CBG MEB

Public Assessment Report

Scientific discussion

Brinaf 400 mg, prolonged release tablets

(nevirapine)

NL/H/3540/001/DC

Date: 5 September 2017

This module reflects the scientific discussion for the approval of Brinaf 400 mg, prolonged release tablets. The procedure was finalised on 27 February 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
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 Brinaf 400 mg, prolonged release tablets from Zentiva k.s.

Brinaf 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 and 4.4).

Brinaf 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 which has been registered in the EEA by Boehringer Ingelheim international GmbH through a centralised procedure (EU/1/97/055/007-009) since 1998.

The concerned member state (CMS) involved in this procedure was the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

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

Each prolonged-release tablet contains 400 mg of nevirapine (as anhydrous).

The prolonged release tablets are packed in polyvinyl chloride (PVC)/aluminium foil blisters or high density polyethylene (HDPE) containers, with a child resistant plastic cap with pulp liners.

The excipients are lactose monohydrate, hypromellose and magnesium stearate.

II.2 Drug Substance

The active substance is nevirapine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Nevirapine is a white to off white granular powder. The active substance is practically insoluble in water. Polymorphic Form-I of the drug substance is used. Nevirapine does not exhibit isomerism.

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. Additional tests are included for identity, polymorphic identity and residual solvents in line with the specifications of the ASMF holder and requirements of the CEP. Furthermore, tests and acceptance criteria for particle size distribution and microbial quality have been specified. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for at least three full scaled batches stored at 25°C/60% RH (60 months), 30°C/75% RH (60 months) and 40°C/75% RH (6 months). The stability data showed no clear changes or trends in any of the tested parameters at all three storage conditions. The proposed retest period of 60 months without any special storage requirements is justified.

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 main development studies concerned the characterisation of the reference product, selection and optimisation of the excipients, optimisation of the manufacturing process and dissolution method development.

Three bioequivalence studies have been performed versus the 400 mg reference product. The test batches used in the bioequivalence studies have been manufactured according to the finalised manufacturing process and composition. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are dry mixing of the intragranular components, wet granulation, drying, sifting and milling of the granules, blending of the granules with the extra granular components and compression. The manufacturing process is considered a non-standard process. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scaled batches.

Control of excipients
The excipients comply with their Ph.Eur. monographs with some additional in-house criteria. 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 description, identification, average weight, water content, dissolution, uniformity of dosage units, related substances, assay and microbiological quality. Except for water content and total impurities, the release and shelf-life limits are identical. 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 three full scaled 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 on three full scaled batches stored at 25°C/60% RH (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 proposed packaging. No clear changes

or trends were observed. The claimed shelf-life of two years with storage condition 'This medicinal product does not require any special storage conditions' is justified. The drug product is photostable.

Stability data has been provided demonstrating that the product remains stable for 30 days following first opening of the HDPE bottle when stored at 25°C/60% RH.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Except for lactose monohydrate no substances from human and/or animal origin are used. The milk used in the production of lactose monohydrate is sourced from healthy animals in the same conditions as milk collected for human consumption. The lactose is prepared without the use of other ruminant materials than milk and calf rennet. The production of calf rennet complies with the applicable EU legislation.

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 Brinaf 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 Brinaf 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

Bioequivalence studies
In accordance with the EMA Guidance on modified release formulations, the MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Brinaf 400 mg (Zentiva k.s., Czech Republic) is compared with the pharmacokinetic profile of the reference product Viramune 400 mg (Boehringer Ingelheim International GmbH, Germany):

- a single dose bioequivalence study under fasting conditions
- a single dose bioequivalence study under fed conditions
- a multiple dose study under fasting conditions

The choice of the 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.

Single dose bioequivalence study under fasting conditions
Design
A single-dose, randomised, open-label, balanced, two-treatment, parallel bioequivalence study was carried out under fasted conditions in 160 healthy male subjects, aged 20-43 years. 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. Both groups were balanced with regard to age, BMI, weight, and height. In each study arm, 80 subjects were included. 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.

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. A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC, the tablets can be taken with or without food. As such, the fasting conditions applied in the study are considered adequate. Considering the safety concerns on skin reactions and hepatic toxicity and that both test and reference groups appear to be balanced with regard to age, weight, Body Mass Index (BMI) and height to minimise variability, a parallel design is acceptable in line with the bioequivalence guideline.

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.

