treatment		
	Viagra 50 mg (With Water)	Sildenafil ODT 50 mg (Without Water)	Sildenafil ODT 50 mg (With Water)
N, n	36, 35	36, 36	36, 36
AUC_{inf} (ng*hr/mL)	846.3 (37)	890.8 (37)	840.4 (37)
AUC_{last} (ng*hr/mL)	823.4 (36)	860.9 (36)	813.5 (36)
AUC_{Tmax} (ng*hr/mL)	83.76 (58)	85.04 (66)	89.25 (54)
C_{max} (ng/mL)	296.9 (32)	271.8 (44)	255.4 (33)
T_{max} (hr)	0.750 (0.250-2.00)	0.750 (0.250-2.00)	0.750 (0.250-1.50)
$t_{1/2}$ (hr)	3.012 (15)	3.104 (14)	2.990 (14)

Geometric mean (%CV) for all except: median (range) for Tmax; arithmetic mean (%CV) for t½.
N = Number of subjects in each treatment; n = number of subjects where t½ and AUCinf were determined.
%CV = percent coefficients of variation;

Table PK 2. Statistical analysis for treatment comparison.

Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means	90% CI for ratio
	Test	Reference		
Sildenafil ODT 50 mg (without water) (Test) vs. Viagra 50 mg (with water) (Reference)				
AUC_{inf} (ng*hr/mL)	890.8	846.2	105.27	(100.98, 109.74)
AUC_{last} (ng*hr/mL)	860.9	823.4	104.55	(100.25, 109.03)
C_{max} (ng/mL)	271.8	296.9	91.54	(84.87, 98.72)
Sildenafil ODT 50 mg (with water) (Test) vs. Viagra 50 mg (with water) (Reference)				
AUC_{inf} (ng*hr/mL)	840.4	846.2	99.31	(95.26, 103.52)
AUC_{last} (ng*hr/mL)	813.5	823.4	98.80	(94.74, 103.03)
C_{max} (ng/mL)	255.4	296.9	86.03	(79.76, 92.78)

The ratios (and 90% CIs) are expressed as percentages
Note: Values back-transformed from the log scale.
CI = confidence interval

Study A1481290

Methods

Study design

This was a randomized, open-label, 2-treatment, 2-period, crossover, single-dose food-effect study in healthy male subjects 45 years or older. Twelve (12) male subjects were planned to be enrolled into the study. Dropouts could be replaced at the discretion of the Sponsor and Investigator. Screening evaluation occurred within 28 days prior to the first dose of Period 1. The randomization of subjects to treatment administration was generated using a Latin square design; eligible subjects were assigned to 1 of the 2 treatment sequences to receive the following 2 treatments:

- Treatment A: Sildenafil ODT tablet 50 mg, administered without water under fasted conditions. Subjects were required to wet the mouth by swallowing 20 mL of water directly before placing the ODT on the tongue. Subjects were permitted to consume water as desired without restriction 1 hour post dose.
- Treatment B: Sildenafil ODT tablet 50 mg, administered without water under fed conditions. The meal was a standard high fat breakfast. Subjects were required to wet the mouth by

swallowing 20 mL of water directly before placing the ODT on the tongue. Subjects were permitted to consume water as desired without restriction 1 hour post dose.

Subjects in Treatment B started breakfast 30 minutes prior to administration of the study drug after an overnight fast of at least 10 hours. The meal was to be consumed over a 25-minute period with the study drug administered within 5 minutes after completion of the meal.

Day 0 was defined as the day prior to first day of dosing (Day 1) in each period. Subjects were admitted to the Clinical Research Unit (CRU) on Day 0 of each period and remained at the CRU until the completion of all study procedures on Day 1 for Period 1 and Day 2 for Period 2. There was a minimum 1-day washout period between successive doses. Subjects could be accommodated to stay at the CRU between periods if successive doses were no more than 2 days apart.

Blood samples (6 mL) were collected for each study period to provide a minimum of 2.5 mL plasma for pharmacokinetic (PK) analysis at pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 14 hours post-dose in tubes containing sodium heparin anticoagulant. Sildenafil and UK-103,320 PK parameters were calculated for each subject and treatment group using non-compartmental analysis of concentration-time data.

Test and reference products

Sildenafil citrate ODTs were supplied by Pfizer Global Research & Development (PGRD) as 50 mg tablets to the CRU in bulk labelled blisters.

Population(s) studied

Twelve (12) subjects were assigned and received study treatment. No subjects were discontinued from the study and all 12 subjects completed the study. All subjects were analysed for PK and safety. Six (6) subjects in each of the fed and fasted treatments were analysed for laboratory data in Period 2.

Mean age (standard deviation [SD]) for all subjects was 56.6 (8.2) years. Mean (SD) weight, BMI and height for all subjects were 68.1 (10.8) kg, 24.8 (3.3) kg/m2 and 165.7 (6.0) cm, respectively. All subjects were Asian males.

