European Medicines Agency
Evaluation of Medicines for Human Use

Doc. Ref.: EMA/793633/2009

ASSESSMENT REPORT
FOR
Sildenafil ratiopharm

International Nonproprietary Name: **sildenafil**

Procedure No: EMEA/H/C/001080

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

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 16
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

TABLE OF CONTENTS

Page

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant ratiopharm GmbH submitted on 7 October 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Sildenafil ratiopharm, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

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

The chosen reference product is:

- *Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:*
  - Product name, strength, pharmaceutical form: **Viagra 25 mg, 50 mg, 100 mg film-coated tablet**
  - Marketing authorisation holder: **Pfizer Limited**
  - Date of authorisation: **14 September 1998**
  - Marketing authorisation granted by:
    - Community
  - Community Marketing authorisation number: **EU/1/98/077/002-004, 006-008, 010-019**

- *Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:*
  - Product name, strength, pharmaceutical form: **Viagra 100 mg film-coated tablet**
  - Marketing authorisation holder: **Pfizer Limited**
  - Date of authorisation: **14 September 1998**
  - Marketing authorisation granted by:
    - Community
  - Community Marketing authorisation number: **EU/1/98/077/010-012, 0015**
  - Bioavailability study number: **SLI-P7-116**

The Rapporteur appointed by the CHMP was Philippe Lechat

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

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

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 7 October 2008.
- The procedure started on 22 October 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 January 2009.
- During the meeting on 16-19 February 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 February 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 May 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 July 2009.
- During the CHMP meeting on 20-23 July 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing and by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 21 September 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 7 October 2009 and amendment to the assessment on 15 October 2009.
- During the meeting on 19-22 October 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Sildenafil ratiopharm on 22 October 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 19 October 2009.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 23 December 2009.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Sildenafil ratiopharm 25 mg, 50 mg, 100 mg film-coated tablet is a generic medicinal product containing sildenafil as an active substance. The application was submitted under the Article 10(1) of Directive 2001/83/EC i.e. generic application referring to a reference medicinal product.

Sildenafil ratiopharm contains the same active substance as the reference medicinal product (Viagra) - sildenafil in form of the citrate salt.

Sildenafil is potent inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase (PDE5). During natural erection, nitric oxide (NO) is released and this triggers the synthesis of cGMP which, in turn, relaxes the corpora cavernosa (a key point in the erection process). PDE5 present in the corpus cavernosum breaks down cGMP, sildenafil prevents the breakdown of cGMP and, thus enhances the induced erectile response. Sildenafil has a high potency and selectivity for PDE5 and via smooth muscle relaxation can induce a rise in intracavernosal pressure during stimulation.

The safety and efficacy profile of sildenafil has been demonstrated in several clinical trials details of which can be found in the EPAR for Viagra. In addition, there is a long-term post-marketing experience contributing to the knowledge of the use of this product. Since this application is a generic application referring to the reference medicinal product Viagra, summary of the clinical data of

sildenafil citrate is available and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted.

The indication for Sildenafil ratiopharm is the same as for reference medicinal product. Sildenafil ratiopharm is indicated for 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 sildenafil to be effective, sexual stimulation is required.

2.2 Quality aspects

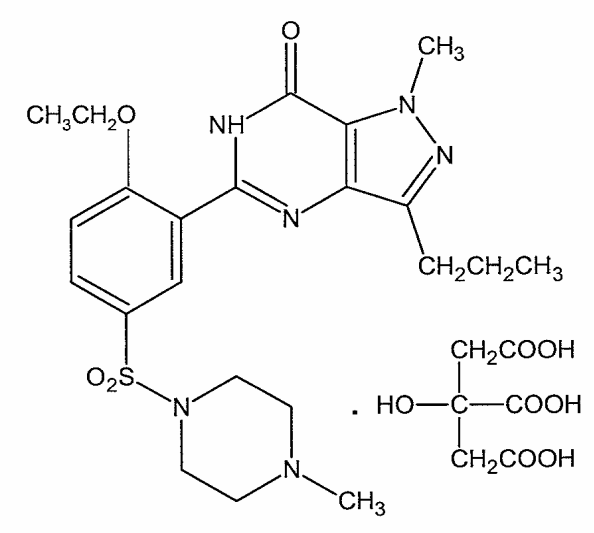
Introduction

Sildenafil ratiopharm is presented as film-coated tablets containing 25 mg, 50 mg or 100 mg of sildenafil (active substance). The active substance is in form of citrate salt. Excipients used in the preparation of Sildenafil ratiopharm are well known excipients used in tablets preparations such as microcrystalline cellulose, calcium hydrogen phosphate, croscarmellose sodium, magnesium stearate (present in the tablet core) and hypromellose, macrogol 6000 and Aqua Polish blue 060.16 composed of hypromellose, macrogol 6000, talc, titanium dioxide, iron oxide red, indigo carmine aluminium lake, which are present in film-coating.

