European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/773997/2009

ASSESSMENT REPORT
FOR

Sildenafil Actavis

International Nonproprietary Name: **sildenafil**

Procedure No. EMEA/H/C/1090

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Actavis Group PTC ehf submitted on 29 October 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Sildenafil Actavis, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

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

The chosen reference product is:

■ *Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:*

- Product name, strength, pharmaceutical form: Viagra 25/50/100 mg, film-coated tablets
- Marketing authorisation holder: Pfizer Limited
- Date of authorisation: 14/09/1998
- Marketing authorisation granted by:
  - Community
- (Community) Marketing authorisation number: EU/1/98/077/ 002-004, 006-008, 010-015

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

- Product name, strength, pharmaceutical form: Viagra 25/50/100 mg, film-coated tablets
- Marketing authorisation holder: Pfizer Limited
- Date of authorisation: 14/09/1998
- Marketing authorisation granted by:
  - Community
- (Community) Marketing authorisation number: EU/1/98/077/ 002-004, 006-008, 010-015

■ 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: 14/09/1998
- Marketing authorisation granted by:
  - Community
- (Community) Marketing authorisation number(s): EU/1/98/077/ 010, 011, 012, 015,
- Bioavailability study(ies) reference number(s)/EudraCT number(s): 761/06

The Rapporteur appointed by the CHMP was Ondrej Slanar

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

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

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 29 October 2008.
- The procedure started on 19 November 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 February 2009.
- During the meeting on 16-19 March 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 March 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 May 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 July 2009.
- During the CHMP meeting on 20-23 July 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant. The final list of outstanding issues was sent to the applicant on 23 July 2009.
- The applicant submitted the responses to the CHMP list of outstanding issues on 24 August 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 4 September 2009.
- During the meeting on 21-24 September 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Sildenafil Actavis on 24 September 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 22 September 2009.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 10 December 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

The product is a generic medicinal product containing sildenafil as sildenafil citrate as active substance.

The reference medicinal product is Viagra 25, 50 and 100 mg film-coated tablets.

Sildenafil is an inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase (PDE5). During natural erection, nitric oxide (NO) is released and this triggers the synthesis of cGMP which, in turn, relaxes the corpora cavernosa (a key point in the erection process). PDE5 present in the corpus cavernosum breaks down cGMP, sildenafil prevents the breakdown of cGMP and, thus enhances the induced erectile response.

The safety and efficacy profile of sildenafil has been demonstrated in several clinical trials details of which can be found in the EPAR for Viagra. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this product. Since this application is a generic application referring to the reference medicinal product Viagra, summary of the clinical data of sildenafil citrate is available and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted with sildenafil citrate.

The indication proposed for Sildenafil Actavis is the same as the reference medicinal product.

2.2 Quality aspects

Introduction

The product is presented as film coated tablets containing 25, 50 and 100 mg of sildenafil citrate as active substance.
Other ingredients are defined in the SPC section 6.1.

The film coated tablets are packed in blisters of PVC/PVDC/ Al foil blisters.

Active Substance

The chemical name of sildenafil is 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenylsulfonyl]-4-methylpiperazine citrate corresponding to the molecular formula $C_{22}H_{30}N_6O_4S \bullet C_6H_8O_7$ and relative molecular mass 666.71.
It appears as a white to off-white, crystalline powder that is slightly soluble in water. Its dissociation constant pK_a has been found to be 5.38 . It does not show polymorphism or enantiomerism.

- Manufacture

Sildenafil is manufactured by two different manufacturers. Two ASMFs have been submitted. The critical process parameters of all stages with appropriate justification have been described. Starting materials as well as synthetic intermediates were described in sufficient detail.
Both manufacturers have confirmed the presence of only the anhydrous form and supply Actavis with the same. To date no polymorphs of this form have been reported in the literature.

- Specification

Tests routinely carried out by the finished product manufacturer are: description, identification, water content, related substances and assay. Other tests are not routinely carried out.

