



European Medicines Agency  
Evaluation of Medicines for Human Use

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**CHMP ASSESSMENT REPORT**

**FOR**

**Nevirapine Teva**

International Nonproprietary Name: nevirapine

**Procedure No. EMEA/H/C/001119**

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted
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Medicinal product no longer authorised

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## 1. BACKGROUND INFORMATION ON THE PROCEDURE

### 1.1 Submission of the dossier

The applicant Teva Pharma B.V. submitted on 7 January 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Nevirapine 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: Viramune 200 mg tablets
- Marketing authorisation holder: Boehringer Ingelheim International GmbH
- Date of authorisation: 5 February 1998
- Marketing authorisation granted by: Community
- (Community) Marketing authorisation number: EU/1/97/055/001 and 003

■ 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: Viramune 200 mg tablets
- Marketing authorisation holder: Boehringer Ingelheim International GmbH
- Marketing authorisation granted by: Community
- (Community) Marketing authorisation number(s): EU/1/97/055/001 and 003
- Bioavailability study number(s): P1HA08002

The Rapporteur appointed by the CHMP was:  
Dr. R.J.Hemmings

#### 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 EMA on 7 January 2009.
- The procedure started on 28 January 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 April 2009.
- During the meeting on 26 – 29 May 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 29 May 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 July 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions 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 Nevirapine Teva on 24 September 2009.

## 2 SCIENTIFIC DISCUSSION

### 3.1 Introduction

This is a generic medicinal product containing nevirapine (anhydrous) as active substance. Each tablet contains 200 mg of nevirapine; the product is indicated in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infected adults, adolescents, and children of any age. The reference medicinal product is Viramune tablets.

Nevirapine is a non-nucleoside reverse transcriptase inhibitors (NNRTIs) of HIV-1. It acts through non-competitive binding to the HIV RT enzyme blocking the RNA dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme catalytic site. It does not have a biologically significant inhibitory effect on the HIV-2 reverse transcriptase.

The safety and efficacy profile of nevirapine for the treatment of HIV-1 has been demonstrated in several clinical trials, details of which can be found in the EPAR for the reference medicinal product. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this active substance. Since this application is a generic application referring to the reference medicinal product Viramune, the pivotal basis is the demonstration of bioequivalence.

The indication proposed for Nevirapine Teva is the same as authorised for the reference medicinal product, which is indicated in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infected adults, adolescents, and children of any age.

### 3.2 Quality aspects

#### Introduction

Nevirapine Teva is presented as tablets containing 200 mg of nevirapine (as anhydrate) as active substance.

Other ingredients are: microcrystalline cellulose, lactose monohydrate, povidone K25, sodium starch glycolate (Type A), colloidal silicon dioxide, and magnesium stearate.

The tablets are packed in PVC/PE/PVdC – Aluminium blisters or OPA/Alu/PVC – Aluminium blisters.

#### Active Substance

Anhydrous Nevirapine is a white or almost white powder which is practically insoluble in water, sparingly soluble or slightly soluble in methylene chloride and slightly soluble in methanol. The material is shown to be non-hygroscopic at 30°C/75 % RH. Nevirapine has the chemical name 11-Cyclopropyl-4-methyl-5,11-dihydro-6*H*-dipyrido [3,2-*b*:2',3'-*e*][1,4]diazepin-6-one.

Nevirapine does not exhibit isomerism but does exhibit polymorphism and is known to exist in the hemihydrate and anhydrous forms. The anhydrous form is used in this product.

- **Manufacture**

The manufacturing of nevirapine consists in three steps. 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. The structure has been elucidated using the following methods: IR, UV, <sup>1</sup>H NMR and MS

- Specification

The specifications of the drug substance include description, solubility (Ph Eur), identification (IR, loss on drying), related substance (HPLC), heavy metals, loss on drying, sulphated ash, assay (HPLC), residual solvents (GC), particle size distribution, bulk density (Ph Eur), tapped density (Ph Eur). The methods and specifications proposed are in accordance with Ph Eur monograph for anhydrous nevirapine.

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

- Stability

The stability studies have been carried out on three batches of active substance in long-term conditions (25°C/60% RH) and in accelerated conditions (40°C/75% RH). The data cover a period of 24 months in long term conditions and 6 months in accelerated conditions. The stability samples have been stored in the marketing pack (in a triple polybag which is placed in a High Density Polyethylene (HDPE) drum/container).

The batches are tested for the following parameters: description, assay, water/loss on drying and related substances.

Photostability studies of Nevirapine Anhydrous have been performed as per ICH guidelines in three batches.

The stability results justify the proposed retest period.

## Medicinal Product

- Pharmaceutical Development

The aim of the development was to obtain immediate-release tablets containing qualitatively and quantitatively the same active substance as the reference medicinal product Viramune 200 mg Tablets and exhibiting the same bioavailability. The dissolution tests described for the finished product were used as discriminating tests in order to select suitable formulations.

Different manufacturing processes for the finished product (direct compression and wet granulation) were tested. Wet granulation technology was chosen as manufacturing process in order to obtain a suitable granule for compression and an acceptable dissolution profile for the tablets.

The final composition of the pilot batches used in the bioequivalence study is identical to the one used for marketing.

The excipients used in the formulation are microcrystalline cellulose (filler, binder and disintegrant), lactose monohydrate (filler), povidone K25 (binder), sodium starch glycolate (Type A) (disintegrant), colloidal silicon dioxide (glidant), and magnesium stearate (lubricant). All the excipients are stated to comply with the quality requirements in Ph Eur and are tested according to the current pharmacopoeial specifications at the time of testing.

The tablets are packaged in two types of blister packs: PVC/PE/PVdC – Aluminium blisters or OPA/Alu/PVC – Aluminium blisters. Stability studies have been performed to show that the selected quality is suitable for the intended use.

- Adventitious Agents

The manufacturers of the lactose have provided statements pertaining to the guideline on “Minimizing the risk of transmitting animal spongiform encephalopathy agents in medicinal products”. Lactose is derived from milk and calf rennet. Milk is sourced from healthy animals in the same conditions as milk collected for human consumption. Lactose prepared using Calf rennet: the BSE risk is negligible

as per the CPMP statement 571/02. Magnesium stearate is of vegetable-base origin and is free of organic volatile impurities

- **Manufacture of the Product**

The manufacturing process is wet granulation. The manufacturing of the product is divided into seven main steps: initial blending, granulation, blending, intermediate blending, final blending, compression and packaging.

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 of active substance (UPLC, UV), uniformity of dosage units (Ph Eur), dissolution (UV), assay (UPLC), impurities/degradation products (UPLC), residual solvents (GC) and microbial quality (Ph Eur).

Batch analysis results confirm consistency and uniformity of manufacture and indicate that the process is under control.

- **Stability of the Product**

Two batches of the finished packed in the intended for marketing primary packaging (PVC/PE/PVdC - aluminium blisters and OPA/Alu/PVC - aluminium blisters) 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 ICH conditions. The following parameters were tested: description, assay, dissolution, impurities/degradation products, and microbiological quality.

The final blend for the finished product stored in bulk was put at 15-25°C / max 70% RH for up to 6 weeks. Photostability studies were also performed, the finished product is not sensible to light.

The results support the shelf life in the SPC.

### **Discussion on chemical, pharmaceutical and biological 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.

### **3.3 Non-clinical aspects**

No non-clinical data were submitted with this application. The applicant provided an acceptable description of the pharmacological, pharmacodynamic and toxicological properties of nevirapine based on published literature obtained through up-to-date literature searches. The non-clinical aspects of the SPC are in line with the SPC of the reference product. No further studies are required and the applicant has justified why no such data was provided.

The impurity profile has been discussed and was considered acceptable. The absence of an environmental risk assessment has been justified by the applicant with the assumption that the introduction of this generic product, which is deemed interchangeable with already marketed products, is unlikely to increase the combined sales volumes of nevirapine-containing products thus not having an adverse effect on the environment. This was considered acceptable.

### 3.4 Clinical aspects

#### Introduction

This is a generic application for tablets containing 200 mg nevirapine. To support the marketing authorisation application the applicant conducted one single dose bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of nevirapine based on published literature; this was considered acceptable. The SPC is in line with the SPC of the reference product.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EPW/QWP/1401/98) in its current version as well as the Questions & Answers on the Bioavailability and Bioequivalence Guidelines (EMA/CHMP/EWP/40326/2006) are of particular relevance.

#### GCP:

The pivotal study was complying with GCP, as claimed by the applicant. The applicant provided a statement to the effect that clinical trial P1HA08002 was conducted outside the community and was carried out in accordance with the ethical standards of Directive 2001/20/EC.

#### Clinical studies

To support the application, the applicant has submitted one bioequivalence study. The details of this study are summarised in Table 1.

**Table 1 Summary of study P1HA08002**

<b>Objective(s) of the Study</b>	<b>Study Design and Type of Control</b>	<b>Test Product(s); Dosage Regimen; Route of Administration</b>	<b>Number of Subjects</b>	<b>Healthy Subjects or Diagnosis of Patients</b>	<b>Duration of Treatment</b>
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, 200 mg, oral	40 enrolled (38 completed)	Healthy subjects	Single-dose

#### Pharmacokinetics

- Methods

#### STUDY DESIGN

Study P1HA08002 was an open label, randomised, two-treatment, two-period, two-sequence, single dose crossover bioequivalence study conducted in healthy, adult subjects under fasting conditions.

Subjects were confined to the clinical facility from at least 10 hours prior to each drug administration until 24 hours after dosing and were requested to return to the clinic for the 36, 48, 72, 120 and

168 hours post-dosing ambulatory samples. For ambulatory samples a  $\pm 1$  hour return window was allowed. Subjects were randomly assigned to one of two dosing sequences.

Subjects fasted from at least 10 hours prior to each drug administration until at least 4 hours after dosing. Fluids were not allowed from 1 hour prior to dosing until 1 hour after dosing with the exception of 240 ml of room temperature water administered with the dose. When fluids were not restricted, water was allowed *ad libitum*. Lunch was provided approximately four hours after dosing and dinner was provided approximately ten hours after dosing during each period.

Blood samples were collected over a period of 168 hours. Nineteen (19) blood samples per period x 2 study periods (total of 38 samples, approximately 228 ml total volume) were taken for pharmacokinetic analysis during each group. The sampling times were as follows: pre-dose, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12, 24, 36, 48, 72, 120 and 168 hours post dosing. The pre-dose samples were taken up to 90 minutes prior to dosing. The actual time of sample collection was documented.

The washout period between the two treatments was 28 days.

The clinical part of the study and the analytical portion of study were performed by contract research organisations.

The study protocol was approved by the ethics review committee.

#### TEST AND REFERENCE PRODUCTS

Test Product: Nevirapine 200 mg tablets  
Manufactured by: TEVA Pharmaceutical Works Private Limited Company (Hungary)  
Batch No.: 0110408  
Manufacturing date: 04/2008

Reference Product: Viramune 200 mg tablets  
Manufactured by: Boehringer Ingelheim Pharmaceuticals Inc. (Germany)  
Batch No.: 709680  
Expiry Date 05/2010

#### POPULATION(S) STUDIED

40 healthy male and female volunteers were enrolled in the study. The participants had to be non-smokers, between 18 and 55 years of age, and had to have a body mass index (BMI) within 19-30 kg/m<sup>2</sup>. The mean demographic data for all enrolled subjects are presented in Table 2.

Inclusion and exclusion criteria were acceptable for the product and for this type of study. Subjects were restricted from having any prescription medication within 14 days of study entry until after the final blood draw (168 hours post-dosing) of the final period of the study, and from having any over-the-counter medication within 7 days of study entry until after the final blood draw (168 hours post-dosing) of the final period of the study, with the exception of topical spermicides. These exclusion criteria were extended to 28 days for any drugs known to induce CYP enzyme drug metabolism of the study drug and 14 days for any drugs known to inhibit CYP enzyme drug metabolism.

Female subjects were required not to use hormone replacement therapy for a period of six months prior to dosing. No female subject had a hormone-containing vaginal ring or insert removed or inserted within 30 days prior to dosing. No female subject received any injectable or implantable contraceptive for a period of 6 months prior to dosing or used hormonal contraceptives within 14 days prior to and throughout the study.

No subject used any herbal or dietary supplements for a period of 14 days prior to dosing. No subject used St. John's Wort for a period of 14 days prior dosing and agreed not to use St. John's Wort for 14



days after the final dose of the study. No subject used a therapeutic dose of any vitamins for a period of 7 days prior to dosing.

38 subjects completed the study and were included in the pharmacokinetic and statistical analysis.

**Table 2 Summary of mean demographic data for enrolled subjects (N = 40)**

	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m <sup>2</sup> )
<b>Min</b>	21	148.5	44.2	19.9
<b>Max</b>	53	193.5	100.0	29.7
<b>Mean</b>	37.7	168.6	74.1	25.9
<b>SD</b>	8.8	9.7	12.5	2.5

#### ANALYTICAL METHODS

Nevirapine was analysed using a LC/MS/MS technique.

The analytical method was considered adequately validated.

