CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Nevirapine Aurobindo 200 mg, tablets
Aurobindo Pharma B.V., the Netherlands

nevirapine anhydrate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2499/001/DC
Registration number in the Netherlands: RVG 111042

17 April 2013

Pharmacotherapeutic group:	non-nucleoside reverse transcriptase inhibitors
ATC code:	J05AG01
Route of administration:	oral
Therapeutic indication:	treatment of HIV-1 infected adults, adolescents, and children of any age in combination with other anti-retroviral medicinal products
Prescription status:	prescription only
Date of authorisation in NL:	12 December 2012
Concerned Member States:	Decentralised procedure with DE, ES, FR, IT, MT, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Nevirapine Aurobindo 200 mg, tablets from Aurobindo Pharma B.V. The date of authorisation was on 12 December 2012 in the Netherlands.

Nevirapine Aurobindo is indicated in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infected adults, adolescents, and children of any age).
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.
A comprehensive description of the indications, posology and warnings is given in the SPC.

Nevirapine is a NNRTI of HIV-1. Nevirapine is a non-competitive inhibitor of the HIV-1 reverse transcriptase, but it does not have a biologically significant inhibitory effect on the HIV-2 reverse transcriptase or on eukaryotic DNA polymerases α, β, γ, or δ.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Viramune 200 mg tablets, which has been registered in the EEA by Boehringer Ingelheim International GmbH since 5 February 1998 through centralised procedure EMEA/H/C/183.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Viramune 200 mg tablets, registered in the EEA. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products. No paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
T The active substance is nevirapine anhydrate, a known active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white powder and is practically insoluble in water (pH-independent); sparingly soluble or slightly soluble in methylene chloride, slightly soluble in methanol. Nevirapine anhydrous does not exhibit optical isomerism, but does exhibit polymorphism. The anhydrous form is consistently produced

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process has been adequately described. No heavy metal catalysts or class I solvents are used in the synthesis. The active substance has been adequately characterized and in general acceptable specifications have been adopted for the solvents. The starting material in the synthesis is acceptable. Sufficient information on presence, carry-over and control of impurities has been provided.

Quality control of drug substance
In general, adequate specifications are applied for the drug substance in view of the route of synthesis and the various European guidelines. General tests are performed as per Ph.Eur. and the methods for assay, related substances and residual solvents are developed or validated in-house. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches.

Stability of drug substance
The stability data on the active substance has been provided for 18 months at long-term (30°C/65% RH) and 6 months at accelerated (40°C/75%RH) storage conditions. No clear trends could be observed and all results were well within limits.
The claimed retest period of 24 months is deemed justified and no specific storage conditions are required.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Nevirapine Aurobindo 200 mg is a white to off-white, oval shaped, biconvex tablet, debossed with "J" and "80" on either side of break line on one side and with break line on the other side. The size is 19.2 mm X 9.3 mm. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The tablets are packed in Clear PVC/PVDC-Aluminium blister packs or HDPE bottles with polypropylene closure containing cotton coil.

The excipients are: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type-A), povidone (K-30), silica colloidal anhydrous, magnesium stearate.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation development has been adequately described. The manufacturing process development has been described adequately. Comparative dissolution testing was performed with the biobatch against the innovator product in three different pH media. Similarity was confirmed. The choice of manufacturing process and packaging material is justified. In general, the pharmaceutical development of the product has been adequately performed. Discriminating power of the dissolution method has been demonstrated.

Manufacturing process
The drug product is manufactured by wet granulation. The process involves sifting, mixing, drying, sifting and compression. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two smallest scale production batches. The product is manufactured using conventional manufacturing techniques. Additional validation on larger scale production batches will be performed post-approval.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, average mass, dissolution, water, uniformity of dosage units, thickness, related substances, assay and microbiological quality. The release and shelf-life specifications are identical.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two smallest commercial-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for two smallest commercial scale batches as used for process validation stored at 25°C/60%RH (12 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 clear PVC/PVdC-Aluminium blisters or white HDPE containers with PP cap (60 or 500 count). Under all conditions, all results remain within limits. A photostability study showed no significant change at these storage conditions. A shelf-life period of 24 months can be granted based on the provided data. The claimed storage condition “No special storage conditions” is justified, as the drug product is not sensitive to light. The provided data of 12 months in-use stability for the HDPE container show chemical and microbiological stability of the tablets. An in-use period does not have to be stated in the SPC, as in daily practice the tablet containers would likely be exhausted at that time.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is prepared from the milk sourced from healthy animals in the same conditions as milk collected for human consumption. None of the other excipients is of human or animal origin, so a theoretical risk on TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Viramune, which is available on the European market. 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.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of nevirapine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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 a bioequivalence study in which the pharmacokinetic profile of the test product Nevirapine Aurobindo 200 mg (Aurobindo Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Viramune 200 mg tablets (Boehringer Ingelheim Pharmaceuticals, Germany).

The choice of the reference product
The choice of the reference product in the bioequivalence study is acceptable, as the product has been registered through a centralised procedure and is therefore identical in different EEA countries.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30 (+ 2 additional) healthy male subjects, aged 19 - 42 years. Each subject received a single dose (200 mg) of one of the 2 nevirapine formulations. The tablet was orally administered with 240 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 31 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 18, 24, 36, 48 and 72 hours after administration of the products.

A single dose, crossover study to assess bioequivalence is considered adequate. A wash-out period of 31 days has been applied, as nevirapine is a drug with a long elimination half-life (about 50 – 60 h). Plasma samples were obtained up to 72 hours, which is acceptable and in accordance with the guideline on bioequivalence. This is agreed.

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
One subject withdrew his consent after check-in for Period I. In addition, 1 stand-by was not dosed. Thirty subjects completed the study and were included in the analysis.

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

Treatment N=30	**AUC_{0-72}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h

Test	99.1 ± 18.6	--	2.29 ± 0.52	2.5 (0.67 – 12.0)	63 ± 33
Reference	102.4 ± 19.0	--	2.41 ± 0.40	2.5 (1.0 – 24.0)	65 ± 21
***Ratio (90% CI)**	0.97 (0.94 – 0.99)	--	0.94 (0.89 - 1.00)	--	--
CV (%)	5.7	--	13.0	--	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of nevirapine under fasted conditions, it can be concluded that Nevirapine Aurobindo 200 mg and Viramune 200 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Nevirapine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of nevirapine. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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).

Risk management plan

Nevirapine was first approved in 1998, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of nevirapine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with the updated Viramune SPC.

Readability test

The package leaflet has not been evaluated via a user consultation study. The lay-out and design of the Nevirapine Aurobindo 200 mg tablets (daughter PIL) is identical to the User tested PILs of Aurobindo's inhouse style (Parent PIL). The MAH has successfully performed User testing with the inhouse lay-out for more than 45 products. Hence, a waiver is requested for conducting user testing on the PIL of Nevirapine Aurobindo 200 mg tablets (Daughter PIL) proposed for DCP as per CMDh Guideline "Consultation with target patient groups - Meeting the requirements of article 59(3) without the need for a full test - Recommendations for Bridging" (October 2007). Therefore, a bridging is submitted to the lay-out and design of Nevirapine Aurobindo 200 mg tablets with Ramipril Aurobindo 5 mg, 10 mg tablets User tested

PIL (Parent PIL), which was approved during the DCP, MT/H/0103/01-02/DC. The member states considered this is acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Nevirapine Aurobindo 200 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Viramune 200 mg 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 Aurobindo 200 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 14 November 2012. Nevirapine Aurobindo 200 mg, tablets was authorised in the Netherlands on 12 December 2012.

The date for the first renewal will be: 14 November 2017.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to perform manufacturing process validation on additional batches of different batch sizes.
- The MAH committed to continue the on going long-term stability studies of the submission batches of the drug product.
- The MAH committed to carry out accelerated and long-term stability studies on the first production batch with minimum batch size and on the first three production batches with maximum batch size.
- The MAH committed to conduct long-term stability studies on a minimum of one marketed production batch per year.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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