Results
Two subjects were withdrawn in period-1 due to an adverse event. Both subjects received the Reference formulation. Therefore 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 N=158	**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*

Single dose bioequivalence study under fed conditions

Design

A single-dose, randomised, open-label, balanced, two-treatment, parallel bioequivalence study was carried out under fed conditions in 160 healthy male subjects, aged 19-43 years. 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. Both groups were balanced with regard to age, BMI, weight, and height. In each study arm, 80 subjects were included. 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.

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. A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC, the tablets can be taken with or without food. As such, the fasting conditions applied in the study are considered adequate. Considering the safety concerns on skin reactions and hepatic toxicity and that both test and reference groups appear to be balanced with regard to age, weight, BMI and height to minimise variability, a parallel design is acceptable in line with the bioequivalence guideline.

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.

Results

Two subjects were withdrawn in period-1 due to an adverse event. One subject received the Test formulation and one subject the Reference formulation. Therefore 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 N=158	**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*

Multiple dose study under fasting conditions

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 fasting conditions in 38 healthy male (n=27) and female (n=11) subjects, aged 26-46 years. The subjects received one 400 mg prolonged release tablet of the test or reference nevirapine formulation from day 1 to day 16 at scheduled dosing time. Except in house doses at study site/hospital, other doses from day 1-5 for period-I and day 9-13 for period-II were administered by the patients/subjects personally on their own. During their in-house stay at the study site, all subjects were in a fasting state for at least 10 hours before scheduled time for dosing. The tablets were administered with 240 ml water after an overnight fast.

- Period-I: Subjects were housed from not less than 10.50 hours pre-dose on day 6 to till 24.00 hours post dose on day 8. Day 6, day 7 and day 8 were at clinical site/hospital and on the morning of day 9 they were checked out from the study site/hospital.
- Period-II: Subjects were housed from not less than 10.50 hours pre-dose on day 14 to till 24.00 hours post dose on day 16. Day 14, day 15 and day 16 were at clinical site/hospital and on the morning of day 17 they were checked out from the study site/hospital. 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 collected 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. The chosen subjects are the target population and are therefore appropriate in a steady-state study. The demographic characteristics are in line with the bioequivalence guideline. The included subjects received concomitant medication either with lamivudine/tenofovir (or lamivudine/zidovudine combination). According to the innovator's SmPC, lamivudine and zidovudine had no effect on the pharmacokinetics of nevirapine. Hence, concomitant medication with these two drugs is acceptable.

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.

Results

Five patients discontinued (two subjects did not report to the facility in period I and three subjects withdrew on their own accord. Therefore, 33 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD)

Treatment N=33	AUC_τ ng/ml/h	C_{max} ng/ml	C_{min} ng/ml	C_τ ng/ml	t_{max} h	PTF% %
Test	126541.68 ± 43943.42	6264.71 ± 2092.70	4375.20 ± 1651.37	4837.86 ± 1889.21	8.0 (2.0 – 24.0)	37.74 ± 14.85
Reference	133154.70 ± 54720.06	6580.96 ± 2755.10	4537.10 ± 2112.94	5035.01 ± 2276.12	4.0 (0.0 – 23.0)	37.82 ± 11.61
***Ratio (90% CI)**	0.96 (0.86 – 1.07)	0.97 (0.87 – 1.09)	--	0.97 (0.86 – 1.09)	--	--

AUC_τ area under the plasma concentration-time curve over the dosing interval
C_{max} maximum plasma concentration
C_{min} minimum plasma concentration
C_τ concentration in plasma at the end of a dosing interval
t_{max} time for maximum concentration
PTF% fluctuation index

Conclusion on bioequivalence studies
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$, AUC_{0-T}, C_{max}, and C_T are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies under fasting and fed conditions, Brinaf 400 mg is considered bioequivalent with Viramune 400 mg.

The MEB has been assured that the bioequivalence study has 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 Brinaf.

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, including 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 (PL) has been performed on the basis of a bridging report making reference to Nevirapine Hetero Europe 200 mg tablets. Indications of the medicines are the same in both PL. The medicine described in the Brinaf PL is presented in a different pharmaceutical form, prolonged-release tablets instead of tablets. The strength in the Brinaf PL is 400 mg whilst in the reference PL is 200 mg. This leads to differences between the two PIL that are compared in some sections of the PL. The impact of these differences on the Brinaf PL have been analysed in the bridging report and are considered acceptable and not to affect the readability. In addition, the text in the Brinaf PL is in line with that of the innovator product Viramune. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Brinaf 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 Brinaf with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 February 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached