28 July 2016
EMA/533666/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mysildecard

International non-proprietary name: sildenafil

Procedure No.: EMEA/H/C/004186/0000

Note

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

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Background information on the procedure

1.1. Submission of the dossier

The applicant MYLAN S.A.S. submitted on 5 November 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Mysildecard, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 March 2015.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indications:

Treatment of adult patients with pulmonary arterial hypertension classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease

and

Treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. Efficacy in terms of improvement of exercise capacity or pulmonary haemodynamics has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Revatio instead of non-clinical and clinical unless justified otherwise.

Information on paediatric requirements

Not applicable

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 submit a critical report addressing the possible similarity with authorised orphan medicinal products.

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: Revatio 20 mg film-coated tablets
- Marketing authorisation holder: Pfizer Limited
- Date of authorisation: 28 October 2005
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation numbers: EU/1/05/318/001, EU/1/05/318/004

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

- Product name, strength, pharmaceutical form: Revatio 20 mg film-coated tablets
- Marketing authorisation holder: Pfizer Limited
- Date of authorisation: 28 October 2005
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation numbers: EU/1/05/318/001, EU/1/05/318/004

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

- Product name, strength, pharmaceutical form: Viagra 100 mg film-coated tablets
- Marketing authorisation holder: Pfizer Limited
- Date of authorisation: 14 September 1998
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation numbers: EU/1/98/077/010-12,15,25
- Bioavailability study number(s): 09-VIN-034

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Ondřej Slanař

- The application was received by the EMA on 5 November 2015.
- The procedure started on 4 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 February 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 3 March 2016.
- During the meeting on 1 April 2016, the CHMP agreed on the consolidated List of Questions to be sent

to the applicant.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 May 2016.
- The Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP/PRAC members on 27 June 2016.
- During the PRAC meeting on 7 July 2016, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- The Rapporteur circulated an updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP/PRAC members on 14 July 2016.
- The CHMP adopted the similarity report by written procedure on 28 July 2016.
- 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 Mysildecard by written procedure on 28 July 2016.

2. Scientific discussion

2.1. Introduction

About the product

The proposed product is an immediate release film-coated tablets containing Sildenafil citrate as active substance. Sildenafil citrate is a chemical substance and the dosage form has been developed as generic product to the centrally authorised product Revatio 20 mg film-coated tablets containing the same active substance in the same pharmaceutical form.

Sildenafil is a potent and selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5), the enzyme that is responsible for degradation of cGMP. Apart from the presence of this enzyme in the corpus cavernosum of the penis, PDE5 is also present in the pulmonary vasculature. Sildenafil, therefore, increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. In patients with pulmonary arterial hypertension this can lead to vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation.

Sildenafil is approved in the EU for the treatment:

Adults

Treatment of adult patients with pulmonary arterial hypertension classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease.

Paediatric population

Treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. Efficacy in terms of improvement of exercise capacity or pulmonary haemodynamics has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease.

Proposed posology and method of administration

Adults

The recommended dose is 20 mg three times a day (TID).

Paediatric population (1 year to 17 years)

For paediatric patients aged 1 year to 17 years old, the recommended dose in patients ≤ 20 kg is 10 mg (1 ml of compounded suspension) three times a day and for patients > 20 kg is 20 mg (2 ml of compounded suspension or 1 tablet) three times a day.

Patients using other medicinal products

In general, any dose adjustment should be administered only after a careful benefit-risk assessment. A downward dose adjustment to 20 mg twice daily should be considered when sildenafil is co-administered to patients already receiving CYP3A4 inhibitors like erythromycin or saquinavir. A downward dose adjustment to 20 mg once daily is recommended in case of co-administration with more potent CYP3A4 inhibitors clarithromycin, telithromycin and nefazodone. Dose adjustments for sildenafil may be required when co-administered with CYP3A4 inducers.

Special populations

Elderly (≥ 65 years)

Dose adjustments are not required in elderly patients. Clinical efficacy as measured by 6-minute walk distance could be less in elderly patients.

Renal impairment

Initial dose adjustments are not required in patients with renal impairment, including severe renal impairment (creatinine clearance < 30 ml/min). A downward dose adjustment to 20 mg twice daily should be considered after a careful benefit-risk assessment only if therapy is not well-tolerated.

Hepatic impairment

Initial dose adjustments are not required in patients with hepatic impairment (Child-Pugh class A and B). A downward dose adjustment to 20 mg twice daily should be considered after a careful benefit-risk assessment only if therapy is not well-tolerated.

Sildenafil is contraindicated in patients with severe hepatic impairment (Child-Pugh class C).

Paediatric population

The safety and efficacy of sildenafil in children below 1 year of age has not been established. No data are available.

Method of administration

Mysildecard is for oral use only. Tablets should be taken approximately 6 to 8 hours apart with or without food.

Type of Application and aspects on development

The Marketing Authorisation Application was submitted under Article 3(3) of Regulation EC 726/2004 "Generic of a Centrally Authorised Medicinal Product" and article 10(1) Generic Application of Directive 2001/83/EC, as amended.

The reference medicinal product is Revatio 20mg tablets by the company Pfizer, originally authorised in the community on 28.10.2005 (marketing authorisation numbers EU/1/05/318/001 and EU/05/318/004)

Bioequivalence with the product Viagra 100mg (sildenafil citrate) tablets by the company Pfizer is claimed, the applicant has requested a biowaiver for the 20mg tablets presentation of sildenafil citrate.

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

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 20 mg of sildenafil as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose (PH 102), calcium hydrogen phosphate, anhydrous, croscarmellose sodium, and magnesium stearate.

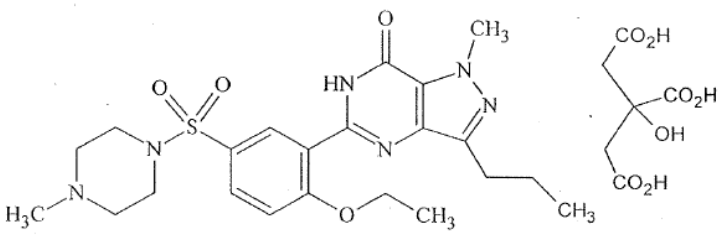
Film coat: hypromellose 6 mPas, titanium dioxide (E171), and triacetin

The product is available in PVC-Al blister packs as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of active substance is 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 corresponding to the molecular formula $C_{28}H_{38}N_6O_{11}S$ and has a relative molecular mass 666.7 and has the following structure:



The active substance is a white or almost white, slightly hygroscopic, crystalline powder, slightly soluble in water and in methanol and practically insoluble in hexane. The solubility is pH dependent.

Sildenafil has neither asymmetric nor chiral carbon atom, hence it does not exhibit optical isomerism.

Sildenafil citrate is known to exist in different salts and their polymorphic forms like anhydrous and hemihydrate. The polymorphism of sildenafil citrate is checked by XRD and DSC. Three consecutive batches of sildenafil citrate were analysed by XRD. The obtained spectra were compared with that of sildenafil citrate literature and are matching with anhydrous form. In addition to this, stability batches at 38th month interval were also analysed by XRD for further confirmation of polymorphic stability. Based on the data, the active substance manufacturer consistently produces anhydrous form.

As there is a monograph of sildenafil in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for sildenafil which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for particle size, impurities (piperazine dimer and sum of 4-nitrocarboxylic acid and 4-nitrocarboxamide) and nickel content. All additional methods have been adequately described and validated according to ICH Q2.

Stability

The re-test period of the substance granted by the CEP is 5 years when stored in a double polyethylene bags (outer black) placed in a polyethylene drum.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Sildenafil Citrate 20 mg film-coated tablets is a white, film-coated, round, biconvex tablet debossed with M on one side of the tablet and SL over 20 on the other.

The development strategy was to design and develop a stable and bioequivalent generic product of Sildenafil Citrate film-coated tablets using commonly used excipients and similar to the reference product.