#### PHARMACOKINETIC VARIABLES

Pharmacokinetic parameters for nevirapine plasma concentration were calculated with SAS Version 9.1 using standard noncompartmental approaches. The following pharmacokinetic parameters for nevirapine concentrations were calculated: AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, AUC<sub>0-t</sub>/AUC<sub>0-∞</sub>, C<sub>max</sub>, T<sub>max</sub>, K<sub>el</sub>, and t<sub>1/2</sub>. Values for the T<sub>max</sub> parameter were analyzed by a non-parametric approach.

The primary pharmacokinetic parameters were ln-transformed values of C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>0-∞</sub>.

#### STATISTICAL METHODS

The statistical analysis was performed using SAS software.

The Analyses of Variance (ANOVA) was calculated based on the ln-transformed pharmacokinetic parameters AUC<sub>0-t</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub>. The ANOVA model included group, sequence, period nested within group and formulation as fixed effects and subject nested within group sequence as a random effect. Sequence was tested using subject nested within group sequence as the error term. A 10% level of significance was used to test the sequence effect. A 5% level of significance was used to test the period effect. Each analysis of variance included calculation of least squares means, the difference between adjusted formulation means and the standard error associated with this difference.

With an intra-subject coefficient of variability of 28% and a fixed type-I error of 5%, a total sample size of thirty-six (36) subjects was expected to attain at least 80% statistical power to detect a difference between the Test and Reference treatments, assuming the difference is within 5%. An additional four subjects were enrolled to account for potential drop-outs.

The CHMP noted that the study was planned in such a way that the decision to continue dosing with Group 2 was determined following the review of the safety (AEs) and pharmacokinetic data from Group 1, and requested clarification on this approach. The applicant explained that after review of the data from Group 1 the study would only have stopped for futility reasons or if there had been a safety concern. Therefore the overall type 1 error was preserved at 5% and the CHMP concluded that it is appropriate to consider the pooled results for group 1 and group 2 for the bioequivalence assessment.

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, and replaced with a “.” in the statistical analysis. The applicant states that there were no unusual features observed in the data.

Bioequivalence was to be concluded if the 90% confidence intervals of Test/Reference ratios of geometric means of  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  were all within the interval of 80.00% to 125.00%.

- Results

38 out of 40 subjects completed the study (19 from each group) and were included in the pharmacokinetic and statistical analysis. Two subjects were excluded during the conduct of the trial due to the following reasons:

- One subject from group 1 voluntarily withdrew prior to period 2 check-in due to schedule conflicts;
- One subject from group 2 voluntarily withdrew prior to period 2 check-in due to an adverse event.

Three subjects had above LLOQ concentrations pre-dose in period II, however all were <1% of  $C_{max}$ .

Protocol deviations that occurred during the conduct of this study was judged by the investigators not to have any significant impact on the accuracy of the study results.

The pharmacokinetic parameters obtained in the 38 subjects who were included in the analysis are presented in Table 3. The results of the statistical analysis for ln-transformed data are displayed in Table 4.

**Table 3 Pharmacokinetic parameters of study P1HA08002 (non-transformed values)**

	Test			Reference		
	N	Mean*	SD**	N	Mean*	SD**
$AUC_{0-t}$ [ng×h/ml]	38	113328.3	25793.1	38	112205.5	26675.8
$AUC_{0-\infty}$ [ng×h/ml]	38	132336.5	38489.1	38	132299.6	36456.2
$AUC_{0-t}/AUC_{0-\infty}$	38	0.87	0.07	38	0.88	0.07
$C_{max}$ [ng/ml]	38	2013.3	438.4	38	2012.3	444.64
$T_{max}$ [h]	38	2.5	---	38	2.5	---
$K_{el}$ [h <sup>-1</sup> ]	38	0.0135	0.0041	38	0.0135	0.0036
$T_{1/2}$ [h]	38	56.28	17.29	38	54.89	14.21

$AUC_{0-\infty}$  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

\* Arithmetic mean

\*\* Standard deviation

**Table 4 Statistical analysis of study P1HA08002 (ln-transformed data)**

Parameter	Least Square Means		Ratio of geometric means (%)	90% CI*		Intra-subject CV (%)
	Test	Reference		Lower (%)	Upper (%)	
<b>AUC<sub>0-t</sub></b> <b>(ng×h/ml)</b>	110120.3	108428.8	101.6	97.18	106.14	11.3
<b>AUC<sub>0-∞</sub></b> <b>(ng×h/ml)</b>	126605.6	127738.4	99.1	97.09	101.18	5.2
<b>C<sub>max</sub></b> <b>(ng/ml)</b>	1963.2	1967.0	99.8	95.08	104.77	12.4

\* 90% confidence intervals based on ln transformed values.

