



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 October 2011
EMA/916997/2011

Assessment report

Efavirenz Teva

International nonproprietary name: efavirenz

Procedure No. EMEA/H/C/002352

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



Table of contents

1	Background information on the procedure	3
1.1	Submission of the dossier	3
1.2	Manufacturers	4
1.3	Steps taken for the assessment of the product	4
1.4	Introduction	5
1.5	Quality aspects.....	5
1.6	Non- Clinical aspects	8
1.7	Clinical Aspects.....	9
1.8	Pharmacovigilance	13
2	Benefit-Risk Balance	13
3	Recommendation.....	15

1 Background information on the procedure

1.1 Submission of the dossier

The applicant Teva Pharma B.V. submitted on 23 November 2010 an application for a Marketing Authorisation to the European Medicines Agency (EMA) for Efavirenz Teva, 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 29 June 2010.

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

The applicant applied for the following indication: antiviral combination treatment of human immunodeficiency virus 1 (HIV 1) infected adults, adolescents and children 3 years of age and older.

The legal basis for this application refers to:

Article 10(1) of Directive 2001/83/EC.

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

Information on Paediatric requirements

Not applicable

Information relating to Orphan Market Exclusivity

Similarity

Not applicable

Market Exclusivity

Not applicable

The chosen reference medicinal product is:

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

Product name, strength, pharmaceutical form: Sustiva 600 mg Film-coated Tablets

Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG

Date of authorisation: 28-05-1999

Marketing authorisation granted by Community - Marketing authorisation number: EU/1/99/110/008 - 10

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

Product name, strength, pharmaceutical form: Sustiva 600 mg Film-coated Tablets

Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG

Date of authorisation: 28-05-1999

- Marketing authorisation granted by Community - Marketing authorisation number: EU/1/99/110/008 - 10

- 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: Sustiva 600 mg Film-coated Tablets

Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG

Date of authorisation: 28-05-1999

Marketing authorisation granted by Community - Marketing authorisation number: EU/1/99/110/008 - 10

Bioavailability study: Details of the Bioavailability study number have been included in the dossier.

Licensing status

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

1.2 Manufacturers

Manufacturer(s) responsible for batch release

TEVA Pharmaceutical Works Private Limited Company
Pallagi út 13, 4042 Debrecen
Hungary

Details of the active substance manufacturer and finished product manufacturers have been included in the dossier.

1.3 Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Ian Hudson:

- The application was received by the EMA on 23 November 2010.
- The procedure started on 15 December 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 04 March 2011 .
- During the meeting on 11-14 April 2011, 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 15 April 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 July 2011.

The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 02 September 2011.

During the CHMP meeting on 19 – 22 September 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant. The final consolidated List of Outstanding Issues was sent to the applicant on 22 September 2011.

The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 28/09/2011.

During the meeting on 17 – 20 October 2011, 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 Efavirenz Teva.

1.4 Introduction

The active substance of the medicinal product is efavirenz. Efavirenz is a NNRTI of HIV-1. Efavirenz is a non-competitive inhibitor of HIV-1 reverse transcriptase (RT) and does not significantly inhibit HIV-2 RT or cellular DNA polymerases (α , β , γ or δ).

The safety and efficacy profile of efavirenz has been demonstrated in several clinical trials, details of which can be found in the EPAR for Sustiva. 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 Sustiva, summary of the clinical data submitted for Sustiva is available and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted.

This application is a generic application, therefore, demonstration of therapeutic equivalence is shown by means of pharmacokinetic studies. Then, new clinical studies are neither required nor submitted.

The relative oral bioavailability of Efavirenz Teva 600 mg film-coated tablets and the European reference medicinal product Sustiva 600 mg film-coated tablets was established by comparing the single dose pharmacokinetics of efavirenz from the two formulations, under fasting conditions, in an open-label, randomised, two period, two sequence, crossover study.