The following attributes of the active substance were considered during the development of the finished product: appearance, solubility, potential isomerism, flow properties, particle size, polymorphism, and active substance-excipient study. The active substance does not exhibit optical isomerism, has poor flow properties and the data shows that no significant impact of particle size is observed on the drug release profile (more than 85% is released within 15 minutes). Active substance-Excipient compatibility study confirms no significant change in the physical appearance and in impurity levels of the binary mixtures.

All the excipients are conventional pharmaceutical ingredients complying with the requirements of European Pharmacopoeia except of film coating agent that is tested according to in house standards. The colorants used in coating material comply with EC regulation 231/2012. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The formulation of Sildenafil Citrate 20 mg film coated tablets was developed based on the literature search and characterization of reference product i.e. Revatio 20 mg film-coated tablets. Development started with Sildenafil Citrate 100 mg film-coated tablets and the same formula was scaled down to lower strengths (i.e. 20mg). Selection of excipients was based on literature search, past experience with film-coated tablet dosage form, drug-excipient compatibility study and the qualitative formula of reference product. To optimize the quantity of disintegrant (croscarmellose sodium), the trials were performed without and with different quantities of croscarmellose sodium i.e. (0 – 4 %). The formula without disintegrant show increased disintegration and a decrease of drug release therefore a 3% of croscarmellose sodium was chosen in the commercial finished product.

To optimize the quantity of water used as granulation agent, trials with different quantity of water were performed. Different quantities of water have no effect on the tablet characteristics and dissolution profile. To optimize the quantity of lubricant (Magnesium stearate), the trials with different quantities of magnesium stearate i.e. (0,5 – 2 %) were performed. The results show no difference in the tablet parameters and dissolution profile. Sildenafil Citrate 20 mg film coated tablets were developed as dose proportional formula to the 100 mg film coated tablets.

A bioequivalence study comparing the 100 mg strength of test product and reference product was carried out as an open label, randomized, two treatment, two period, two sequence, single dose cross-over study comparing the test product Sildenafil Citrate 100 mg film-coated tablets (with the reference product Viagra (Sildenafil) 100 mg film-coated tablets in healthy, adult male subjects under fasting conditions. The dissolution profiles of the tested product and the reference product have been compared in three medias (0.01N HCl, pH 4.5 Acetate buffer, pH 6.8 Phosphate buffer). More than 85% of the active substance was released within 15 minutes in tested and reference product at 0.01N HCl and at pH 4.5 Acetate buffer. The amount of drug released from both (tested and reference) products was found incomplete (51 – 57 %) after 45 min at pH 6.8 Phosphate buffer. The discriminatory power of the dissolution method has been demonstrated. The test product against European reference product has been proven to be bioequivalent.

A bio waiver justification was provided for the use of Sildenafil 100 mg film coated tablets in the bioequivalence study instead of 20 mg strength. The conditions for waiver according to the Guideline CPMP/EWP/ QWP/1401/98 Rev. 1 were fulfilled. The test product i.e. Sildenafil Citrate 20 mg film-coated tablets against Sildenafil Citrate 100 mg film-coated tablets (used in bioequivalence study) are exhibiting

similar dissolution profiles with 85 % of drug release in 15 minutes in both 0.01N Hydrochloric acid and pH 4.5 Acetate buffer. The dissolution profile between the test product i.e. Sildenafil Citrate 20 mg film coated tablets against Sildenafil Citrate 100 mg film-coated tablets (used in the bioequivalence study) was found to be similar in pH 6.8 Phosphate buffer. Since all the requirements to waive bioequivalence studies as mentioned in CPMP guideline on the Investigation of Bio-equivalence – CPMP/EWP/QWP/1401/98- Rev 01 are fulfilled, the bioequivalence study results of Sildenafil Citrate 100 mg film-coated tablets can be extended to Sildenafil Citrate 20 mg film-coated tablets.

As the active substance have very poor flow properties, a wet granulation manufacturing process was developed. The active substance is BCS class II drug having low solubility hence wet granulation approach was considered to improve its wettability. The manufacturing process was optimized at following stages: dry mixing, blending time, hardness (resistance to crushing) challenge studies, machine speed trails.