The 90% confidence intervals for the ratio of geometric means of AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub> (ln-transformed data) are within the limits of 80% to 125%.

While the mean ratio of AUC<sub>0-t</sub>/AUC<sub>0-∞</sub> for test and reference suggest an extrapolation of < 20% of the overall AUC, individual patient data suggest that in 7/38 patients (18%) the ration of AUC<sub>0-t</sub>/ AUC<sub>0-∞</sub> is < 0.8, indicating a > 20% extrapolation. However, as the sampling scheme goes beyond 72 h post dose, this is considered acceptable as the absorption phase and most of the elimination phase were covered.

#### Safety data

In total 20 adverse events (AEs) were observed, 10 each with the test and reference formulation. With both the test and the reference formulation, 9 out of 10 AEs were considered mild, while 1 event with each formulation was considered to be of moderate severity. No serious AEs were reported. With the test formulation, 3 AEs were judged to be possibly or likely related to the study drug. With the reference formulation, 9 AEs were judged to be possibly or likely related to the study drug.

#### ▪ Conclusions

Based on the presented bioequivalence study Nevirapine Teva is considered bioequivalent with Viramune.

#### **Pharmacodynamics**

No new pharmacodynamic data have been provided by the applicant. These data are not required for this particular application.

#### **Post marketing experience**

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

### **3.5 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.

- User consultation

The results of a user consultation of the Package leaflet have been provided and the qualitative and qualitative evaluation was considered acceptable.

## Discussion on Clinical aspects

For the demonstration of bioequivalence an open label, randomised, two-treatment, two-period, two-sequence, single dose crossover study was conducted in healthy, adult subjects under fasting conditions. The overall design of the study as well as inclusion and exclusion criteria defining the study population were acceptable.

The product is an immediate release formulation. According to the SPC of the reference product, the product can be taken with or without food. There is no relevant accumulation with repeated doses. Therefore, a single dose bioequivalence study in the fasting state is appropriate.

The 200 mg dose (i.e. administration of one single tablet of test and reference product, respectively) was selected for the bioequivalence study. This is acceptable considering that the standard daily dose of nevirapine in adults is 400 mg in two divided doses and that nevirapine has linear pharmacokinetics after a single dose administration in a dose range of 200 mg to 400 mg.

The sampling time and blood collection times were adequate to estimate pharmacokinetic parameters. There were three subjects with positive plasma concentrations at the beginning of period II, in all cases the plasma concentration relative to  $C_{max}$  was low (<1%). This is not considered to significantly affect the study results. The washout period of 28 days is hence judged to be acceptable.

The analytical method used for quantification of nevirapine in the bioequivalence study is sufficiently sensitive and allows accurate and reproducible quantification.

The pharmacokinetic variables and evaluation criteria follow the applicable European requirements and are appropriate for this study. The statistical methods are adequately described.

For nevirapine, the Test/Reference ratios of geometric means were 101.6% (90% CI 97.18–106.14%) for  $AUC_{0-t}$ , 99.1% (90% CI 97.09–101.18%) for  $AUC_{0-\infty}$ , and 99.8% (90% CI 95.08 – 104.77%) for  $C_{max}$ . The point estimates and their 90% confidence intervals were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. It can be concluded that bioequivalence of test product and reference product under fasting conditions has been demonstrated.

## 3.6 Overall conclusions, risk/benefit assessment and recommendation

### Overall conclusion and Benefit/risk assessment

This application concerns a generic version of nevirapine tablets. The reference product Viramune is indicated for the treatment of HIV -1 infection in combination with other antiretroviral agents. No nonclinical studies have been provided for this generic application but an adequate summary of the available nonclinical information for the active substance was presented. 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 nevirapine; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The pivotal basis forms a standard bioequivalence study with a two-period, two-sequence crossover design. The study design was adequate to evaluate the bioequivalence of an immediate release oral formulation and was in line with the respective European requirements. A single dose fasting study was appropriate as there is no food effect on the bioavailability of nevirapine. 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 200 mg Nevirapine Teva met the protocol-defined criteria for bioequivalence when compared with the 200 mg reference product (Viramune). 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 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.

### **Recommendation**

Based on the CHMP review of available data, the CHMP considered that the benefit/risk ratio of Nevirapine Teva in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infected adults, adolescents, and children of any age was favourable and therefore recommended the granting of the marketing authorisation.

Medicinal product no longer authorised