1.5 Quality aspects

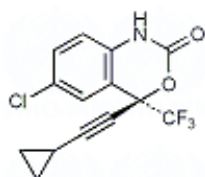
1.5.1 Introduction

Efavirenz Teva is available as 600 mg film-coated tablets for oral administration containing efavirenz as the active ingredient. The full list of ingredients is defined in section 6.1 of the SmPC. The film-coated tablets are yellow capsule shaped debossed with "TEVA" on one side and "7541" on the other packaged in either White opaque PVC/PVdC-Aluminium blisters or Aluminium-Aluminium blisters.

1.5.2 Active Substance

At the time of the CHMP opinion, the active substance efavirenz is not described in the European Pharmacopoeia. The ASMF procedure is applied.

Efavirenz has the following chemical name (4S)-6-chloro-4-(2-cyclopropylethynyl)-4-(trifluoromethyl)-2,4-dihydro-1H-3,1-benzoxazin-2-one (4S)-6-chloro-4-(cyclopropylethynyl)-1, 4-dihydro -4-trifluoromethyl)-2H-3, 1-benzoxazin-2-one, chemical formula C₁₄H₉ClF₃NO₂, and the following chemical structure:



The substance is a white to slightly pink powder freely soluble in methanol, practically insoluble in water. Efavirenz possesses one asymmetric carbon atom and is expected to be optically active. Efavirenz exists in five polymorphic forms known as Form-I, Form-II, Form-III, Form-IV and Form-V as reported in literature.

Manufacture

Information about the manufacturing process has been provided in the Active Substance Master File (ASMF) procedure. Detailed information about the manufacturing process, control of starting materials, reagents and solvents, control of critical steps and intermediates and process development and process validation of the active substance has been supplied in the form of the active substance master file (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

Specifications have been set that are appropriate in view of the Ph Eur Monograph 'Substances for Pharmaceutical use' and the ICH Q6A Guideline on Setting Specifications of active substances and medicinal products.

The specifications of the active substance include description, solubility, identification (IR and HPLC), polymorphic identity (DSC, XRD), loss on drying, specific optical rotation, heavy metals, chiral purity, related substances (HPLC), assay (HPLC) and residual solvents (GC) are considered to reflect all relevant quality attributes and are found to be adequate to control the quality of the active substance.

Limits of specified and unspecified related substances are set in line with ICH Q3A guidelines. The maximum level of total impurities is set at a level which is qualified with regard to safety. The limits for residual solvents are in line with ICH Q3C and Ph. Eur. requirements. The limits for assay are based on general pharmacopeial limits for active substances.

Satisfactory data have been provided regarding Ph. Eur. and in-house analytical test methods.

Analytical results of three production scale batches confirm batch to batch consistency and uniformity of the quality of the substance and indicate that the manufacturing process under control.

Stability

Satisfactory stability data of three production scale batches of the active substance stored under ICH conditions at $30^{\circ} \pm 2^{\circ}\text{C}/ 65 \% \pm 5 \% \text{RH}$ and $40^{\circ} \pm 2^{\circ}\text{C}/ 75 \% \pm 5 \% \text{RH}$, have been provided to support the proposed re-test period of 2 years without any special storage condition. The container closure system used in the stability studies is comparable to that proposed for the market. All results comply with the specifications and no trends are observed.

1.5.3 Finished Medicinal Product

Pharmaceutical Development

The main objective of the formulation development was to develop a medicinal product that is pharmaceutically and therapeutically equivalent to the reference product Sustiva 600 mg film-coated tablets.

The comparative qualitative composition of the reference product and proposed product is provided. All the excipients used are well recognised for their role in pharmaceutical formulations and have been previously approved. The choice and compatibility of all the excipients has been appropriately justified. All the excipients comply with their respective Ph. Eur. monograph apart from Opadry II yellow which complies with Directive 2008/128/EC. The excipients were selected on basis of the compatibility studies and formulation trials. No difference in the safety and efficacy profile are expected from the differences in the qualitative composition of the excipients between the reference and proposed product.