The primary packaging is PVC-Al blister packs. The material complies with Ph Eur and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 11 main steps: verification of dispensed raw material, sifting of intragranular materials, granulation, drying, dry screening, sifting of extragranular materials, blending, compression, coating, inspection, and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process (preparation of lubricated blend, compression, coating and packaging) have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (UPLC, UV, titanium dioxide, for citrate ion), dissolution (UV), uniformity of dosage units (Ph Eur), assay (UPLC), loss on drying (Ph Eur), microbiological test (Ph Eur), related substances (UPLC).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for impurities testing has been presented.

Batch analysis results are provided for 3 pilot scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data of 3 pilot scale batches of finished product stored under long term conditions for 36 months at 25 ºC / 60% RH, under intermediate conditions for 12 months at 30 °C / 75% RH and for up to 6 months

under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, loss on drying, related compounds, dissolution, assay and microbiological test. The analytical procedures used are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

The stability data presented indicated that the product complies with proposed finished product shelf life specification and no significant changes have been observed. The photostability study results infer that there is no significant difference observed charged at different study conditions, namely direct exposure and protected samples (dark control samples) when compared to initial results. Thus, it can be concluded that the finished product is photostable.

Based on available stability data, the proposed shelf-life of 36 months without storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

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 performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

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

generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

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

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Mysildecard is considered 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 Environmental Risk Assessment is expected to be similar and not increased.

2.3.3. Discussion and conclusion on non-clinical aspects

Mysildecard is approvable from the non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for tablets containing sildenafil. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

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. A QA statement has been also provided.

The applicant has also provided a list of GCP inspections at the clinical and analytical sites.

Exemption

The applicant has requested a biowaiver for the 20mg presentation with the justification provided below:

According to Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1 – August 2010), Sildenafil Citrate 20 mg film-coated tablets satisfy the conditions for waiver of bioequivalence studies conducted on Sildenafil Citrate 100 mg film-coated tablets as discussed below:

- Both strengths, Sildenafil Citrate 20 mg & 100 mg film-coated tablets are manufactured by the same manufacturer at the same manufacturing site using similar manufacturing process.

- The qualitative composition of core tablets of Sildenafil Citrate 20 mg and 100 mg film coated tablets is the same
- Sildenafil Citrate film-coated tablets 20 mg and 100 mg are direct scale up/scale down formulations and the ratio between the amounts of each excipient to the amount of the active substance is the same.
- AUC and Cmax were dose-proportional over single Sildenafil Citrate doses from 1.25 to 200 mg (Langtry HD et al., 1999).
- The in vitro dissolution characteristics demonstrates that dissolution profiles of Sildenafil Citrate 20 mg and 100 mg film-coated tablets of Mylan Laboratories Limited are similar across the physiological pH range i.e. pH 2.0 (0.01N), pH 4.5 and pH 6.8.

The dissolution profiles have been compared between the:

- Test product Sildenafil Citrate 100 mg film-coated tablets (manufactured by Mylan Laboratories Limited, India) against European reference product Viagra® (Sildenafil) 100 mg film-coated tablets of Pfizer Limited, Sandwich, Kent CT139NJ, United Kingdom used in the bioequivalence study.
- Test product used in the bioequivalence study i.e. Sildenafil Citrate 100 mg film-coated tablets against the lower strength of the test product i.e. Sildenafil Citrate 20 mg film-coated tablets.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study, study 09-VIN-034.

2.4.2. Pharmacokinetics

To support the application, the applicant has submitted one bioequivalence Study 09-VIN-034: A randomized, open-label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Sildenafil Citrate 100 mg tablets of Matrix Laboratories Limited, India and Viagra (Sildenafil citrate) 100 mg tablets of Pfizer Limited, Sandwich Kent CT13 9NJ in healthy human adult male subjects under fasting conditions.

Methods

Study design

The study was conducted as a randomized, open label, single dose, cross-over bioequivalence trial.

Basic information about the study is summarized in the **Table 1** below.