The drug substance specification as tested by the finished product manufacturer includes tests for appearance (visual), identification (IR), water content (Ph.Eur.), sulphated ash (Ph.Eur.), heavy metals (Ph.Eur.), assay (titration), related substances (HPLC), residual solvents (GC).
Satisfactory Certificates of Analysis have been provided for two batches from each source. For each of the presented batches, the original Certificate of analysis from the active substance manufacturer is followed by Certificate of analysis issued by finished product manufacturer. All four batches comply with the proposed finished product manufacturer specification. The results from active substance testing are comparable with the results presented by finished product manufacturer for the same batch.

- Stability

Stability data for three production scale batches have been provided for sildenafil citrate from the first manufacturer. The substance was packaged in a packaging simulating the proposed commercial container closure system and stored at long-term 25°C/60% RH for 24 months and accelerated conditions 40°C/75%RH for 6 months. Results of all tested parameters remained within the specification limits.
Stability data for several production scale batches have been provided for sildenafil citrate from the second manufacturer. Three batches were stored under the ICH conditions at long-term 25°C/60% RH for up to 60 months and two batches at accelerated conditions 40°C/75%RH for 6 months.
. Results of all tested parameters remained within the specification limits.
In addition results from forced degradation (in solid state and solution) including photostability studies were presented.
The proposed re-test period as well as storage conditions are acceptable from both manufacturers.

Medicinal Product

- Pharmaceutical Development

The aim of the initial development work was to formulate a 50 mg tablet bioequivalent to the reference product Viagra. The formulation was intended to be a conventional film-coated tablet with a relatively rapid drug release similar to that of the reference product.
The drug substance can be assigned to Class 1 according to the BCS being highly soluble (as per BCS definitions) and highly permeable. Based on solubility and dissolution data, particle size was considered to be of moderate importance. The excipients used in the formulation are well known and widely used in the pharmaceutical industry for the stated purposes.
Both direct compression and wet granulation were investigated, but wet granulation was promoted for further development because results were better. Three different compositions manufactured by wet granulation were compared from the physico-chemical point of view. The composition with promising results in respect of hardness, disintegration, dissolution and stability was chosen. All strengths are produced out of the same powder mixture.
The development of the film-coating process was performed using tablets that had identical shape and core weight as Sildenafil 100 mg tablets.
During scale-up various factors and conditions were tried and optimised.
Two pilot scale batches per strength were produced using Sildenafil citrate manufactured by one of the active substance manufacturers. One smaller scale batch per strength was later manufactured with Sildenafil citrate raw material by the other manufacturer. The dissolution profiles of all these batches were compared with profiles obtained for the originator product. No differences were observed.
Comparative impurity profiles from one batch of all three strengths of Sildenafil Actavis tablets and with one batch of 100 mg Viagra have been presented. All impurities were presented in very low level, and the products can be concluded as similar from the impurity point of view.
Bioequivalence study was performed on the 100mg strength in accordance with the *Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98.*

- Manufacture of the Product

The manufacturing process is a conventional wet granulation, sieving, compression and coating process that uses standard equipment. Satisfactory list of process controls performed during the manufacture of Sildenafil citrate tablets has been provided. The proposed holding times are supported by adequate data.

- Product Specification

The product release and shelf-life specifications include tests for appearance (visual), identification (sildenafil: HPLC, HPLC-DAD, titanium dioxide and indigo carmine aluminium lake: chemical reaction – non-routine test), Average tablet mass (weighing), uniformity of dosage units (Ph. Eur.), resistance to crushing (PhEur), dissolution (PhEur), assay (HPLC), related substances (HPLC) and microbiological quality (Ph.Eur.- Non-routine test).
Process validation has been performed on the first three commercial batches of each strength, two of which were manufactured using active substance from one manufacturer and one using active substance from the other. In addition, satisfactory validation protocol for full-scale batches has been included.

- Adventitious Agents

Sildenafil tablets contain lactose monohydrate derived from animals for which satisfactory BSE statement has been provided. The lactose conforms with the Note for Guidance EMEA/410/01 rev 2.
Magnesium stearate used in the formulation of Sildenafil tablets is of vegetable origin.

- Stability of the Product

Two pilot scale batches and a smaller scale batch of each strength have been stored for up to 24 months at 25±2°C/60±5% RH, for up to 12 months at 30±2°C/65±5% RH and for 6 months at 40±2°C/75±5% RH. The same packaging as proposed for marketing was used and all tested batches were manufactured by the proposed manufacturing route.
In addition stability data on two smaller scale batches of the 50mg tablets and three smaller scale batches of each of the 25mg and 100mg strengths manufactured using active substance from a third supplier were are also presented as supportive data. 60 months results are available at 25±2°C/60±5% RH and 12 months results at 30±2°C/60±5% RH for these batches.

All pilot scale batches complied with the shelf-life specification during the tested period, except for appearance (fading) at 40±2°C/75±5% RH. The results available to date support the proposed shelf-life and the storage conditions.

Discussion on chemical, and pharmaceutical aspects

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

2.3 Non-Clinical aspects

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

The non-clinical overview on the pharmacology, pharmacokinetics and toxicology is based on literature searches and adequate scientific literature has been provided. The overview justifies why

there is no need to generate new non-clinical pharmacology, pharmacokinetics and toxicology data. There is thus no need for conducting tests on animals.

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

2.4 Clinical Aspects

Introduction

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

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

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

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

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

GCP aspects

The bioequivalence study provided in support of the application was performed by a contract research organisation based in India (CRO). The clinical part of the study was conducted in compliance with Good Clinical Practice (GCP), as claimed by the sponsor.

The EMEA inspected the clinical facilities in February 2009 with no critical findings.

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

Clinical studies

To support the application, the applicant has submitted 1 bioequivalence study with the highest strength of sildenafil, 100 mg. This bioequivalence study was performed with healthy male volunteers under fasting conditions.

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

Pharmacokinetics

- **Methods**

STUDY DESIGN:

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

In each period, subjects were housed from at least 13 hours before dosing until after the 24 hours post dosing. The subjects were not allowed to consume any xanthines containing foods and/or beverages for 24 hours before dosing and throughout the study sessions; alcohol for 48 hours before dosing and throughout the study sessions or grapefruit for 10 days before dosing and throughout the study. Subjects were allowed to be smokers but needed to refrain from smoking 24 hours prior to dosing.
In each period, subjects received a single oral 100 mg dose of sildenafil with 240 ml of water on the morning of Day 1. Meals were standardised throughout the study sessions. The physical activity of volunteers was also standardised. The bioequivalence study was performed under fasting conditions, after minimum 10-hour fast, since the concomitant food intake reduces the rate of absorption of sildenafil with T_{max} being delayed by approximately 60 minutes and C_{max} reduced by 29% according to the SmPC of the reference product. Subjects were allowed to leave the clinical site after 24-hour blood draw.

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

A total of 20 blood samples were collected in each period at pre-dose and at 0.17, 0.33, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours post-dose. Blood samples were processed at 4°C afterwards and plasma samples were collected and stored at (-) 50°C pending assay.

The protocol and the informed consent form were approved by an independent ethics committee.

TEST AND REFERENCE PRODUCTS:
Test and reference product used in the study were as follows:

Drug Code	Test	Reference
Formulation	Sildenafil 100 mg Film-Coated Tablet	Viagra® 100 mg Film-Coated Tablet
Manufacturer	Actavis Ltd. Malta	Pfizer PGM, France
Batch No.	S08408	5159804D
Manufacturing Date	May 2006	NA
Expiry Date	NA	June 2010

POPULATION(S) STUDIED

32 healthy male subjects, non-smokers or light smokers (up to 10 cigarettes per day), were enrolled in the study. The main age was 23 (18-39), BMI ranged from 18.5 to 24.9 kg/m^2. All subjects were of South Asian race. All subjects were in compliance with the inclusion and exclusion criteria and were judged eligible for enrolment in the study based on medical and medication histories, demographic data, physical examination, vital sign measurements, ECG, X-ray and clinical laboratory tests (haematology, biochemistry, urinalysis, Human Immunodeficiency Virus [HIV], hepatitis C antibodies, and hepatitis B surface antigen [HBSAg]). Any medication was prohibited for 14 days preceding the study and during the entire study. Vitamin supplements and natural products (including herbal remedies, garlic supplements and St. John's wort) were prohibited for 7 days preceding the study.

