COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Nevirapine Vocate 400 mg, prolonged-release tablets

(nevirapine)

NL/H/4667/001/DC

Date: 28 January 2020

This module reflects the scientific discussion for the approval of Nevirapine Vocate 400 mg, prolonged-release tablets. The procedure was finalised at 11 December 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Nevirapine Vocate 400 mg, prolonged-release tablets from Vocate Pharmaceuticals S.A.

The product is indicated in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infected adults, adolescents, and children three years and above and able to swallow tablets (see SmPC section 4.2).

Nevirapine Vocate prolonged-release tablets are not suitable for the 14-day lead-in phase for patients starting nevirapine.
Other nevirapine formulations, such as immediate-release tablets or oral suspension, may be checked for their availability and used accordingly (see SmPC section 4.2).

Most of the experience with nevirapine is in combination with nucleoside reverse transcriptase inhibitors (NRTIs). The choice of a subsequent therapy after nevirapine should be based on clinical experience and resistance testing (see SmPC section 5.1).

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Viramune 400 mg prolonged-release tablets (EU/1/97/055/007-009) which has been centrally registered in the EEA by Boehringer Ingelheim international GmbH since 1998 (original product).

The concerned member state (CMS) involved in this procedure was Greece.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Nevirapine Vocate is a white to off-white oval shaped biconvex prolonged-release tablet debossed with ‘H’ on one side and ‘N1’ on other side. The prolonged-release tablet should not be divided.

And contains as active substance 400 mg of nevirapine.

The prolonged-release tablet is packed in polyvinyl chloride (PVC)/aluminium foil blisters.

The excipients are: lactose monohydrate, hypromellose E464, and magnesium stearate E470b.

II.2 Drug Substance

The active substance is nevirapine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is practically insoluble in water, sparingly soluble or slightly soluble in methylene chloride and slightly soluble in methanol. The drug substance is non-hygroscopic and photo stable. The polymorph for nevirapine manufactured is crystalline Form-I.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for six batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified. The manufacture and composition of the bio-batches used in bioequivalence studies is identical to the marketed product. Comparative dissolution at three pHs is shown. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The tablets are manufactured by wet granulation. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity of active substance, average weight, water content, dissolution, assay, uniformity of dosage units by mass variation, related substances and microbiological examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from five batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided three full scaled batches stored at 25°C/60% RH (up to 24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the intended blisters. No clear trends were observed under any of the storage conditions. On basis of the data submitted, a shelf life was granted of two years without any special storage conditions.

Photostability data in accordance with ICH show that the product is stable when exposed to light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Lactose monohydrate is the only excipient of animal origin. Lactose monohydrate is manufactured using no ruminant materials other than milk and calf rennet. The milk used in the process is sourced from healthy animals in the same conditions as milk collected for human consumption.

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Nevirapine Vocate has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Nevirapine Vocate is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Viramune which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Nevirapine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Nevirapine Vocate 400 mg, prolonged-release tablets (Vocate Pharmaceutical S.A., Greece) is compared with the pharmacokinetic profile of the reference product Viramune 400 mg prolonged-release tablets (Boehringer Ingelheim International GmbH, Germany):

- Study 110-14-EM: a single dose bioequivalence study with the 400 mg tablet under fasting conditions.
- Study 111-14-EM: a single dose bioequivalence study with the 400 mg tablet under fed conditions.
- Study 127-15-EM: a multiple dose bioequivalence study with the 400 mg tablet.

Reference product
The choice of the reference product in the bioequivalence studies has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Study 110-14-EM: single dose study under fasing conditions
Design
A single-dose, randomised, open-label, balanced, two-treatment, randomised, parallel bioequivalence study was carried out under fasted conditions in 160 healthy male subjects, aged 20-43 years. Each subject received a single dose (400 mg) of one of the two nevirapine formulations. The tablet was orally administered with 240 ml water after an overnight fast. The study had two treatment arms, one in which the subjects received the test formulation and one in which the subjects received the reference formulation.

Blood samples were collected pre-dose and at 2, 4, 6, 10, 12, 16, 20, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 28, 30, 32, 34, 36, 48, 72, 120, 168, 216, 264, 312 and 360 hours after administration of the products.

The design of the study is acceptable.

Results
Two subjects were withdrawn due to an adverse event. Both subjects received the reference formulation. 158 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of nevirapine under fasted conditions.

Treatment	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test N=80	291 ± 112	314 ± 112	2.59 ± 1.13	24.0 (6.0 – 74)	85 ± 26
Reference N=78	292 ± 127	315 ± 140	2.71 ± 1.16	24.0 (4.0 – 72)	83 ± 25
***Ratio (90% CI)**	1.03 (0.91 – 1.16)	1.04 (0.93 – 1.17)	0.97 (0.85 – 1.10)	--	--
CV (%)	48.6	46.4	50.4	--	--

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Study 111-14-EM: a single dose bioequivalence study with the 400 mg tablet under fed conditions.