Table 1: Study09-VIN-034 basic details

Sponsor	Matrix Laboratories Ltd.
Study centres	Clinical, PK and biostatistics: Veeda clinical research Pvt. Ltd. Shivalik Plaza – A, Near I.I.M., Ambawadi

	Ahmedabad – 380 015 India Analytical: Matrix Laboratories Ltd. Clinical Research Centre Saradhi Chambers; beside Poulomi Hospital, A.S. Rao Nagar, Hyderabad – 500 062 India
Study initiation date (clinical)	18.2.2009
Study completion date (clinical)	27.2.2009
Study initiation date (bioanalytical)	26.3.2009
Study completion date (bioanalytical)	10.4.2009
Date of final report	21.5.2009
Date of the bioanalytical report	11.5.2009 (signed)
Date of the validation report	2.2.2009 (signed) Addendum 01-00: 6.3.2009 Addendum 02-00: 17.4.2009

Study 09-VIN-034 was randomized, crossover bioequivalence study conducted under fasting conditions. Subjects were housed in the clinical facility from a time adequate to ensure 10 hours fasting before dosing and were allowed to leave the facility after 24 hours post-dose sample in each period.

Test and reference products

Table 2: Test and Reference Product

	Test product (T)	Reference product (R)
Formulation	Sildenafil citrate 100 mg tablets	Viagra (sildenafil citrate) 100 mg tablets
Manufacturer	Matrix Laboratories Limited, India	Pfizer Limited, Sandwich, Kent
Batch number	1009484	7139805F
Batch size	190 000 tablets	NA
Manufacturing date	10.2008	NA
Expiry date	9.2010	12.2012

Assay content	99.77 mg (99.8 % w/w)	101.90 mg (101.9 % w/w of labelled amount of sildenafil)

Mysildecard manufactured by MYLAN S.A.S. (batch No. 1009484, manufacturing date; 10:2008, exp. date September 2010) has been compared to viagra + 100mg manufactured by (Batch No: 7139805F , exp. Date 12.2012).

Population(s) studied

Forty four (44) healthy adult male subjects were enrolled in the study. All subjects were between 18 and 55 years of age (both included), with a BMI between 18.5 and 24.9, normal laboratory test results and vital signs. All subjects signed an informed consent prior to the study initiation.

Thirty nine subjects completed all periods of the study as per protocol, and plasma samples from 39 subjects were used for PK evaluation. In addition, plasma from subject 24 was analysed for safety. Subjects number 10, 17, 24, 25 and 42 were withdrawn from the study.

Reasons for withdrawal were following:

- Subject No.10 was tested positive for drugs in urine prior to period II.
- Subject No. 17 was tested positive for drugs in urine prior to period II.
- Subject No. 24 experienced adverse event.
- Subject No. 25 was tested positive for drugs in urine prior to period II.
- Subject No. 42 withdrew consent prior to period I.

Analytical methods

Sildenafil and its metabolite N-desmethyl-sildenafil were determined by HPLC method using tandem mass spectrometry detection (Analytical Method Procedure No. SAP-010-00). The interface used with the API 2000 LC/MS/MS was a Turbo IonSpray. The positive ions were measured in MRM mode. Analytes and internal standard (sildenafil-d3) were extracted from K_3EDTA plasma by solid phase extraction technique.

The active metabolite (piperazine N-desmethylsildenafil reported here as N-desmethylsildenafil) data were submitted as supportive therapeutic outcome.

The study samples were measured using the same instrumentation as in validation phase (an API 2000 LC/MS/MS system equipped with a pumps Shimadzu LC-20ADvp, an autosampler Shimadzu SIL-HTc), analytical column Betasil C18 (50x3.0mm, 3µm).

Calibration curves ranged from 9.640 to 1447.340 ng/mL and from 4.060 to 811.200 ng/mL for sildenafil and N-desmethyl-sildenafil, respectively. Quantitation was based on peak area ratio of sildenafil versus internal standard. A least squares linear regression with weighing factor $1/x^2$ was used. All data were generated by Applied Biosystems Analyst® Software 1.4.2.

The calibration curve standards and the QC samples were prepared with stock solutions from separate weighing. The working standard & QC solutions were stored in the refrigerator at 2–8°C.

Certificates of analysis for sildenafil citrate (Batch No. SDC/0709002, Retest Date August 2009), desmethyl-sildenafil (Batch No. RAM-38-4554, Expiry Date April 2010) and sildenafil-D3 (Batch No. SD-5796, Expiry Date August 2010) were attached to the Bioanalytical report.

There was one protocol deviation in plasma samples storage conditions during clinical period of the study which may not have significant impact on the study outcome.

Incurred sample reanalysis was not performed. The study had been carried out before the requirement of ISR was introduced into the Guideline on bioanalytical method validation in February 2012. Scientific justification should be provided to evaluate the performance of the method.

Bioanalytical method validation

The validation results of a high performance liquid chromatographic method using tandem mass spectrometry detection for determination of sildenafil and N-desmethyl-sildenafil in human plasma (Analytical Method Procedure No. SAP-010-00) are presented in the Validation Report No.: VR-010-00. The method was validated in CRC Matrix Laboratories Ltd. in 2009. The long term stability data of sildenafil and N-desmethyl-sildenafil in solutions and in human plasma were submitted in Addenda 01-00 and 02-00 to the validation report.

Pharmacokinetic Variables

The PK parameters for sildenafil and piperazine N-desmethyl sildenafil were calculated by using non-compartmental model by WinNonlin Professional Software (version 5.0) with the data from 39 subjects.

From the time/concentration values, various pharmacokinetic parameters (C_{max}, T_{max}, AUC_{0-t}, K_{el}, $AUC_{0-\infty}$, $AUC_{0-t}/AUC_{0-\infty}$ and $t_{1/2}$) were calculated and these were used in the statistical analysis to compare the bioequivalence of the test and reference products. The pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, were estimated to evaluate bioequivalence of Sildenafil.

Statistical methods

Blinding

This study comprised of a randomized, open label design. Being a bioequivalence study an open label design was selected, however analysts were blinded to the sequence of administration of test and reference formulations.

Randomization

The order of receiving the Test and Reference product for each subject during each period of the study was determined according to the randomization schedule. The dosing (treatment) of Test and Reference product was divided into two sequences (RT or TR).

Determination of sample size

Sample size was based on estimates obtained from reported literature and previous studies. Assuming a formulation ratio (T/R) ranging from 0.95 - 1.05 and with the maximum observable intra-subject variability of 30%, a sample-size of 42 subjects would be sufficient to prove bioequivalence between the two formulations with a power of at least 80% considering the drop-outs and withdrawals 44 subjects were considered.

Statistical analysis plan

The statistical comparison of the pharmacokinetic parameters was carried out using SAS Version 9.2 (SAS Institute Inc., USA) for Sildenafil.

Analysis of variance (ANOVA) was carried out using SAS Version 9.2 (SAS Institute Inc., USA) for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Sildenafil. ANOVA model included sequence subject nested into sequence, period and formulation effects. Subject nested into sequence was used as error term for checking the significance of Sequence. The sequence effect was tested at the 0.10 level of significance and all other main effects were tested at the 0.05 level of significance.

Results

Table 3: Pharmacokinetic parameters for sildenafil (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$	1853.52	740.80	1918.56	776.83
$AUC_{(0-\infty)}$	1927.95	759.61	1992.74	789.96
C_{max}	558.92	229.57	608.25	241.81
T_{max} *	1.00 (0.50 – 3.50)		0.83 (0.50 – 2.50)	
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 4: Statistical analysis for sildenafil (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	97.63 %	92.25 % – 103.33 %	14.92
C_{max}	92.83 %	85.23 % – 101.11 %	22.65
* estimated from the Residual Mean Squares			

The applicant has also provided results for the active metabolite piperazine N-desmethyl sildenafil as supportive data. These are summarized further below.

