CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Nevirapine Mylan 200 mg, tablets
Mylan B.V., the Netherlands

nevirapine

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/2061/001/DC
Registration number in the Netherlands: RVG 107898

18 October 2011

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:	27 September 2011
Concerned Member States:	Decentralised procedure with BE, DE, ES, FR, LU, PL, PT, RO, SK, 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 Mylan 200 mg, tablets from Mylan B.V. The date of authorisation was on 27 September 2011 in the Netherlands.

Nevirapine Mylan 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, as this is not required for a generic application.

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
The active substance is nevirapine, an established 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, sparingly soluble or slightly soluble in methylene chloride, slightly soluble in methanol. Nevirapine anhydrous does not exhibit optical isomerism, but does exhibit polymorphism. The MAH demonstrated that the anhydrous form II 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. An adequate discussion 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, microbiological quality and residual solvents were 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 9 months at long-term (25°C/60%RH) and intermediate (30°C/65%RH) condition, and for 6 months at accelerated (40°C/75%RH) storage conditions. No clear trends could be observed and all results were well within limits. The results of the photostability study, performed in line with ICH Q1B, demonstrate the photostability of the drug substance. The claimed retest period of 18 months is deemed justified. No specific storage conditions are necessary.

** 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 Mylan 200 mg is a white to off-white oval, biconvex tablet of 19 mm debossed with "NE" and "200" on one side of the tablet, separated by a score line and debossed with "M" on the other side, with a score line.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The film-coated tablets are packed in PVC/Aluminium blisters and HDPE bottle with a child-resistant polypropylene screw cap.

The excipients are: lactose monohydrate, microcrystalline cellulose E460, povidone (E1201), sodium starch glycolate (Type A), silica colloidal anhydrous (E551), magnesium stearate (E572).

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation development and the manufacturing process development have been described adequately. Comparative dissolution testing was performed with the biobatch against the innovator product. Similarity was confirmed at all four pH values tested. The choice of manufacturing process and packaging material is justified. In general, the pharmaceutical development of the product has been adequately performed.

Manufacturing process
The drug product is manufactured by wet granulation and includes steps of sifting, mixing, drying and milling. The lubricated blend is analyzed, compressed and packed.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot-cale batches and three production-scale batches. The product is manufactured using conventional manufacturing techniques. Holding times of 60 days of the blend and the compressed tablets are justified with stability data.

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, uniformity of dosage units, identification, dissolution, related substances, assay, loss on drying, hardness, friability and microbiological quality. The release and shelf-life specifications are identical, except for the limits for loss on drying. The specification is adequately justified.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on four pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three pilot-scale batches as used for process validation stored at 30°C/75%RH (48 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline, although not the European climate zone. As the long-term condition applied is more stringent, no objection was made. The batches were stored in clear PVC-Alu blisters or white HDPE containers with PP cap. Bulk stability data in LDPE bags has been provided, justifying a bulk shelf-life of 12 months.
Under all conditions, only an increase in loss on drying was observed with significant variability between time-points. All results remain within limits. The proposed shelf-life of 48 months is justified. The claimed storage condition “No special storage conditions” is justified. The drug product is demonstrated to be photostable and an in-use stability study has been performed for the HDPE container. The MAH committed to perform an in-use stability study on one batch packed in HDPE containers at the end of shelf-life in line with the Note for Guidance on in-use stability testing.

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 nevirapine, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Nevirapine Mylan 200 mg tablets (Mylan B.V., NL) 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, single-period, randomised, two-treatment, parallel comparative bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 19-41 years. Twenty-four subjects received a single dose (200 mg) of the test nevirapine formulation and twenty-four subjects received a single dose (200 mg) of the reference nevirapine formulation. The tablets were administered in solid form with 240 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. As this was a parallel study, there was only 1 dosing period.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

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
Fourty-eigth healthy male subjects, aged 19-41 years, were included in this study. There were no dropouts. All 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=24 per group	**$AUC_{0-72\ h}$** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg /ml	**t_{max}** h	**$t_{1/2}$** h

Test	104 ± 17	--	2.7 ± 0.5	2.81 ± 0.85	55 ± 28
Reference	107 ± 17	--	2.5 ± 0.4	4.67 ± 4.91	55 ± 18
***Ratio (90% CI)**	0.97 (0.90-1.05)	--	1.05 (0.97-1.14)	--	--
CV (%)	16.5	--	17.0	--	--

$AUC_{0-\infty}$ 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*

Nevirapine is a drug with a long elimination half-life (till about 50 – 60 h) and although a crossover study may be feasible, a parallel study is considered acceptable. The median t_{max} for test was 3.0 h (range 1.0–4.5) and for reference 3.0 h (range 1.0 – 24.0h). The late t_{max} values observed in 3 subjects (12, 12 and 24 h) for reference can be explained due to the long elimination half-life and a less fast distribution phase. This is considered not attributed to formulation differences.

The 90% confidence intervals calculated for AUC_{0-72h} 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 Mylan 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 SPC for Viramune.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 2 participants,

followed by two rounds with 10 participants each. A total of eighteen questions have been evaluated with regard to the use of finding, ease of understanding and subjective impression of the PIL by the participants. The responses were recorded satisfactory. The user test showed that the leaflet enabled more than of the 90% of participants to find the information and more than 90% of those understood the information good or in detail.

The main objectives of the user testing have been achieved and the conclusions of the MAH are accurate. Furthermore the overall impression of the methodology and the overall impression of the leaflet structure are positive. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Nevirapine Mylan 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 Mylan 200 mg, tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 20 July 2011. Nevirapine Mylan 200 mg, tablets was authorised in the Netherlands on 27 September 2011.

The date for the first renewal will be: 19 July 2016.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to perform an in-use stability study on one batch packed in HDPE containers at the end of shelf-life in line with the Note for Guidance on in-use stability testing.

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