All of 32 volunteers included in the study received the two treatments and were included in the statistical analysis.

ANALYTICAL METHODS:

The analytical part of the study was conducted at bioanalytical facilities of a CRO based in India. The analysis of plasma samples of sildenafil and N-desmethyl-sildenafil was performed using the LC/MS/MS method.

A detailed and comprehensive description of the analytical procedures is provided in the documentation.

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

PHARMACOKINETIC VARIABLES

Relevant PK parameters of sildenafil and its N-desmethyl metabolite were estimated using a non compartmental analysis (NCA).

The primary pharmacokinetic parameters according to protocol were area under the plasma concentration curve from administration to last observed concentration at time t (AUC_{0-t}), AUC extrapolated to infinity (AUC_{0-inf}) and maximal plasma concentration (C_{max}). Secondary variables were determined as time of the C_{max} – T_{max}, terminal half-life – $T_{1/2}$, and elimination rate constant – K_{el}.

STATISTICAL METHODS

SAS software release 9.1 was used to analyse the data. ANOVA was carried out on ln-transformed AUC_{0-t} AUC_{0-inf}, C_{max}, and untransformed $t_{1/2}$ values. Factors of subjects, treatments, sequence, and period were also evaluated in the model. A non-parametric test was carried out to compare the T_{max} values between treatments. Descriptive statistics was used to summarise the results.
AUC_{0-t}, AUC_{0-inf}, and C_{max} were considered as primary parameters for bioequivalence conclusion with standard acceptance range of 80-125%.

- **Results**

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

Sildenafil: Pharmacokinetic parameters (AUC and C_{max}: arithmetic mean ± SD, t_{max}: median, range): Single 100 mg oral dose (n=32).

Treatment	**AUC_{0-t}** ng*h/ml	**AUC_{0-inf}** ng*h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	2365.152	2402.2	701.348	1.23
(S.D.)	(970.672)	(991.013)	(264.587)	(0.72)
Reference	2326.312	2361.871	621.615	1.5
(S.D.)	(977.895)	(989.199)	(247.714)	(0.89)
***Ratio (90% CI)**	[96; 107]%	[96; 106]%	[102; 125]%	ns
Point estimate	101 %	101 %	113 %	
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **T_{max}** time for maximum concentration : median, min and max				

**log-transformed values*

For sildenafil, the mean K_{el} was 0.2105 $hours^{-1}$ for the test formulation and 0.1973 $hours^{-1}$ for the reference product. The mean $T_{1/2el}$ value for the test and reference product was 3.96 hours and 3.67 hours, respectively.

N-desmethyl sildenafil: Pharmacokinetic parameters (AUC and C_{max}: arithmetic mean ± SD, t_{max}: median, range): Single 100 mg oral dose (n=32).

Treatment	**AUC_{0-t}** ng*h/ml	**AUC_{0-inf}** ng*h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	396.950	416.299	83.887	1.15
(S.D.)	(131.230)	(134.488)	(28.873)	(0.69)
Reference	402.845	423.032	77.996	1.43
(S.D.)	(161.713)	(165.672)	(32.321)	(0.76)
***Ratio (90% CI)**	[95;106]%	[95; 106]%	[100;122]%	ns
Point estimate	101 %	100 %	110 %	

AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration : median, min and max

**log-transformed values*

For N-desmethyl sildenafil, the mean K_{el} was 0.1851 $hours^{-1}$ for the test formulation and 0.1813 $hours^{-1}$ for the reference product. The mean $T_{1/2el}$ value for the test and reference product was 3.92 hours and 4.10 hours, respectively.