Table 5: Pharmacokinetic parameters for piperazine N-desmethyl sildenafil (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$	562.90	218.81	586.71	230.03
$AUC_{(0-\infty)}$	602.09	227.41	633.74	234.49
C_{max}	138.18	48.75	149.59	56.62
T_{max} *	1.00 (0.50 – 3.50)		0.83 (0.50 – 2.50)	

<AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours>

<AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours>

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

C_{max} maximum plasma concentration

T_{max} time for maximum concentration (* median, range)

Safety data

There were no deaths or serious adverse events observed during the study. Two subjects reported adverse events, which were not considered serious and did not require hospitalisation. Subject No. 24 experienced high-grade fever associated with chills and rigors after administration of the test product. No other associated complaints were reported. The subject was administered paracetamol 500 mg one tablet three times daily for four days. Relation to the investigational medicinal products was evaluated as unlikely. Subject No. 30 experienced a single episode of vomiting after administration of the reference medicinal product, without any other associated complaints. The relation to investigational medicinal product was evaluated as possible.

Individual laboratory values of the subjects at the time of post-study laboratory assessment were also reviewed. The laboratory test for those investigations, which were found to be abnormal were repeated on the follow-up. All out-of-range parameters were evaluated for their clinical significance, or were followed until they became normal.

None of the subjects showed clinically significant abnormalities, but several had their laboratory parameters out of range. This is however not considered of concern.

Conclusions

Based on the presented bioequivalence study Mysildecard is considered bioequivalent with Revatio.

2.4.3. Pharmacodynamics

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

2.4.4. Post marketing experience

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

2.4.5. Discussion on clinical aspects

To support the application, a literature review of the preclinical and clinical data for the active substance has been submitted, together with the results of a bioequivalence study conducted with the 100 mg presentation. In this application, an essential similarity is claimed to the original product Revatio 20 mg, but the study has been conducted with the reference medicinal product Viagra 100 mg. Based on the fact that Revatio and Viagra have the same qualitative composition, proportional quantitative composition, and are manufactured by the same manufacturing process, extrapolation of the bioequivalence findings to another originator product is considered justified. Submitted bioequivalence study was randomized, crossover, single-dose study conducted under fasted conditions. The study has been declared to be conducted in GCP setting, and list of GCP inspections of the clinical, analytical and statistical sites have been submitted.

Bioanalytical method was of satisfactory performance, and adequately validated. Apart from sildenafil PK parameters, the applicant has also submitted values for the active metabolite piperazine N-desmethyl sildenafil as supportive data. Statistical evaluation of the obtained data demonstrated bioequivalence between test and reference product for sildenafil. Regarding the N-desmethyl metabolite, no formal bioequivalence analysis has been explored. Considering that bioequivalence has been demonstrated for the parent drug, further analysis of the metabolite is not considered necessary.

Furthermore, the applicant has requested biowaiver for the 20mg presentation. To support the request, a justification and results of comparative dissolution tests have been provided. Sildenafil exhibits linear pharmacokinetics up to 200 mg after single dose administration, and after repeated administration linearity has been demonstrated until 80 mg. Furthermore, proportionality in the composition between 20mg and 100mg strength has been shown. The dissolution profiles of the test and reference product has been fully addressed, and no more data are needed. Details of the dissolution profile assessment can be found in the quality assessment report. Provided that the applicant adequately addresses the abovementioned issue, biowaiver could be granted for sildenafil 20 mg.

2.4.6. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Mysildecard was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

Results of the study 09-VIN-034 suggest bioequivalence between the Mysildecard and Viagra 100 mg. Biowaiver criteria are considered fulfilled and biowaiver can be granted for 20mg strength.

In conclusion, Mysildecard is approvable from the clinical point of view.

2.5. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP):

The PRAC considered that the RMP version 1.0 (dated 09 October 2015) could be acceptable if the Applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report dated 03 March 2016.

The CHMP endorsed this advice.

The Applicant implemented all changes to the RMP as requested by the PRAC and the CHMP.

The CHMP endorsed the RMP version 3.0 (dated 8 July 2016) with the following content:

Safety concerns

Table 6– *Summary of the safety concerns*

Important identified risks	• Nitrate interaction (PT: Drug interaction) • Vaso-occlusive crisis in patients with sickle cell disease (PT: Sickle cell anaemia with crisis) • Increase relative mortality in the paediatric population • Epistaxis/bleeding events (SMQ: Haemorrhage) • Interaction with bosentan (and other CYP3A4 Inducers) (PT: Drug interaction)
Important potential risks	• Hypotension (PT: Hypotension) • Non-arteritic anterior ischaemic optic neuropathy (NAION) (PT: Optic ischaemic neuropathy) • Hearing loss (PT: Deafness) • Important potential interactions: epoprostenol, iloprostInteraction (PT: Drug interaction) • Pulmonary haemorrhage in off-label paediatric use (PT: Pulmonary haemorrhage)
Missing information	• Long-term ocular safety • Safety in Pregnancy • Safety in patients with renal impairment • Safety in patients with cardiovascular diseases • Long-term mortality

Pharmacovigilance plan

Not applicable

Risk minimisation measures

Table 7 – Summary Table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Nitrate interaction (PT: Drug interaction)	Wording in SmPC section 4.3 and 4.5 Prescription only medicine	None
Vaso-occlusive crisis in patients with sickle cell disease (PT: Sickle cell anaemia with crisis)	Wording in SmPC section 4.4 Prescription only medicine	None
Increase relative mortality in the paediatric population	Wording in SmPC section 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 Prescription only medicine	None
Epistaxis/bleeding events (SMQ: Haemorrhage)	Wording in SmPC section 4.4 and 4.8 Prescription only medicine	None
Interaction with bosentan (and other CYP3A4 Inducers) (PT: Drug interaction)	Wording in SmPC section 4.2, 4.4, 4.5 and 5.1 Prescription only medicine	None
Important potential risks		
Hypotension (PT: Hypotension)	Wording in SmPC section 4.3, 4.4, 4.5 and 4.8 Prescription only medicine	None
Non-arteritic anterior ischaemic optic neuropathy (NAION) (PT: Optic ischaemic neuropathy)	Wording in SmPC section 4.3, 4.4 and 4.8 Prescription only medicine	None
Hearing loss (PT: Deafness)	Wording in SmPC section 4.8 Prescription only medicine	None
Important potential interactions: epoprostenol, iloprost (PT: Drug interaction)	Wording in SmPC section 4.4, 4.5 and 4.8 Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Pulmonary haemorrhage in off-label paediatric use (PT: Pulmonary haemorrhage)	Wording in SmPC section 4.1 and 4.2 Prescription only medicine	None
Missing information		
Long-term ocular safety	Prescription only medicine	None
Safety in pregnancy	Wording in SmPC section 4.6 Prescription only medicine	None
Safety in patients with renal impairment	Wording in SmPC section 4.2 Prescription only medicine	None
Safety in patients with cardiovascular diseases	Wording in SmPC section 4.3 and 4.4 Prescription only medicine	None
Long-term mortality	Wording in SmPC section 4.4 and 5.1 Prescription only medicine	None

Conclusion

The CHMP and PRAC considered that the RMP version 3.0 (dated 8 July 2016) is acceptable.

2.6. PSUR submission

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.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

The latest approved PI of the reference product is being implemented (Revatio procedure EMEA/H/C/ 00638/ II73).

3. Benefit-risk balance

This application concerns a generic version of sildenafil citrate tablets. The reference product Revatio is indicated for patients with pulmonary arterial hypertension. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a cross over randomised study. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. The study design, (fasting status, choice of dose, sampling points, overall sampling time as well as wash-out period) was adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of sildenafil citrate met the protocol-defined criteria for bioequivalence when compared with Viagra. Viagra contains the same active substance as Revatio but is indicated for another indication (male erectile dysfunction). The bioequivalence study was performed with Viagra, which is considered acceptable as it contains the same active substance as Revatio. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

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

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Mysildecard is favourable in the following indication:

Adults

Treatment of adult patients with pulmonary arterial hypertension classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease.

Paediatric population

Treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. Efficacy in

terms of improvement of exercise capacity or pulmonary haemodynamics has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

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.