15 September 2016
EMA/645375/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Granpidam

International non-proprietary name: sildenafil

Procedure No. EMEA/H/C/004289/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

BCS	Biopharmaceutics Classification System
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human use
EDQM	European Directorate for the Quality of Medicines
EC	European Commission
GC	Gas Chromatography
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
KF	Karl Fischer titration
MAA	Marketing Authorisation Applicant
MAH	Marketing Authorisation Holder
PAH	Pulmonary Arterial Hypertension
Ph. Eur.	European Pharmacopoeia
PVC	Poly vinyl chloride
QC	Quality Control
RH	Relative Humidity
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Ltd submitted on 9 November 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Granpidam, 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 24 September 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 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:

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.

and

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.

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 number(s): EU/1/98/077/011
- Bioavailability study number(s): 084-09

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: Kolbeinn Gudmundsson

- The application was received by the EMA on 9 November 2015.
- The procedure started on 4 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 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 final consolidated List of Questions was sent to the applicant on 4 April 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 13 July 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 19 August.
- During the PRAC meeting on 2 September 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 draft List of Outstanding Issues to all CHMP/PRAC on 8 September 2016.
- The CHMP adopted the similarity report on 15 September 2016.
- During the meeting on 15 September 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 Granpidam.

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 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 three times a day and for patients > 20 kg is 20 mg three times a day. Higher than recommended doses should not be used in paediatric patients with PAH. The 20 mg tablet should not be used in cases where 10 mg TID should be administered in younger patients. Other pharmaceutical forms are available for administration to patients ≤ 20 kg and other younger patients who are not able to swallow tablets.

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

Granpidam 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 October 2005 (marketing authorisation numbers EU/1/05/318/001 and EU/05/318/004)

Bioequivalence with the product Viagra 100 mg (sildenafil citrate) tablets by the company Pfizer is claimed, the applicant has requested a biowaiver for the 20 mg 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 citrate) as active substance. Other ingredients are:

Tablet core: microcrystalline cellulose, calcium hydrogen phosphate anhydrous, croscarmellose sodium, hypromellose 5 cp (E464) and magnesium stearate.

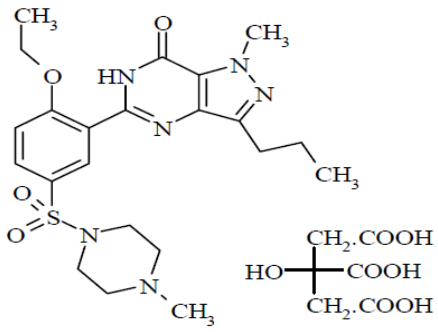
Film coat: hypromellose 15 cp (E464), titanium dioxide (E171), lactose monohydrate and triacetin.

The product is available in PVC/aluminium blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of sildenafil citrate is 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate corresponding to the molecular formula $C_{22}H_{30}N_6O_4S.C_6H_8O_7$. It has a relative molecular mass of 666.71 g/mol and the following structure:



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

Proof of structure has been provided in the CEP. The active substance is a white or almost white, slightly hygroscopic crystalline powder, slightly soluble in water. It is achiral. The manufacturing route routinely delivers the proposed commercial polymorphic form as documented in the CEP.

Manufacture, characterisation and process controls

The relevant information on manufacture, characterisation, process controls, and the container closure system was assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance specification includes the specification parameters and test methods described in the Ph. Eur. monograph and CEP for Sildenafil Citrate, along with a number of additional specification parameters. The following parameters are tested: appearance, identity (IR, HPLC), identity of citrate (colour test), polymorphic form (XRD), water content (KF), sulfated ash (Ph. Eur.), heavy metals (Ph. Eur.), impurities (Ph. Eur. and HPLC), assay (HPLC), citric acid content (titrimetry), residual solvents (GC) and microbiological examination (Ph. Eur.). No limit for particle size is necessary as this was demonstrated not to impact the performance (i.e. dissolution) of the finished product.

All non-compendial methods have been adequately validated and described according to ICH Q2. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on three pilot to production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on ten batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25 ºC / 60% RH) according to the ICH guidelines were provided. Stability data on four of these batches stored for up to 6 months under accelerated conditions (40 ºC / 75% RH) were also provided. Samples were tested, in accordance with active substance specification, for identity, water content, impurities, polymorphic form and assay. A commitment to test microbiological quality at the end of the re-test period was deemed acceptable. The analytical methods used

were the same as for release and are stability indicating. All test results were in compliance with the active substance specification throughout the duration of the studies.

