European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

Sildenafil TEVA

International Nonproprietary Name: sildenafil

Procedure No. EMEA/H/C/001073

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 Teva Pharma B.V. submitted on 1 October 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Sildenafil Teva, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

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

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Viagra 25 mg , 50 mg, 100 mg film-coated tablets
- Marketing authorisation holder: Pfizer Limited, United Kingdom
- Date of authorisation: 14 September 1998
- Marketing authorisation granted by: Community
- (Community) Marketing authorisation number: EU/1/98/077/002-004, EU/1/98/077/013; EU/1/98/077/006-008, EU/1/98/077/014; EU/1/98/077/010-012, EU/1/98/077/015

■ 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, United Kingdom
- Date of authorisation: 14 September 1998
- Marketing authorisation granted by: Community
- (Community) Marketing authorisation number: EU/1/98/077/010
- Bioavailability study number: 2008-1683

The Rapporteur appointed by the CHMP was Dr. Prieto Yerro.

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 1 October 2008.
- The procedure started on 22 October 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 January 2009).
- During the meeting on 16 – 19 February 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 February 2009).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 May 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 6 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 applicant submitted the responses to the CHMP consolidated List of outstanding issues on 24 July 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 09 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 Teva on 24 September 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 Teva 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:
Tablet core: microcrystalline cellulose, calcium hydrogen phosphate anhydrous, croscarmellose sodium, magnesium stearate.
Film-coating: Poly vinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, indigo carmine aluminium lake (E132).
The film coated tablets are packed in blisters of PVC/ Al foil blisters and PVC/Aluminium perforated unit dose blisters.

Active Substance

Sildenafil citrate is a white to off-white, crystalline powder. Sildenafil citrate has the chemical name 1-{4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazol[4,3-d]pyrimidin-5-yl]phenylsulfonyl]-4-methylpiperazine citrate. It does not show polymorphism or enantiomerism.

The solubility of sildenafil citrate in water has been determinate as being 3.5 mg/ml. Solubility determinations in various buffers showed a maximum solubility of approximately 24 mg/ml at pH 2.0.

Sildenafil citrate is designated as a *class 1* drug substance according to BCS classification: highly soluble and highly permeable.

- Manufacture

It is manufactured in 2 chemicals steps, in accordance with Good Manufacturing Practices. The information on the manufacturing process is provided in an ASMF.

Adequate In-Process Controls are applied during the manufacture of the active substance. The specifications and control methods for intermediate products, starting materials and reagents, have been presented and are satisfactory.

- Specification

The specifications of the active substance include description, identification, water, sulphated ash, heavy metals, assay, chromatographic purity, residual solvents, particle size and bulk density.

Batch analysis data (n=3) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

- Stability

Seven batches of the active substance were put on long-term (25°C/60%RH) for up 9, 18, 24 and 48 months, and five batches under accelerated (40°C/75%RH) for up 6 months stability testing ICH conditions. Photostability test following ICH guidelines Q1B was performed on two batches. The following parameters were tested: appearance, water, content and related substances of sildenafil and content of citric acid. The stability results justify the proposed retest period.

Medicinal Product

- Pharmaceutical Development

The aim of the pharmaceutical development was to obtain an immediate-release tablet containing the same active substance as the reference medicinal product, and with the same bioavailability.

In order to demonstrate the essential similarity with the reference medicinal product, comparative studies on the composition, dissolution and impurity profile were performed. A direct compression with a non-micronized active substance was selected as manufacturing process because of the improved flow of the blend and the tablet compressibility. The compatibility of the excipients is demonstrated by means of the stability data.

The choice and function of the excipients in the formulation was provided, the tablets cores contain cellulose microcrystalline and calcium hydrogen phosphate that are used as diluents, croscaromellose sodium as disintegrant and magnesium stearate as lubricant. The coating employs an aqueous suspension of Opadry Blue that contains polyvinyl alcohol-part hydrolyzed, lactose, macrogol/PEG, titanium dioxide, talc, blue indigo carmine and aluminium lake.

The excipients used in the formulation are: microcrystalline cellulose (filler/binder), calcium hydrogen phosphate anhydrous (filler/binder), croscarmellose sodium (disintegrant), magnesium stearate (lubricant) and film coat (poly vinyl alcohol, titanium dioxide, macrogol 3350, talc, indigo carmine aluminium lake).

Blister PVC with aluminium foil have been selected in order to provide a good protection of the tablets. The components of the packaging are standard pharmaceutical grade material and its selection is supported by the results of stability study. Detail descriptions of the packaging material were provided. Specifications and test method summaries are provided for the individual packaging components.

- Manufacture of the Product

The manufacturing process is a standard dry compression method. The process comprises the following steps: mixing, compression and coating.
The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process.
The batch analysis data show that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation

- Product Specification

The finished product specifications include appropriate tests for description, identification (UV, HPLC), assay (HPLC), uniformity of content (HPLC), water content (Ph Eur), dissolution (UV), degradants (HPLC), identity for Titanium Dioxide, identity for blue dye, microbiological quality (Ph Eur).

Batch analysis results (n=3) confirm consistency and uniformity of manufacture and indicate that the process is under control. Impurity limits in the specification are justified by toxicology studies.

- Stability of the Product

Three production scale batches of the finished product (25, 50 and 100 mg) were put on long-term (25°C/60%RH) for up 12 months, and accelerated (40°C/75%RH) for up 6 months stability testing in accordance with ICHQ1A guideline. The specifications and analytical procedures are the same as for the release analysis.
The results support the shelf life and storage conditions as defined in the SPC.

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

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. Therefore, non-clinical testing strategy did not 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 Teva is unlikely to result in any significant increase in the combined sales volumes for all sildenafil containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

Discussion on Non-Clinical aspects

There are no non-clinical objections to approve Sildenafil Teva 25, 50 and 100 mg film-coated tablets.

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 Teva, in three strengths 25 mg, 50 mg, 100 mg.

This application is made in accordance with Art 3(3) of Regulation (EC) No 726/2004 "A generic medicinal product of a reference medicinal product authorised by the Community" and Art 10(1) "generic application" of Directive 2001/83/EC. The reference medicinal product is Viagra 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; a biowaiver for the lower 50 and 25 mg strengths was applied for (please see below) 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 Canada (CRO). The clinical part of the study was conducted in compliance with Good Clinical Practice (GCP), as claimed by the sponsor.

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

Clinical studies

To support the application, the applicant has submitted 1 bioequivalence study with the highest strength of 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 an open-label, single-dose, two-period, two-sequence, two-treatment, comparative bioavailability study.

In each period, subjects were confined to the clinical facility from at least 10 hours before dosing and for at least 24 hours following drug administration. The following items were restricted for the 14 days preceding drug administration until completion of the entire study: all medications (prescription or over-the-counter), herbal/natural products and nutritional supplements. Non-systemic, topically applied products (prescription or otherwise) or occasional use of common analgesics were allowed. Subjects abstained from ingesting products containing grapefruit, alcohol, caffeine, or xanthine for 48 hours prior to each study period and until after the last sample from each period was collected.

In each period, subjects received a single oral 100 mg dose of sildenafil with 240 ml of water starting in the morning of Day 1. The bioequivalence study was performed under fasting conditions (after a 10-hour overnight 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 7 day wash-out was used in the study. The terminal half-life of sildenafil is 3 to 5 hours; hence the washout period length is acceptable.

A total of 23 blood samples from 22 time points were collected in each period at pre-dose and at 0.25, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 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 (-) 70°C and shipped for analysis.

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	Novopharm Limited, Canada	Pfizer Limited, UK
Batch No.	35303254	7108603U
Manufacturing Date	14th February 2008	NA
Expiry Date	NA	10-2012
Measured Content	101.3% of label claim	100.4% of label claim

POPULATION(S) STUDIED

40 non-smoking, healthy male subjects were enrolled in the study. The mean age was 36 (20-49), BMI ranged from 22 to 29.5 kg/m^2. Approximately half of the subjects were Caucasian, 20% were Black, 20% Hispanic and 10% Asian. Subjects were in good health as determined by medical history, physical examination, ECG, laboratory tests (haematology, biochemistry, urinalysis). All the subjects met inclusion criteria including negative HIV, Hepatitis B and C tests as well as negative screening for ethyl alcohol and drug of abuse in urine.

Of the total of 40 volunteers included in the study 38 received the two treatments and were included in the statistical analysis. Two subjects withdrew from the study prior to period 2 for personal reasons.

ANALYTICAL METHODS:

The analysis of plasma samples of sildenafil and N-desmethyl-sildenafil was performed using the HPLC equipment with tandem mass spectrometry detection (MS-MS).

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

Standard PK parameters of sildenafil were estimated using a non compartmental analysis (NCA) and linear trapezoidal rule.

STATISTICAL METHODS

Analysis of variance (ANOVA) was applied to log-transformed AUC_t, AUC_{inf}, C_{max} and to untransformed K_{el} and $T_{1/2}$ parameters. The significance of the sequence, period, treatment, and subject within-sequence effects were tested. The least square means, the differences between the treatments least square means, and the corresponding standard errors of these differences were estimated for log-transformed AUC_t, AUC_{inf}, and C_{max} parameters. Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% confidence intervals were calculated. Values for the T_{max} parameter were analysed by a non-parametric approach.

Results

The pharmacokinetic variables of 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)

Analyte: Sildenafil (N = 38)

Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)
		Arithmetic	(CV%)	Geometric			Lower	Upper	
Based on Measured Data									
AUC_{0-t}	A	1393.032	(38)	1285.066	A vs. B	97.53	92.10	103.28	15
*(ng*h/mL)*	B	1435.798	(38)	1317.664					
AUC_{0-inf}	A	1410.943	(38)	1300.870	A vs. B	97.51	92.08	103.25	15
*(ng*h/mL)*	B	1454.690	(39)	1334.106					
Cmax	A	485.053	(38)	450.924	A vs. B	100.77	90.40	112.34	29
(ng/mL)	B	502.779	(43)	447.461					
Tmax	A	0.88	(70)						
(h)	B	1.17	(78)						
Kel	A	0.1735	(30)						
(1/h)	B	0.1742	(30)						
Thalf	A	4.29	(25)						
(h)	B	4.28	(26)						

**log-transformed values*

A statistically significant difference ($\alpha = 0.05$) was detected between the two periods of the study in the analysis of C_{max} ($p=0.0245$). All clinical procedures were under strict control and kept the same between the two periods of the study; hence, it is possible that the observed effect is a chance finding. The least-squares means of the formulation effect were adjusted for the period effect. Therefore, the final results are deemed not to be influenced by the statistically significant period effect noticed for C_{max}.

- **Conclusions**

In conclusion, the conventional CI for log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} for sildenafil were within the acceptance range. 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 sildenafil.

Protocol deviations (mainly blood sampling time deviation) 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 in accordance with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), section 5.4. To grant a waiver the following criteria should be fulfilled:

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.

Not all these criteria were satisfied in the initial application; hence the CHMP requested the comparative *in vitro* dissolution profiles at pH 1.2, 4.5 and 6.8 and 50 rpm for the three different strengths of Sildenafil Teva (25, 50 and 100 mg). The dissolution profiles of all strengths in three media (pH 1.2, pH 4.5 and pH 6.0 due to low solubility of sildenafil at pH 6.8), were provided. They showed that the 25 and 100 mg strengths released 85% sildenafil within 15 minutes, whereas the dissolution profile was not similar between 50 and 100 mg strengths at pH 4.5. Consequently, the applicant was requested to investigate this issue further. In response the applicant provided data on re-testing of dissolution profiles showing similar dissolution behaviour in pH 4.5 acetate buffer for the 50 and 100 mg strengths.

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 considered acceptable.

CLINICAL SAFETY

The safety analysis includes the thirty-eight (38) subjects who entered the study and received at least one of the treatments. There were 72 adverse events (AEs) involving 24 subjects in the study. All AEs were judged to be mild. There were no deaths or other serious or significant adverse events reported during this study. None of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results.

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 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.

- **Risk Management Plan**

The application for a generic medicinal product is based on a reference product for which no safety concern requiring specific risk minimisation activities has been identified. Therefore, a risk management plan was not considered necessary for this generic medicinal product.

Discussion on Clinical aspects

To support the application, 1 bioequivalence study conducted in thirty-eight healthy volunteers with the highest strength of sildenafil, i.e. 100 mg was submitted.

Of 40 subjects enrolled in the pivotal study 38 received the two treatments and were included in the statistical analysis. Two subjects withdrew from the study prior to period 2 for personal reasons.

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 log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} for sildenafil were within the acceptance range of 80-125%. No significant difference in T_{max} was evidenced by the non-parametric test. The presence of a significant period effect in C_{max} was considered irrelevant since the results were adjusted for this effect. 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 following the results of additional dissolution studies demonstrating similar dissolution profiles of all tested strengths. Consequently, all criteria for a biowaiver listed in the applicable guidance were fulfilled.

The adverse events observed in the study were graded mild and were comparable to the originator. None of the events were considered serious.

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 25mg, 50mg, 100mg 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 100mg film-coated tablet of Sildenafil Teva and the reference product, Viagra 100mg film-coated tablet. The extrapolation of the study results to lower strengths of sildenafil, i.e. 50mg and 25mg, 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 Teva 25mg, 50mg and 100mg film-coated tablets in the treatment of erectile dysfunction was favourable and therefore recommended the granting of the marketing authorisation.