Sildenafil ratiopharm film-coated tablets are blue, oval with edge and packed in polyvinylidene chloride/polyvinyl chloride/aluminium (PVdC/PVC/alu) blisters.

Active Substance

The active substance, sildenafil citrate, is chemically designated as 5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1,6-dihydro-1-methyl-3-propylpyrazolo[4,3-*d*]pyrimidin-7-one citrate; 1-{[3-(6,7-Dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl}-4-methylpiperazone citrate and has the following structure:



Sildenafil citrate is a white to off-white crystalline powder soluble in DMF, acetic acid and slightly soluble in methanol. Solubility of sildenafil citrate is pH dependent and it decreases with increase of pH. pH ranges between 3.7 and 3.8 and the pKa from 8.2 to 9.6.

Sildenafil citrate is an achiral substance. No polymorphic forms of sildenafil citrate have been observed. The assessment of possible polymorphism was performed using X-ray powder diffraction and supported by publicly available literature data.

- Manufacture

Information about manufacturing process has been provided using Active Substance Master File (ASMF) procedure – two ASMFs from different manufactures have been proposed. A detailed description of the manufacturing process including process flow diagram and in process controls was provided in the restricted parts of the ASMFs. Critical parameters and accompanying in-process controls, to ensure quality of the final compound, have been defined.

Confirmation of the chemical structure of sildenafil citrate was provided by elemental analysis (confirmation of the determined elementary composition), spectroscopic methods as FT-IR, NMR (^{1}H-NMR and ^{13}C-NMR), mass spectrum and X-ray powder diffraction (XRD). X-ray diffraction studies confirmed the morphology of sildenafil citrate. Other physico-chemical data such as UV absorption spectra, thermal studies (melting range), and solubility studies, pH of water solution, dissociation constant and partition coefficient provided further supportive evidence of chemical structure.

Potential impurities have been well discussed in relation to their origin and potential carry-over into the final drug substance, including potential for the formation of genotoxic impurities.

- Specification

The drug substance specifications include tests for appearance, clarity and colour of the solution, identification (UV/IR and HPLC), citrates and their content, water content, melting point, residue on ignition, sulphated ash, heavy metals, purity (HPLC), assay (HPLC), particle size (laser diffraction) and residual solvents (GC).

A detailed description for all analytical methods was provided. Full method validation data was provided for the non-compendial (in-house) analytical methods: HPLC methods for identification, assay, chromatographic purity and related substances and GC method for residual solvents.

The HPLC methods have been validated for specificity, absorptivity factor (i.e. RRF), linearity and range, limit of quantitation, limit of detection, accuracy, precision (system precision, method precision i.e. repeatability, intermediate precision), robustness, solution stability, forced degradation and peak purity.

The GC method has been validated for specificity, linearity, limit of quantitation, limit of detection, accuracy, precision (method precision i.e. repeatability, intermediate precision) and robustness with regards to specified solvents. All acceptance criteria were in line with ICH recommended limits

In general analytical methods proposed are suitable to control the quality of the drug substance.

Data on three consecutive batches of sildenafil citrate manufactured according to the proposed manufacturing process as described in the relevant ASMFs was provided by the ASMF Holders. All batches represented full scale production and complied with the requirements in the drug substance specification.

- Stability

Stability studies were carried out according to ICH guidelines for real time (25°C/60% RH), intermediate (30ºC/65%RH) and accelerated conditions (40°C/75% RH). Data for several commercial scale batches were given with 60 months real time and intermediate conditions, and 6 months accelerated data. No trends were found at long-term and accelerated conditions for tested parameters.

In addition forced degradation studies were performed. Results form this study proved that sildenafil citrate degrades under stress conditions (acidic and alkaline conditions, oxidation, UV irradiation, light and thermal treatment) to the known impurities. No unknown impurities were detected during stability testing.

The stability studies confirmed the proposed re-test period.

Medicinal Product

- Pharmaceutical development

The aim of the pharmaceutical development was to obtain an immediate release film-coated tablet, containing quantitatively and qualitatively the same active substance as the reference medicinal product and to be bioequivalent.

Similarity to the reference medicinal product was addressed by way of composition comparisons, solubility and dissolution studies, and comparative impurity profiles.

Composition of Sildenafil ratiopharm film-coated tablets is qualitatively similar to the reference medicinal product.

Solubility of sildenafil citrate was tested in buffered solutions over the physiological pH range 1.0 to 7.5 as this information was relevant for the design of the dosage form in terms of release and resorption of the active substance, because with increasing pH, solubility decreases and a tendency of precipitation cannot be excluded in the gastrointestinal tract after dissolution.

Similarity between two products was also shown with dissolution testing. Dissolution studies were carried out in line with the Ph Eur. Raw and graphical data showed comparable dissolution profiles of the product and the reference product in 3 tested media. In addition the influence of particle size of the active substance on the dissolution profile has been included in the development program.

An impurity comparison of Sildenafil ratiopharm film-coated tablets and the reference product was undertaken and no differences in results obtained have been observed.
The formulation development was performed including the development of two different formulations, a pilot study, scale-up batches comprising the production of pilot batches with two different active substance manufacturers and a pivotal bioequivalence study.

During the development program it has been proven that Sildenafil ratiopharm film-coated tablets were bioequivalent with the reference product. A single-dose, randomised, two-period, two-sequence crossover open-label study under fasting conditions was conducted to compare the relative bioavailability of Sildenafil ratiopharm 100 mg film-coated tablets to that of the reference medicinal product – Viagra 100 mg film-coated tablets. Data obtained conclude that the 90% confidence intervals were within the acceptance range for both, sildenafil and its major metabolite. Results therefore show the two products to be bioequivalent under fasted conditions.

The bioequivalence study was performed with the highest strength (100 mg film-coated tablets) and for the lower strengths (50 mg and 25 mg) a biowaiver was requested. This request was found acceptable since all criteria for a biowaiver listed in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) were fulfilled, namely:

1. The pharmaceutical products are manufactured by the same manufacturer and process;
2. The drug input has been shown to be linear over the therapeutic dose range;
3. The qualitative composition of the different strengths is the same;
4. The ratio between amounts of the active substance and excipients is the same;
5. The dissolution profiles are similar under identical conditions for the additional strength and the strength of the batch used in the bioequivalence study.

The drug product manufacturing process development was also performed. Details were provided for experimental batches manufactured to establish optimum manufacturing conditions.
Roller compaction as manufacturing process was considered to be the granulation method of first choice due to the general advantages of this granulation method in comparison to other processes e.g. high shear granulation or fluid bed granulation and due to company specific reasons.
The general advantages of dry granulation (roller compaction) are avoidance of interaction between water added in the process and active substance/excipients and possible related stability issues,

avoidance of a drying-process to remove the water added, thereby no increased product temperatures, and also savings of energy and time and high reproducibility and no scale-up problems in the case of modern roller compactors with integrated gap control, because larger masses to be produced are run on the same machine by simply extending the process duration. As a consequence the aim of the manufacturing process development was to develop a dry granulation process. No critical issues could be revealed during formulation development, scale-up and during the site transfer therefore roller compaction was considered to be the granulation method of choice.

- Adventitious Agents

None of the excipients present in the formulation are of animal or human origin. Magnesium stearate used in the manufacturing process of the medicinal product is of vegetable origin.

- Manufacture of the Product

The manufacturing process has been sufficiently described and a flow diagram with detailed description of the manufacturing process has been provided.

Briefly, the manufacturing process involves (1) Blending – sildenafil citrate is mixed with part of excipients; (2) Dry granulation – the active substance mixture is compacted and equalized; (3) Final blending – the granulate is mixed homogeneously with the remaining excipients; (4) Compression – the homogenized granulate is tabletted into tablets of the specified size; (5) Film-coating – the tablets cores are film coated; (6) Packaging.

The critical steps in the manufacturing process have been identified. The sampling for product-related in-process controls is carried out during the tabletting process.