Forced degradation studies were carried out on solid samples exposed to heat, UV light and sunlight, and in acidic, neutral, basic and oxidizing aqueous solutions. While significant degradation occurs under oxidizing conditions and acid causes slight degradation, sildenafil citrate proved stable under all other stressed conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months in the proposed container without special storage conditions.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Granpidam is presented as 20 mg white to off-white round, biconvex film-coated tablets debossed with “20” on one face.

Development work was aimed at producing a robust, stable solid oral dosage form bioequivalent to the reference product Revatio and with an equivalent dissolution profile. Sildenafil citrate is slightly soluble in water but more so under acidic conditions of the stomach and is considered to be BCS class I. Particle size distribution was found not to impact dissolution, other than a slight reduction at early time-points. Complete dissolution is observed within 15 minutes under acidic conditions and thus no limit for particle size is applied to the active substance. Since sildenafil citrate has poor flow properties, a wet granulation process was selected.

Excipients were chosen based on the reference product and compatibility studies. The excipient content is qualitatively similar to Revatio with the addition of hypromellose as a binder. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. 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 2.2.1 of this report.

Various studies were carried out in order to optimise the relative amounts of excipients and to determine appropriate lubrication, compression and coating parameters.

The dissolution method was developed by investigating different media and apparatus. While rapid dissolution was observed at pH 1.2 and 4.5, sink conditions were not possible at pH 6.8 without the addition of a surfactant. The latter conditions were selected as the QC method. Being a BCS class I compound, absorption of sildenafil is liable to be impacted by disintegration time and thus the discriminatory power of the dissolution method was investigated using batches containing less and no disintegrant. Significant differences in dissolution rate were shown at early time points.

Four quantitatively proportional tablet strengths were developed, as sildenafil is used at different doses to treat PAH (20 mg, Revatio) and erectile dysfunction (Viagra, 25, 50 and 100 mg). A bioequivalence study was carried out using 100 mg tablets of Granpidam, with 100 mg Viagra tablets as a comparator, and bioequivalence was thus demonstrated. The use of Viagra as comparator was deemed acceptable as Revatio and Viagra are qualitatively and quantitatively identical, except for the colour of the non-functional film coating. Comparison of *in vitro* dissolution was carried out between the Granpidam 100 mg biobatch and Viagra. Rapid dissolution (>85% in 15 mins) of both at pH 1.2, 4.5 and under QC conditions was demonstrated. Significantly slower dissolution was observed at pH 6.8 without surfactant (non-sink conditions) for the biobatch compared to Viagra, reflecting the slower disintegration of Granpidam tables.

A proportionality biowaiver was requested for the 20 mg tablets applied for in this MAA given that they have the same relative composition as the 100 mg tablets and that sildenafil citrate is BCS class I. The dissolution profiles of 20 mg Granpidam tablets were compared to those of 100 mg Granpidam tablets and 20 mg Revatio tablets under various conditions. Rapid dissolution of all three tested products was observed at pH 1.2, 4.5 and under QC conditions. At pH 6.8 without surfactant, complete dissolution did not occur for any of the tested products but the profiles are considered similar based on calculated f_2 values. Therefore, the proportionality biowaiver is considered acceptable.

The primary packaging is PVC/Alu blisters. The materials comply 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 six main steps: blending of intra-granular excipients, wet granulation followed by drying and sizing, blending with extra-granular excipients, compression, film-coating and packing. The process is considered to be a standard manufacturing process.

The main steps of the manufacturing process have been validated on three consecutive batches of blended granules and subsequently compressed film-coated tablets. 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 and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, average weight of tablets (in house), identity (UV, HPLC), identity of citrate counter ion (colour test), identity of titanium dioxide (colour test), dissolution (UV), water content (Ph. Eur.), impurities (HPLC), uniformity of dosage units (Ph. Eur.), assay (UV) and microbiological quality (Ph. Eur.).

Specification limits for impurities are below the qualification threshold. There are no new impurities as compared to the active substance.

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 assay and impurities testing has been presented.

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

Stability of the product

Stability data from three production scale batches of finished product from the proposed manufacturer and stored for up to 60 months under long term (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, dissolution, water content, impurities, assay and microbiological quality. The analytical procedures used are stability indicating. No significant changes to any of the measured parameters under either condition were observed.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes to any of the measured parameters were observed, indicating that Granpidam tablets are photostable.

Data on three batches of finished product stored for up to 6 months in bulk in a polypropylene co-polymer (PPCP) container was also provided. The results support a bulk holding time of 6 months in the PPCP container.

Based on available stability data, the proposed shelf-life of 60 months without specific storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Magnesium stearate and triacetin are of vegetal origin. No other 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.

The product has been shown to be bioequivalent to the reference product and a strength biowaiver has been deemed adequate.

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. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- microbiological quality of the active substance should be tested at the end of its re-test period.

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 Granpidam manufactured by Accord Healthcare Limited 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 ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

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

A valid justification for not submitting ERA is given.

2.3.4. Conclusion on the non-clinical aspects

There are no objections to approval of Granpidam from a 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.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09) and Question number 10 of the Questions & Answers: Positions on specific questions addressed to the Pharmacokinetics Working Party (PKWP) EMA/618604/2008 Rev. 13 are of particular relevance.

GCP

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

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

This application for marketing authorisation is for the 20 mg sildenafil strength. One bioequivalence study was conducted on the 100 mg strength and a biowaiver is requested for the 20 mg strength.

The results of study 084-09 with 100 mg formulation could be extrapolated to the other strength 20 mg, according to conditions in the Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1/Corr**).

Clinical studies

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

Table 1. Tabular overview of clinical studies

Study No.	Study Title
Project No. 084-09	An open label, single dose, bioequivalence study of two formulations of Sildenafil citrate tablets 100 mg in healthy, adult, human, male subjects under fasting conditions.

2.4.2. Pharmacokinetics

To support the application, the applicant has submitted one (1) bioequivalence study.

Methods

Study design

The study was an open label, balanced, randomised, laboratory-blinded, two-sequence, two-treatment, two-period, single oral dose, cross-over bioequivalence study comparing two different formulations of sildenafil 100 mg tablets in healthy, adult human male subjects under fasting conditions.

Test and reference products

Sildenafil citrate 100 mg film-coated tablets by Intas Pharmaceuticals Ltd., India has been compared to VIAGRA® 100 mg film-coated tablets by Pfizer PGM (from the UK market).

Population(s) studied

Thirty-six (36) healthy adult male subjects were randomised and dosed. There was one dropout from the study. Thirty-five (35) subjects completed both periods of the study and were included in the final statistical analysis of AUC and C_{max}.

Analytical methods

A LC-MS/MS method for the determination of sildenafil concentration in K_2EDTA human plasma was validated pre-study and within study.

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

The primary pharmacokinetic parameters C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and the secondary pharmacokinetic parameters T_{max}, λ_Z, $t_{1/2}$ and AUC_%Extrap_Obs were estimated for sildenafil by a standard non-compartmental model using WinNonlin Professional Software Version 5.0.1 (Pharsight Corporation, USA). Standard methods were used.

Statistical methods

Analysis of variance was carried out by employing PROC MIXED of SAS® Release 9.1.3 (SAS Institute Inc., USA) for un-transformed and ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for sildenafil. ANOVA model included sequence, formulation and period as fixed effects and subject (sequence) as a random effect. Sequence effect was tested using subject (sequence) as error term.

Two one-sided tests for bioequivalence and 90% confidence interval for both the un-transformed and ln-transformed ratios of the least squares mean between the formulations were calculated for sildenafil. Ratio of least squares means of test and reference formulation was computed for un-transformed and ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for sildenafil.

Criteria for conclusion of bioequivalence:

Bioequivalence of the test product B vs. the reference product A was concluded, if the 90% confidence interval for the ratio of the least square means for the ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for sildenafil fell within the acceptance range of 80.00-125.00%.

Results

The results of bioequivalence study no. 084-09 are found in tables 1 and 2 below.

Table 1: Pharmacokinetic parameters for sildenafil citrate (non-transformed values)

Pharmacokinetic parameter	**Test**		**Reference**	
	arithmetic mean	**±SD**	**arithmetic mean**	**±SD**
$AUC_{(0-t)}$ (ng.h/ml)	2222.284	908.4766	2100.913	783.3562
$AUC_{(0-\infty)}$ (ng.h/ml)	2257.410	927.4603	2131.189	806.8909
C_{max}	626.950	226.3433	589.580	210.2451
T_{max}*	1.250	(0.500-2.500)	1.250	(0.500-2.500)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t 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 2: Statistical analysis for sildenafil citrate (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	104.7	100.00%-109.59%	11.3
C_{max}	105.3	98.21%-112.95%	17.4
* estimated from the Residual Mean Squares			

The test product B (Sildenafil Citrate Tablets 100 mg – Manufactured by Intas Pharmaceuticals Ltd., India) when compared with the reference product A (Viagra®, Sildenafil Citrate Tablets 100 mg – Manufactured by Pfizer PGM France, Marketing Authorisation Holder – Pfizer Limited, UK) under fasting conditions meets the bioequivalence criteria with respect to the rate and extent of absorption of sildenafil.

Safety data

A total of four post-dose adverse events (AEs) (headache, vomiting and pruritus) were reported by three subjects during the conduct of the study. One AE was reported in a subject who had received the reference product and three AEs were reported in subjects who had received the test product. All the AEs were mild in nature and were followed up till resolution. Two AEs (headache and pruritus) required treatment with medication (paracetamol 500 mg and cetirizine 10 mg, respectively) prior to resolution.

Data from this study demonstrated that both the test and the reference drugs were well tolerated. There were no serious and significant adverse events reported during the course of the study. There were no clinically significant findings in the vital signs assessment, the laboratory tests and ECGs.

2.4.3. Pharmacokinetic conclusion

Based on the presented bioequivalence study Granpidam 100 mg film-coated tablets are considered bioequivalent with Viagra® 100 mg film-coated tablets. The applicant is applying for the marketing authorisation of the 20 mg strength only and therefore requesting a biowaiver for the 20 mg strength. The results of study 084-09 with 100 mg formulation could be extrapolated to the 20 mg strength, according to conditions in the Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1/Corr**).

The acceptability of the biowaiver is further discussed below.

2.4.4. Pharmacodynamics

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

2.4.5. Additional data

In vitro dissolution tests complementary to the bioequivalence study

Comparative dissolution tests were conducted between the 100 mg strength of the test and reference biobatches in 0.01N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer.

In 0.01N HCl and pH 4.5 acetate buffer more than 85% was dissolved in 15 min for both products. At pH 6.8 phosphate buffer the The calculated f_2 value is 27 and the dissolution profiles can thus not be considered comparable. However, a valid justification for the discrepancy has been addressed and justified.The results of comparative in vitro dissolution do not reflect bioequivalence as demonstrated in vivo.

In vitro dissolution tests in support of biowaiver of strengths

Comparative dissolution tests were conducted between the 100 mg test biobatch and 20 mg test product (different batches) in 0.01N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer.

In 0.01N HCl and pH 4.5 acetate buffer more than 85% was dissolved in 15 min for all tested products. At pH 6.8 phosphate buffer the calculated f_2 value was 53 and thus the dissolution profiles can be considered similar.

In conclusion the data provided support the biowaiver request.

2.4.6. Post marketing experience

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

2.4.7. Discussion on clinical aspects

This is a generic application for the marketing authorisation of Granpidam 20 mg film-coated tablets. One bioequivalence study on the 100 mg strength is submitted to support the application and a biowaiver is requested for the 20 mg strength.

Based on the presented bioequivalence study Granpidam 100 mg film-coated tablets are considered bioequivalent with Viagra® 100 mg film-coated tablets. It is acceptable to use Viagra 100mg as it contains the same active substance as Revatio. However the strength differs (see below discussion on the biowaiver).

The applicant is applying for the marketing authorisation of the 20 mg strength only and therefore requesting a biowaiver for the 20 mg strength. The results of study 084-09 with 100 mg formulation can be extrapolated to the 20 mg strength, according to conditions in the Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1/Corr**).

It is acknowledged that the study #084-09 and validation of the analytical method were conducted before the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev.1 Corr. 2**) came into force and ISR was not preformed. The applicant has provided a valid justification of the lack of ISR data in line with Question 10. Requirement to perform incurred sample reanalysis of Questions & Answers: positions on specific questions addressed to the Pharmacokinetics Working Party (PKWP) (EMA/618604/2008 Rev. 13). The bioanalytical method can be considered reliable and thus the study results are considered acceptable. Thus the biowaiver request is acceptable.

2.4.8. Conclusions on clinical aspects

The application contains an adequate review of published clinical data and the bioequivalence has been shown between Granpidam and Viagra® 100 mg film-coated tablets. A biowaiver for the 20 mg strength is considered acceptable.

Conclusions

Based on the presented bioequivalence study Granpidam is considered bioequivalent with Viagra (reference product used).

The results of study 084-09 with 100mg formulation can be extrapolated to other strengths 20mg, according to conditions in the Guidelines.

2.5. Risk management plan

Summary of the safety concerns

Summary of safety concerns	
Important Identified Risks	• Nitrate interaction • Vaso-occlusive crisis in patients with sickle cell disease • Increased relative mortality in the paediatric population • Epistaxis/bleeding events • Interaction with bosentan
Important Potential Risks	• Potential drug interactions: epoprostenol, iloprost • Pulmonary haemorrhage in off label paediatric use • Non-arteritic anterior ischaemic optic neuropathy • Hearing loss • Hypotension
Missing Information	• Safety in pregnancy • Safety in patients with cardiovascular diseases • Long term mortality • Long term ocular safety • Safety in patients with renal impairment

Pharmacovigilance Plan

Not applicable

Risk minimisation plan

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: Nitrate interaction	Section 4.3 and 4.5 of Proposed Granpidam SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important identified risk: Vaso-occlusive crisis in patients with sickle cell disease	Section 4.4 and 4.8 of proposed Granpidam SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important identified risk: Increased relative mortality in the paediatric population	Section 4.4 and 5.1 of proposed Granpidam SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important identified risk: Epistaxis/bleeding events	Section 4.4 and 4.8 of proposed Granpidam SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important identified risk: Interaction with bosentan	Section 4.4, 4.5 and 5.1 of proposed Granpidam SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important potential risk: Potential drug interactions: epoprostenol, iloprost	Section 4.5, 4.8 and 5.1 of Proposed Granpidam SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important potential risk:	None proposed	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Pulmonary haemorrhage in off label paediatric use		
Important potential risk: Non-arteritic anterior ischaemic optic neuropathy	Section 4.3, 4.4 and 4.8 of Proposed Granpidam SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important potential risk: Hearing loss	Section 4.8 of Proposed Granpidam SmPC and corresponding section of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important potential risk: Hypotension	Section 4.3, 4.4, 4.5 and 4.8 of proposed Granpidam SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Missing information: Safety in pregnancy	Section 4.6 and 5.3 of Proposed Granpidam SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Missing information: Safety in patients with cardiovascular diseases	Section 4.3 and 4.4 of Proposed Granpidam SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Missing information: Long term mortality	Section 5.1 of Proposed Granpidam SmPC has information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Missing information: Long-term ocular safety	None proposed	None proposed
Missing information: Safety in patients with renal	Section 4.2 and 5.2 of proposed Granpidam SmPC and corresponding section of PIL have information on	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
impairment	this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.0 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

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

Except MAH specific details, all the critical /less critical sections are identical to that of reference PIL and therefore the key messages including all safety messages are exactly same for both the PIL. As the complete text is adopted from reference package leaflet, difference in design and layout, if any, will not have any impact on readability.

Based on the above justification the daughter PIL is considered comparable with the parent PIL and assessed as readable in compliance with Articles 59(3) and 63(2) of Directive 2001/83/EC as amended.

3. Benefit-risk balance

This application concerns a generic version of Revatio 20 mg film coated tablets. The reference product Revatio is indicated for 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. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. The study was an open label, balanced, randomised, laboratory-blinded, two-sequence, two-treatment, two-period, single oral dose, cross-over bioequivalence study comparing two different formulations of sildenafil 100 mg tablets in healthy, adult human male subjects under fasting conditions. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. Of note the reference product used was Viagra 100mg. Viagra contains the same active substance as Revatio , the reference product for this application. The strength used is 100 mg compared to the 20 mg applied for in the PAH indication. A biowaiver has been submitted and is considered applicable. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Grandipam met the protocol-defined criteria for bioequivalence when compared with the 100 mg tablet Viagra. 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 decision that the benefit-risk balance of Granpidam 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.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.