The comparative impurity profile of the test and the reference product is also provided. The degradation profiles are similar.

Satisfactory comparative dissolution data between the generic and reference product were provided.

Adventitious agents

The supplier confirmed that lactose monohydrate is derived from milk and is therefore compliant with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and Veterinary Medicinal Products (EMA/410/01 Rev. 2). No excipients derived from human origin have been used.

Manufacture of the product

The manufacturing process is a conventional technology consisting of a granulating step followed by mixing and tableting steps and film coating with a ready to use mixture.

The main process steps are supervised by suitable in-process controls and their acceptance criteria are specified.

Process evaluation has been carried out on pilot scale batches. The manufacturing process is a well recognized standard process and therefore the data for validation of pilot batch is sufficient at this stage. Results of tested parameters are comparable batch to batch and are within proposed limits. Additional results were provided to demonstrate that same polymorphic form of efavirenz is maintained in the drug product during manufacture. The applicant has provided a commitment to validate the first three commercial batches.

Product Specification

The specifications of the drug product include: appearance, uniformity of dosage units, identification by HPLC and UV, related substances (HPLC), dissolution (HPLC) and microbiological purity. The finished product specifications are standard for immediate release tablets. The proposed test procedures and acceptance criteria comply with the requirements of the Ph.Eur. and ICH guidelines. All tests included in the specification have been satisfactorily described and validated.

Certificates of analysis of pilot batches are provided. The batch analysis results show that the finished product meets the proposed specifications and confirm the consistency & uniformity of manufacture indicating that the process is under control.

Stability of the product

Stability data are presented for the batches stored under ICH conditions: 25°C ± 2°C/60% ± 5%RH and 40°C ± 2°C/75% ± 5%RH). The control tests and specifications of drug product are adequately drawn up. Photostability tests were also performed and the medicinal product was found not to be photolabile. Based on the stability data provided the proposed shelf-life is granted, please consult the SmPC.

1.5.4 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.

1.5.5 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 have been presented to give reassurance on viral/TSE safety.

1.5.6 Recommendation(s) for future quality development

Not applicable.

1.6 Non-Clinical aspects

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.

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

No Environmental Risk Assessment was submitted. It is considered that the introduction of Efavirenz Teva is unlikely to result in any significant increase in the combined sales volumes for all efavirenz containing products and consequently in the exposure of the environment to the active substance.

1.7 Clinical Aspects

1.7.1 Introduction

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

GCP

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

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

1.7.2 Pharmacokinetics

Clinical study

A single bioequivalence study has been submitted in support of the application..

To support the marketing authorisation application the applicant conducted one bioequivalence study; the details of this study are summarised in Table 1.

Table 1 Summary of study

Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Determination of the relative bioavailability between a generic medicinal product and a reference product under fasting conditions	Open-label, randomised, two period, two sequence, crossover study	Two tablet formulations, 600 mg, oral	36 enrolled (34 completed)	Healthy subjects	Single-dose

Methods

Study design

The Study 2010-2409 was an open label, randomised, two-treatment, two-period, two-sequence, single dose crossover bioequivalence study conducted in healthy, adult subjects under fasting conditions.

The study was performed in Canada. The clinical part of the study was undertaken from 27 June 2010 to 28 July 2010.

A single oral dose of 600mg of test and reference formulation was administered in each period.

During each period, each subject received one of the following: one tablet of Efavirenz Teva, 600 mg or one tablet of Sustiva, 600 mg, Bristol-Myers Squibb, taken with 240mL of water. Subjects fasted

overnight for at least 10 hours prior to drug administration and for at least 4 hours following drug administration. Standardised xanthine-free meals with caffeine-free beverages were provided to subjects at least 4 hours after drug administration in each period. A compliance check was performed immediately after drug administration. Blood samples were collected at predose, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48, and 72 hours post dosing. The actual time of sample collection was documented. centrifugation.