At the time of submission only validation results for several pilot-scale batches for each strength manufactured at proposed manufacturing sites have been submitted. This is acceptable as according to CPMP/QWP/848/96, Note for Guidance on Process Validation a two stage approach when production scale data are not available, can be applied. First evaluation and characterisation of the pilot scale batches and second formal validation program on the production scale batches. In addition roller-compaction is regarded as a standard manufacturing process.

Also the applicant committed to perform validation on the first three production scale batches.

- Product Specification

The product specification is standard for tablets and contains tests with suitable limits for appearance, average mass, resistance to crushing, disintegration time, loss on drying, identity of sildenafil (HPLC), sildenafil citrate (UV) and citrate, identification of colorant (titanium dioxide and iron oxide), assay (HPLC), uniformity of dosage units (HPLC), purity (HPLC), in-vitro dissolution (with UV evaluation) and microbiological purity.

Full details of all analytical methods have been provided. All non pharmacopoeial methods have been satisfactory validated. The HPLC method for identity, assay and purity test has been suitably validated with respect to specificity, precision, linearity, accuracy, detection limit, quantitation limit, robustness, stability of sample and standard solution.

The in-vitro dissolution test has been validated for linearity (considering amounts expected for of all dosages), accuracy, selectivity and repeatability. Robustness test considered the influence of the filters. Sink conditions were demonstrated for the highest dosage up to 3 tablets/ vessel.

Batch analysis data was provided for each strength on one laboratory scale batch, 4 pilot scale pilot scale batches manufactured at the development site and 2 commercial scale batches manufactured at the proposed manufacturing site. Batches met the proposed specification limits. Results showed that tablets can be manufactured reproducibly according to the finished product specifications.

- Stability of the Product

Stability studies were carried out under ICH conditions of 25ºC/60%RH (long term), 30ºC/65%RH (intermediate) and 40ºC/75%RH (accelerated). During the stability program a bracketing concept was applied to 50 mg strength since the tablets are dose linear. The 25 mg and 100 mg were tested at three recommended ICH conditions and all the packages intended for marketing were considered as well as both sources of the active substance. Five batches of each strength have been placed on stability, from which four batches are of a commercial scale size and one of a pilot scale. Accelerated and intermediate testing for all batches has been finalised. No significant changes were observed. 18 months real-time stability data are available. The real-time stability data show no significant change over the time. The extrapolation for purpose of calculation of a shelf-life is justified by the data provided.

In addition photostability testing was performed according to the "Note for Guidance on the Photostability Testing of New Active Substances and Medicinal Products" (CPMP/ICH/279/95). The tablets were tested outside of the primary packaging material, i.e. in an open petri dish, exposed alongside a dark control sample.

The results from stability studies, including photostability testing, demonstrate that tablets are stable and no significant changes in tested parameters were observed during the storage.

Based on the stability data the proposed shelf-life and storage conditions as defined in the SPC are acceptable.

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow-Up Measures after the opinion, within an agreed timeframe.

2.3 Non-Clinical aspects

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

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

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

Discussion on Non-Clinical aspects

There are no non-clinical objections to approve Sildenafil Ratiopharm 25, 50 and 100 mg coated tablets. As mentioned in the Quality part of the report, potential impurities have been well discussed in relation to their origin and potential carry-over into the final drug substance, including potential for the

formation of genotoxic impurities (triethyl orthoformate), and these are being clarified as a part of follow-up measures.

2.4 Clinical Aspects

Introduction

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

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

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

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

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

GCP aspects

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

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

Exemption

Transferability of study results to other strengths

The applicant submitted a Bioequivalence study with the highest strength (100 mg tablets) and requested biowaiver for the lower 50 and 25 mg strengths. This request was found acceptable since all criteria for a biowaiver listed in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) were fulfilled, namely:

1. The pharmaceutical products are manufactured by the same manufacturer and process;
2. The drug input has been shown to be linear over the therapeutic dose range;
3. The qualitative composition of the different strengths is the same;
4. The ratio between amounts of the active substance and excipients is the same;
5. The dissolution profiles are similar under identical conditions for the additional strength and the strength of the batch used in the bioequivalence study.

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

Clinical studies

To support the application, the applicant has submitted 2 bioequivalence studies.

- Pilot study: Report n° SLI-P6-299

In this pilot study two development prototypes were tested and compared to the brand leader following a classical crossover three-way design. This study allowed the sponsor to select the adequate formulation that was further developed and tested in the pivotal study detailed below. The pilot study is not included in the present assessment report.

- Pivotal study: Report n° SLI-P6-116:

This final study conducted in fifty-eight healthy male subjects under fasting conditions is analysed hereafter.

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

Pharmacokinetics

- Methods

STUDY DESIGN

The study was designed according to an open-label, randomised, single-dose, two-period, two-sequence crossover classical scheme.

In each period, subjects were to arrive at least 10 hours before dosing and stay until after the 24-hour post-dose events. Subjects were instructed to avoid alcohol, and food or beverages containing xanthine for 58 hours prior to dosing and during each study protocol. Subjects were also instructed to avoid food or beverages containing grapefruit for 7 days prior to dosing and during each study protocol. Subjects who were light-smokers were requested to abstain from smoking for 2 hours prior to drug administration and until 4 hours after drug administration.

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

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

A total of 18 blood samples were collected in each period at pre-dose and at 0.25, 0.333, 0.42, 0.58, 0.75, 0.92, 1.08, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose. Blood samples were processed at 4°C afterwards and plasma samples were collected and stored at (-) 20°C and shipped for analysis.

The clinical part of the bioequivalence study, the bioanalytical and statistical analysis were performed at different CROs located in Canada between 08/12/2007 and 10/01/2008.

The protocol and the informed consent form were approved by an institutional review board (ETHIPRO) on 15/11/2007. The final study report was signed in June 2008.

TEST AND REFERENCE PRODUCTS

Test and reference product used in the study were as follows

Drug Code	Test	Reference
Formulation	Sildenafil 100 mg Film-Coated Tablet	Viagra® 100 mg Film-Coated Tablet
Manufacturer	Merckle GmbH, Germany for	Pfizer PGM, France

	Ratiopharm GmbH, Germany	
Batch No.	GE042807	5169811DR2
Manufacturing Date	17/07/2007	N/AV
Expiry Date	07/2008 (retest date)	07/2010
Measured Content	101.2% of label claim	100.6 % of label claim

POPULATION(S) STUDIED

58 male healthy subjects were enrolled in the study. The mean age was 32 (18-45), BMI ranged from 19 to 29.9 kg/m2. The majority of subjects were White. Subjects were in good health as determined by medical history, physical examination, ECG, laboratory tests (haematology, biochemistry, urinalysis). Subjects were instructed not to take any OTC medication for the 7 days prior to dosing, any prescription medication for 14 days prior to dosing, enzyme modifying drugs for 28 days prior to Day 1 and nitrates for 30 days prior to dosing and during the study. All the subjects met inclusion criteria including negative HIV, Hepatitis B and C tests as well as negative screening for ethyl alcohol and drug of abuse in urine.

Of the total of 58 volunteers included in the study 58 received the two treatments and 57 were included in the statistical analysis, i.e. 33 subjects in the first group (17 in sequence AB and 16 in sequence BA) and 24 subjects in the second group (12 in each of the two sequences). One subject was withdrawn following dosing of period 2 for abnormal stools.

ANALYTICAL METHODS

The analytical part of the study was conducted at bioanalytical facility of a CRO in Canada. The analysis of plasma samples of sildenafil and N-desmethyl-sildenafil was performed using the HPLC equipment with MS-MS tandem detection.

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

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

PHARMACOKINETIC VARIABLES

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

STATISTICAL METHODS

The pharmacokinetic analysis was performed at the Department of biometry and statistics of the CRO in Canada. Parametric ANOVA on ln-transformed AUC0-t, AUC0-∞ and Cmax was carried out for both analytes: Sildenafil and its N-desmethyl metabolite. The statistical model included sequence, period and treatment factors as fixed effects and subject within sequence as a random effect. According to the protocol the bioequivalence could be concluded if the least square means ratio with corresponding 90% CI between the test and reference product for ln-transformed AUC0-t, AUC0-∞ and Cmax fell within 80-125% range. The parameter Tmax was analysed using a non-parametric approach.

- Results

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

Sildenafil: Pharmacokinetic parameters (AUC and Cmax: arithmetic mean ± SD, tmax: median, range)

Treatment	**AUC_{0-t}** pg*h/ml	**$AUC_{0-\infty}$** pg*h/ml	**C_{max}** pg/ml	**t_{max}** h
Test	*1492.8*	*1510.5*	*441.4*	*0.92*
(S.D.)	*(683.2)*	*(700.9)*	*(186.8)*	*(0.42-4)*
Reference	*1500.9*	*1516.3*	*456.2*	*0.667*
(S.D.)	*(643.8)*	*(651.8)*	*(233.7)*	*(0.42-3)*
***Ratio (90% CI)**	*[93;*	*[93;*	*[90;*	*ns*
Point estimate	*104]%*	*104]%*	*108]%*	
	98.7 %	*98.8 %*	*98.6 %*	
Intra-subject CV (%)	*17.8%*	*17.7%*	*29.5%*	
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **T_{max}** time for maximum concentration : mediane, min and max				

**log-transformed values*

For sildenafil, the mean Kel was 0.2108 hours-1 for the test formulation and 0.2041 hours-1 for the reference product. The mean T1/2el value for the test and reference product was 3.66 hours and 3.83 hours, respectively. The intra-subject coefficient of variation was 29.5%, 17.8%, and 17.7% for Cmax, AUC0-t and AUC0-inf, respectively.

N-desmethyl sildenafil: Pharmacokinetic parameters (AUC and Cmax: arithmetic mean ± SD, tmax: median, range)

Treatment	**AUC_{0-t}** ng*h/ml	**$AUC_{0-\infty}$** ng*h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	453.6	465.2	136.9	0.92
(S.D.)	(190.5)	(195.9)	(72.1)	(0.42-4)
Reference	465.2	477.6	134	0.92
(S.D.)	(192.2)	(198.4)	(65.8)	(0.58-4)
***Ratio (90% CI)**	[94; 102]%	[94; 101]%	[93; 110]%	
Point estimate	97.8%	97.8%	100.9%	
Intra-subject CV (%)	12.3%	11.9%	27%	
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **T_{max}** time for maximum concentration : mediane, min and max				

**log-transformed values*

For N-desmethyl sildenafil, the mean Kel was 0.1670 hours-1 for the test formulation and 0.1588 hours-1 for the reference product. The mean T1/2el value for the test and reference product was 4.40 hours and 4.61 hours, respectively. The intra-subject coefficient of variation was 27%, 12.3% and 11.9% for Cmax, AUC0-t and AUC0-inf, respectively.

CLINICAL SAFETY

The safety analysis includes the fifty-eight (58) subjects who entered the study and received at least one of the treatments. Thirty-six (36) subjects participating in the trial reported adverse events throughout the course of this study. The maximal intensity reported for these events ranged from mild to severe. None of these events were considered to be serious. One adverse event (injury) required the use of concomitant medication (acetaminophen). No subject was withdrawn from the study because of an event.

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

- Conclusions

In conclusion, the conventional CI for ln-transformed AUC0-t, AUC0-inf and Cmax for sildenafil and N-desmethyl sildenafil were within the acceptance range. No significant difference in Tmax was evidenced by the non-parametric test. Therefore, this study was considered to have met the bioequivalence criteria as defined by the study protocol since all 90% confidence intervals were within the acceptance range for both, sildenafil and its major metabolite.

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

Pharmacodynamics

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

Post marketing experience

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

2.5 Pharmacovigilance

- **PSUR**

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

- **Description of the Pharmacovigilance system**

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

The MAH must ensure that the system of pharmacovigilance, as described in version 2.2 dated October 2007 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

- **Risk Management Plan**

Risk Management Plan has not been submitted. The application is based on a reference medicinal product for which no safety concerns requiring specific risk minimization activities have been identified.

Discussion on Clinical aspects

To support the application, 2 bioequivalence studies were submitted: the pivotal study conducted in fifty-eight healthy volunteers with the highest strength of sildenafil, i.e. 100 mg, and a pilot study performed in order to select the adequate formulation to be further developed and tested in the pivotal study.

All 58 subjects enrolled in the pivotal study received the two treatments and 57 were included in the statistical analysis. As claimed by the applicant the exclusion of the subject was decided before the conduct of the analytical phase of the study, hence the CHMP has considered the subsequent statistical analysis to be valid.

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

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

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

The adverse events observed in the study were graded mild to severe and were comparable to the originator. None of the events were considered serious. One adverse event (injury) required the use of concomitant medication.

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

2.6 Overall conclusions, benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

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

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

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

Recommendation

Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Sildenafil ratiopharm in the treatment of men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance was favourable and therefore recommended the granting of the marketing authorisation.