Analytical methods

For analysis of sildenafil and the active metabolite UK-103,320, validated LC-MS/MS methods were applied, with a lower limit of quantitation of 1 ng/ml. Run performance for the calibration standards as well as for the QC samples during study sample analysis were within the standard criteria, as indicated in the EMA guideline on bioanalytical method validation. Incurred samples reanalysis showed good reproducibility.

Pharmacokinetic variables

The primary PK variables of the study were defined as area under the plasma concentration-time profile from time 0 to final measurable time point ($AUC_{[0-t]}$) and maximum observed plasma concentration (C_{max}) of sildenafil and secondary PK variables included area under the plasma concentration-time profile from time 0 to infinity by extrapolation (AUC_{inf}) , time to achieve maximum plasma concentration (T_{max}) and half-life of sildenafil.

Statistical methods

Natural log transformed $AUC_{(0-t)}$, AUC_{inf} and C_{max} of sildenafil were analyzed using a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (Test – Reference) and corresponding 90% CI were obtained from the model. The adjusted mean differences and 90% CI for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. Treatment A was the Reference treatment while Treatment B was the Test treatment. The food effect was estimated as the ratio of adjusted geometric means for Test treatment relative to the Reference treatment for $AUC_{(0-t)}$ and C_{max}. The PK parameters $AUC_{(0-t)}$, AUC_{inf}, C_{max}, T_{max} and terminal elimination half-life (t1/2) were summarized descriptively by treatment. For $AUC_{(0-t)}$, AUC_{inf}, and C_{max}, individual subject parameters were plotted by treatment. Concentrations were listed and summarized descriptively by PK sampling time and treatment. Individual subject and summary profiles (median and mean) of the concentration-time data was plotted by treatment. For summary statistics and median plots by sampling time, the nominal PK sampling time was used, for individual subject plots by time, the actual PK sampling time was used.

Results

In the food effect study A1481290, the effect of standard breakfast was evaluated in 12 healthy subjects. Intake of food delayed the rate of absorption by more than 3 hours. As a result, C_{max} was decreased by 59%. In addition, AUC_t decreased by about 12%. These results are in line with those observed for the immediate-release tablet formulation, however appears to be more pronounced. Previous available data for the immediate-release formulation showed that if taken with food, the rate of absorption is reduced with a mean delay in t_{max} of 60 minutes and a mean reduction in C_{max} of 29%, while AUC_t was not affected.

Table PK 3. Mean pharmacokinetic variables of sildenafil after administration of the final proposed 50 mg ODT formulation with and without a standard breakfast.

Parameter, (Units)	Parameter Summary Statistics by treatment Sildenafil 50 mg ODT (fasted) N=12	 Sildenafil 50 mg ODT (fed) N=12
AUC_{inf} (ng*hr/mL)	838.6 (23)	804.0 (34)
AUC_{last} (ng*hr/mL)	813.2 (22)	712.8 (33)
C_{max} (ng/mL)	296.6 (31)	121.0 (44)
T_{max} (hr)	0.625 (0.25-1.50)	4.00 (0.50-6.00)
$t_{1/2}$ (hr)	3.039 (16)	2.503 (14)

Geometric mean (%CV) for all except: median (range) for Tmax; arithmetic mean (%CV) for t½.
9 subjects contributed to the mean for t½ and AUCinf
N = Number of subjects in the treatment group
%CV = percent coefficients of variation

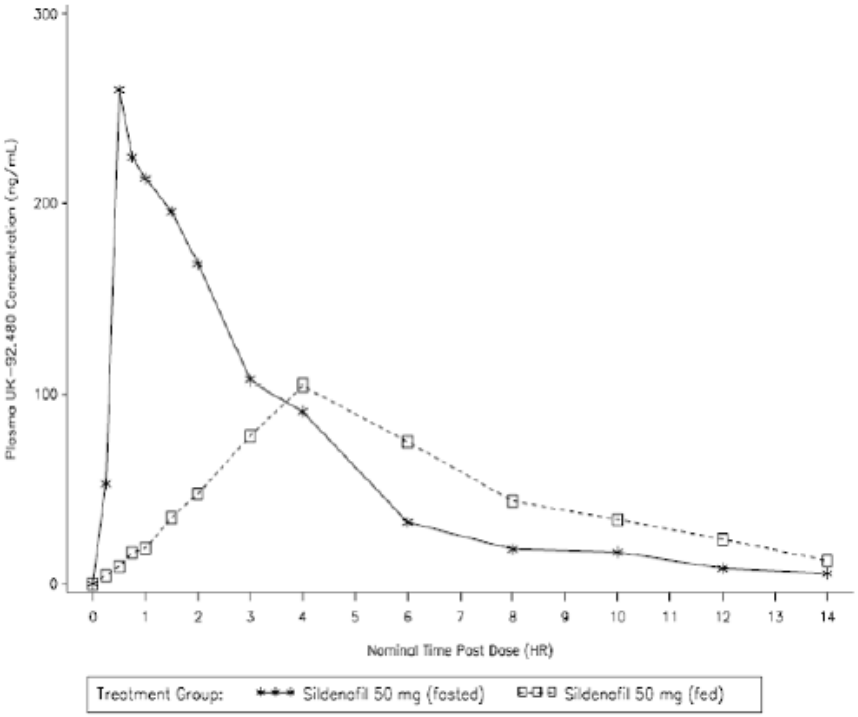

Figure PK 1. Mean sildenafil plasma concentration-time curves after administration of the final proposed 50 mg ODT formulation with and without a standard breakfast.

Conclusions

Based on the presented bioequivalence study the 50 mg orodispersible tablet is considered bioequivalent with the 50 mg immediate release film-coated tablet.

In the food effect study the intake of food resulted in a decrease of C_{max} and AUC_t. Such food effect has in principle also been observed with the immediate-release tablet formulation, and is anticipated to affect the onset of effect. The SmPC for the orodispersible tablet sufficiently took into account the results of this food interaction study, i.e. the ODT is recommended to be taken on an empty stomach as concomitant intake with food delays absorption and delays the effect of the orodispersible tablet. Also the SmPC advises that based on efficacy and tolerability, the dose may be increased to 100 mg. The directions in the SmPC are adequate to manage this food effect on the formulation.

2.5. Pharmacodynamics

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

2.6. Clinical efficacy

No studies were conducted to evaluate the efficacy of sildenafil ODT in a patient population and no changes to the recommended dosing regimen or therapeutic indication are being sought in this application.

2.7. Clinical safety

The safety data for sildenafil citrate are well established, have been extensively described in previous regulatory submissions, and are considered to be accurately reflected in the currently approved product labelling. Safety data from recent studies using the ODT (A1481265, A1481273, A1481289, A1481290) were consistent with the known safety profile of sildenafil citrate, and no new safety concerns were identified with the use of sildenafil citrate ODT formulation developed for commercialization. There were no deaths, SAEs, severe AEs, or discontinuations due to AEs.

2.8. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

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

Risk Management Plan

The MAH has not submitted an updated Risk Management Plan as part of this application. The MAH considered that efficacy and safety data from the use of the Viagra ODT formulation in healthy subjects as well as patients did not introduce any significant change to the overall benefit/risk of the compound in the treatment of patients with ED. No specific pharmacovigilance and risk minimization activities beyond those currently in place for this product –and described in the current Viagra RMP (v3.1) – are deemed necessary hence not requiring an update to this RMP. This was considered acceptable by the CHMP because the sildenafil ODT formulation was bioequivalent to currently approved film-coated oral tablet and its safety was considered to be similar to that of the conventional film-coated tablet.

2.9. User consultation

The patient information leaflet for the Viagra orodispersible tablets takes into account the results of a readability test which was approved as part of the latest renewal application in 2008. The new pharmaceutical form applied for introduces minor changes to the Viagra patient information leaflet in terms of administration and patient readability. The MAH's justification for not conducting further user testing was accepted.

3. Benefit-Risk Balance

Benefit-risk balance

This application concerns the introduction of a new pharmaceutical form: 50 mg orodispersable tablet (ODT). No changes to the recommended dosing regimen or therapeutic indication were sought in this application.

The bioequivalence study A1481289 forms the pivotal basis with a three period, cross over design investigating the new ODT formulation with and without water in comparison with the immediate-release formulation. 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. In this pivotal study, using the proposed final 50 mg ODT formulation, bioequivalence was demonstrated between the ODT administered without water and the 50 mg immediate-release tablet. In case the ODT formulation is administered with water, bioequivalence could formally be proven for AUC only. For Cmax, the lower limit of the 90% confidence interval was just outside the standard requirement. However, taken also into consideration the overall data this marginal deviation was considered acceptable.

Like for the already approved immediate-release formulation there is a food effect with delayed rate of absorption by more than 3 hours resulting in a decrease of both C_{max} and of the AUC_t. This is likely to affect the onset of action hence appropriate guidance was included in the SmPC that the product is recommended to be taken on an empty stomach.

No further clinical studies were conducted with this new pharmaceutical form (orodispersible tablets) to evaluate the efficacy and safety of sildenafil ODT in a patient population. Indeed, the safety and efficacy data for sildenafil citrate are well established, have been extensively described in previous regulatory submissions, and are considered to be accurately reflected in the currently approved product labelling. Safety data from PK/PD studies using the ODT were consistent with the known safety profile of sildenafil citrate and no new safety concerns were identified.

In conclusion, based on the pharmacokinetic data and the long-term knowledge on the safety and efficacy of Viagra film-coated tablets (sildenafil citrate), it is considered that benefit risk for this new orodispersible tablet formulation is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Viagra 50 mg orodispersible tablet in 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 VIAGRA to be effective, sexual stimulation is required.”

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

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web portal.

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.