A 28 day washout period was observed between doses.

This application contains 1 strength of efavirenz, this strength was selected for the bioequivalence study. Efavirenz film-coated tablets is an immediate release formulation. According to the SmPC, the product should be taken without food. There is no relevant accumulation with repeated doses. A single dose BE study in the fasting state is appropriate. The design of the study is acceptable.

Test and reference products

Test Product	Efavirenz 600 mg film- coated tablets
Dose	1 x 600 mg
Administration	Oral
Lot number	K-44276

Reference Product	Sustiva 600 mg film-coated tablets (Bristol-Myers Squibb Pharma, France)
Dose	1 x 600 mg
Administration	Oral
Lot number	B074
Expiry Date	November 2010

Population(s) studied

Thirty six (36) healthy male and female volunteers aged 18 years and older were entered in the study. Body mass indices (BMI) were within 18.5 and 30 kg/m². The subjects were non-smokers. All subjects were randomly assigned to one of the two sequences in a balanced manner.

The population chosen was acceptable. Inclusion and exclusion criteria were presented and acceptable.

Analytical methods

The analytical method was validated. Plasma concentrations of the active efavirenz were determined measured according to a liquid chromatographic (LC) tandem mass spectrometric detection (MS/MS) achiral method. The analytical method used for quantification of efavirenz in the bioequivalence study allows accurate and reproducible quantification. Within-study accuracy and precision were within the acceptance range based on back-calculated concentrations of quality control (QC) samples and calibration curve samples. The analytical validation was of a good standard. The number of repeated samples was low and the reasons presented for repeating were acceptable.

Pharmacokinetic Variables

The pharmacokinetic variables follow the current European standard and are appropriate for this study. The protocol specified 80-125% as criteria for bioequivalence. The data evaluation follows regulatory standards.

Statistical methods

Pharmacokinetic parameters for efavirenz plasma concentration were calculated with SAS using standard noncompartmental approaches.

Descriptive statistics were estimated for the pharmacokinetic parameters in each treatment. Analysis of variance (ANOVA) was applied to log-transformed AUC₀₋₇₂, C_{max} and T_{max} parameters. The significance of the sequence, period, treatment, and subject-within-sequence effects were tested. The least-squares means, the differences between the treatments least-squares means, and the corresponding standard errors of these differences were estimated for log-transformed AUC₀₋₇₂ and C_{max} parameters. Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% confidence intervals were calculated.

A sample size of 32 was calculated to be necessary to obtain 90% probability that 90% confidence intervals will fall within 80-125% range, based on a (literature based) assumption of an 18% intra-subject C_{max} variability and a difference between the treatment means of 7.5% or less (a true ratio of means between 92.5 and 107.5%). Four (4) extra subjects were included as per protocol to account for drop-outs.

Bioequivalence was to be declared if the Test/Reference ratios of geometric means of C_{max}, and AUC_{0-72h}, and their 90% confidence intervals were all contained in the interval 80.00 to 125.00% for efavirenz.

All values below the lower limit of quantification (BLQ) were considered as zero during the pharmacokinetic and statistical analysis. Any missed samples or non-reportable values were considered missed as if they had not been scheduled for collection.

The statistical methods were adequately described and were deemed acceptable. In line with the CPMP guideline on bioequivalence (CPMP/QWP/EWP/1401/98 Rev.1) an AUC_{0-72h} (AUC truncated at 72 h) was used as an alternative to AUC(0-t) for comparison of extent of exposure. This is acceptable as the absorption phase has been covered by 72 h for immediate release formulations.

There were no major protocol deviations.

Results

Thirty- four (34) out of 36 subjects completed both study periods. Two subjects were dismissed from the study during period I and at period II check- in, respectively, as they were suspected by the investigator to participate in multiple clinical studies concurrently.

There were three subjects with positive plasma concentrations at the beginning of period 2. In all cases the plasma concentration relative to C_{max} was low (<2.5%).

The pharmacokinetic parameters results obtained in the 34 subjects who were included in the analysis are presented in Table 2.

Table 2 Statistical Summary of Ln-transformed Pharmacokinetic Parameters for Efavirenz 600mg film coated tablets (A= test, B= reference formulation)

Analyte: Efavirenz (N = 34)

Parameter	TRT	Means		Contrast	Ratio	90% CI		Intra-Sub CV(%)	
		Arithmetic	(CV%) Geometric			Lower	Upper		
<i>Based on Measured Data</i>									
AUC ₀₋₇₂ ($\mu\text{g}\cdot\text{h}/\text{mL}$)	A	56.9727	(21)	55.8726	A vs. B	97.60	93.55	- 101.83	10
	B	58.4186	(22)						
Cmax ($\mu\text{g}/\text{mL}$)	A	2.9865	(28)	2.8682	A vs. B	95.99	89.32	- 103.15	18
	B	3.0882	(28)						
Tmax (h)	A	2.92	(44)						
	B	2.94	(45)						

The 90% confidence intervals for the ratio of geometric means of AUC₀₋₇₂ and Cmax of the test to reference product are within the limits of 80% to 125%. Therefore, the results obtained demonstrate bioequivalence of the 600 mg film-coated with the reference product.

Safety data

In total 100 adverse events (AEs) in 29 subjects were observed, 55 and 45 each with the test and reference formulation. With both the test and the reference formulation. All AEs were considered mild.

Of these 100 AEs, 66 (39 with the test formulation and 27 with the reference formulation) were considered possibly related to the study drug, while 34 AEs were judged to be likely unrelated to the study drug.

None of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results.

Conclusions

A standard BE study with two-period, two-sequence crossover design was conducted. The study design was adequate to address the BE of an immediate release oral formulation and was in line with the respective NfG and GCP requirements. A single dose fasting study was appropriate as the product is recommended to be taken on an empty stomach.

The analytical part of the study adhered to the GLP requirements. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of 600 mg Efavirenz film-coated tablets (TEVA Pharma B.V.) met the protocol-defined criteria for bioequivalence when compared with 600 mg Sustiva film-coated tablets (Bristol-Myers Squibb Pharma) administered as a single dose of 1 x 600 mg under fasting conditions. Bioequivalence of the two formulations was shown.

1.7.3 Pharmacodynamics

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

1.7.4 Post marketing experience

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

1.8 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

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

PSUR submission

The PSUR submission schedule should follow the PSUR schedule for the reference product. The next data lock point for the reference medicinal product is 16.06.2012. The next PSUR should cover the period from 17.04.11 to 16.04.12.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

2 Benefit-Risk Balance

This application concerns a generic version of efavirenz film-coated tablets. The reference product Sustiva 600 mg film-coated tablets (Bristol-Myers Squibb Pharma, France) is indicated in antiviral combination treatment of human immunodeficiency virus 1 (HIV 1) infected adults, adolescents and children 3 years of age and older. 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 clinical overview based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with an open label, randomised, two-treatment, two-period, two-sequence, single dose crossover bioequivalence study conducted in healthy, adult subjects under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Efavirenz Teva met the protocol-defined criteria for bioequivalence when compared with the reference medicinal product. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t}, AUC_{0-∞}, and C_{max} were all contained within the protocol-defined acceptance range of 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.

3 Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Efavirenz Teva indicated in antiviral combination treatment of human immunodeficiency virus 1 (HIV 1) infected adults, adolescents and children 3 years of age and older is favourable and therefore recommends the granting of the marketing authorisation.

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management System

Not applicable

PSUR cycle

The PSUR cycle for the product will follow PSURs submission schedule for the reference medicinal product.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable.

Paediatric Data

Not applicable.