Effect of sequence has been statistically significant for sildenafil AUC_{0-t}, and AUC_{inf} and N-demethyl sildenafil AUC_{0-t}, AUC_{inf}, and C_{max}. Period effect was statistically significant for N-demethyl sildenafil AUC_{0-t}, and AUC_{inf}. These findings are deemed not to have affected the treatment comparisons.

- **Conclusions**

In conclusion, the conventional CI for ln-transformed AUC_{0-t}, AUC_{0-inf} for sildenafil and AUC_{0-t}, AUC_{0-inf} and C_{max} N-desmethyl sildenafil were within the acceptance range. The upper 90% CI value for C_{max} of the parent compound was on the border of the acceptance range. This situation is, however, still considered sufficient for a positive BE conclusion (CHMP/EWP/40326/06). No significant difference in T_{max} was evidenced by the non-parametric test. Therefore, this study was considered to have met the bioequivalence criteria as defined by the study protocol since all 90% confidence intervals were within the acceptance range for both, sildenafil and its major metabolite.

Protocol deviations (blood sampling time deviation and deviation from housing duration prior to drug administration) were judged to have no significant influence on bioequivalence assessment.

Transferability of study results to other strengths

The applicant submitted a Bioequivalence study with the highest strength (100 mg tablets) and requested biowaiver for the lower 50 and 25 mg strengths. This request was found acceptable since all criteria for a biowaiver listed in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) were fulfilled, namely:
1. The pharmaceutical products are manufactured by the same manufacturer and process;
2. The drug input has been shown to be linear over the therapeutic dose range;
3. The qualitative composition of the different strengths is the same;
4. The ratio between amounts of the active substance and excipients is the same;
5. The dissolution profiles are similar under identical conditions for the additional strength and the strength of the batch used in the bioequivalence study.

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

CLINICAL SAFETY

One adverse event of elevated ALT (SGPT) was observed during the study. The event was mild in intensity and deemed not related to the study product. There were no serious adverse events in the study.

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

Pharmacodynamics

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

Post marketing experience

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

2.5 Pharmacovigilance

- **PSUR**

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

- **Description of the Pharmacovigilance system**

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

The company should ensure that the pharmacovigilance activities are in line with the current safety measures applied to the reference medicinal product.

- **Risk Management Plan**

The application is based on a reference medicinal product for which no safety concerns requiring additional risk minimization activities have been identified.

Discussion on Clinical aspects

To support the application, 1 bioequivalence study with the highest strength of sildenafil, i.e. 100 mg was submitted. The study was designed according to a randomised, single-dose, laboratory-blinded, two-period, two-sequence crossover classical scheme.

All 32 subjects enrolled received the two treatments and were included in the statistical analysis.

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

The results of the bioequivalence study showed that the conventional confidence intervals for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} for sildenafil and N-desmethyl sildenafil were within the acceptance range of 80-125%. No significant difference in T_{max} was evidenced by the non-parametric test. Therefore, based on the available data it was concluded that bioequivalence of the two products had been demonstrated.

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

One adverse event of elevated ALT (SGPT) was observed during the study. The event was mild in intensity and deemed not related to the study product. There were no serious adverse events in the study. No subject was withdrawn from the study because of an event.

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

- **User consultation**

The results of user consultation provided indicates that the Package leaflet is well structured and organized, easy to understand and written in a comprehensible manner. The test shows that the leaflet is readable in patients /users are able to act upon the information that it contains.

2.6 Overall conclusions, benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

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

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

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

Recommendation

Based on the CHMP review of available data, the CHMP considered that the benefit/risk ratio of Sildenafil Actavis 25 mg, 50 mg and 100 mg film-coated tablets in the treatment of erectile dysfunction was favourable and therefore recommended the granting of the marketing authorisation.