Design

A single-dose, randomised, open-label, balanced, two-treatment, randomised, parallel bioequivalence study was carried out under fed conditions in 160 healthy male subjects, aged 19-43 years. Each subject received a single dose (400 mg) of one of the two nevirapine formulations. The tablet was orally administered with 240 ml water, 30 minutes after the start of the intake of a high fat, high caloric breakfast. The breakfast had to be completed within 30 minutes. The study had two treatment arms, one in which the subjects received the test formulation and one in which the subjects received the reference formulation.
Blood samples were collected pre-dose and at 2, 4, 6, 10, 12, 16, 20, 22, 22.5, 23, 23.5, 24, 24.5, 25.5, 26, 28, 30, 32, 34, 36, 48, 72, 120, 168, 216, 264, 312 and 360 hours after administration of the products.

The design of the study is acceptable.

Results

Two subjects were withdrawn due to an adverse event. One subject received the reference formulation and one subject the test formulation. 158 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of nevirapine under fed conditions.

Treatment	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test N=79	376 ± 141	418 ± 167	3.30 ± 0.99	22.5 (4.0 – 34)	83 ± 34
Reference N=79	393 ± 150	429 ± 175	3.42 ± 1.09	22.0 (10.0 – 34)	83 ± 31
***Ratio (90% CI)**	0.93 (0.83 – 1.05)	1.00 (0.89 – 1.12)	0.97 (0.89 – 1.06)	--	--
CV (%)	48.4	43.8	35.2	--	--

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Study 127-15-EM: a multiple dose bioequivalence study with the 400 mg tablet.

Design

An open-label, balanced, two-treatment, two-period, two-sequence, multicentre (four centres), multiple dose (steady state), two-way crossover bioequivalence study was carried out under fasted conditions in 38 healthy male subjects, aged 18-45 years. Subjects received one 400 mg prolonged-release tablet of the test or reference nevirapine formulation in two periods from day 1 to day 16 at scheduled dosing time. Doses from day 1-5 for period-I and day 9-13 for period-II were administered by the subjects on their own. During in-house stay at the study site on the remaining days, all subjects were in a fasting state for at least ten hours before scheduled time for dosing:

- Period-I: Day 1-8 (subjects were housed from not less than 10.5 hours pre-dose on day 6 to till 24 hours post dose on day 8)
- Period-II: Day 9-16 (subjects were housed from not less than 10.5 hours pre-dose on day 14 to till 24 hours post dose on day 16)

There is no washout period between each investigational product administration.

On day 8 for period-I and on day 16 for period-II blood samples were taken at pre-dose and at 2, 4, 6, 8, 10, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24 hours after administration of the products.

The design of the study is acceptable.

Results

Five subjects were withdrawn due to an adverse event. 33 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of nevirapine under fasted conditions.

Treatment	$AUC_{0-\tau}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	C_{min} (ng/ml)	PTF% %
Test N=79	126541.678 ± 43943.421	6264.71 ± 2092.701	8.0 (2.0 – 24.0)	4375.198 ± 1651.371	37.737 ± 14.848
Reference N=79	133154.696 ± 54720.055	6580.961 ± 2755.104	4.0 (0.0 – 23.0)	4537.198 ± 2112.940	37.821 ± 11.607
***Ratio (90% CI)**	0.96 (0.86 – 1.07)	0.97 (0.87 – 1.09)	--	--	--
CV (%)	26.4	27.8	--	--	--

AUC_{0-t}	area under the plasma concentration-time curve over the dosing interval
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
C_{min}	minimum plasma concentration
PTF%	fluctuation index
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Nevirapine Vocate is considered bioequivalent with Viramune.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Nevirapine Vocate.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	• Skin rash, including severe or life-threatening skin reactions e.g. Stevens-Johnson syndrome

	and toxic epidermal necrolysis • Severe and life-threatening hepatotoxicity incl. fatal fulminant hepatitis • Granulocytopenia, particularly in paediatric population
Important potential risks	--
Missing information	--

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Viramune. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Nevirapine Hetero Europe 200 mg tablets. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

The medicine described in the Nevirapine Vocate package leaflet is presented in a different pharmaceutical form, prolonged-release tablets instead of tablets. The strength in the Nevirapine Vocate package leaflet is 400 mg whilst in the Nevirapine Hetero Europe package leaflet is 200 mg. The impact of these differences on the Nevirapine Vocate package leaflet have been analysed in the bridging report and are considered acceptable and not to affect the readability. In addition, the package leaflet text is in line with that of the innovator product Viramune.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Nevirapine Vocate 400 mg, prolonged-release tablets has a proven chemical-pharmaceutical quality and is a generic form of Viramune 400 mg prolonged-release tablets. Viramune is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Nevirapine Vocate with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 December 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse