Public Assessment Report

Mutual Recognition Procedure

Nevirapine 400 mg prolonged-release tablets

(Nevirapine)

Procedure No: UK/H/5652/001/E/001

UK Licence No: PL 04569/1455

Generics (UK) Limited (trading as Mylan)
LAY SUMMARY

Nevirapine 400 mg prolonged-release tablets

This is a summary of the Public Assessment Report (PAR) of Nevirapine 400 mg prolonged-release tablets (PL 04569/1455; UK/H/5652/0001/DC). It explains how the application for Nevirapine 400 mg prolonged-release tablets was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Nevirapine 400 mg prolonged-release tablets.

For practical information about using Nevirapine 400 mg prolonged-release tablets, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Nevirapine’ or ‘Nevirapine prolonged-release tablets’ in this lay summary, for ease of reading.

What is Nevirapine what is it used for?
Nevirapine prolonged-release tablets is a ‘generic medicine’. This means that Nevirapine prolonged-release tablets is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Viramune 400 mg prolonged release tablets (Boehringer Ingelheim International GmbH, Germany), which was first authorised in the EU on 05 February 1998.

Nevirapine prolonged-release tablets is indicated for the treatment of Human Immunodeficiency Virus (HIV)-1 infected adults, adolescents and children three years and above and able to swallow tablets. Nevirapine must be taken together with other antiretroviral medicines. The patient’s doctor will recommend the best medicines for the patient. Nevirapine prolonged-release tablets should only be used after a two-week treatment with another type of nevirapine (immediate-release tablets or suspension) unless the patient is currently on nevirapine and is switching to the prolonged-release form.

How does Nevirapine work?
Nevirapine prolonged-release tablets contains the active substance, nevirapine (as anhydrous nevirapine), which belongs to a class of anti-HIV medicines called non-nucleoside reverse transcriptase inhibitors (NNRTIs). Reverse transcriptase is an enzyme that HIV needs in order to multiply. Nevirapine stops reverse transcriptase from working. By stopping reverse transcriptase from working, nevirapine helps control HIV-1 infection.

How is Nevirapine used?
Nevirapine should be taken by mouth with a liquid. The prolonged-release tablets should not be chewed or broken. The patient may take Nevirapine with or without food.

Nevirapine should not be use on its own. Nevirapine should be taken with at least two other antiretroviral medicines. The patient’s doctor will recommend the best medicines suitable for the patient.

The patient should always take this medicine exactly as his/her doctor or pharmacist has advised. The patient should check with his/her doctor or pharmacist if unsure.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.
Nevirapine can only be obtained with a prescription.

**What benefits of Nevirapine has been shown in studies?**
As Nevirapine prolonged-release tablets is a generic medicine, studies in patients have been limited to tests to determine that Nevirapine prolonged-release tablets is bioequivalent to Viramune 400 mg prolonged-release tablets/Viramune prolonged release 400mg (Boehringer Ingelheim International GmbH, Germany). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Nevirapine?**
As Nevirapine prolonged-release tablets is a generic medicine of the reference medicine Viramune 400 mg prolonged release tablets (Boehringer Ingelheim International GmbH, Germany), the benefits and possible side effects are taken as being the same as those of the reference medicine.

For the full list of all side effects reported with Nevirapine, see Section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

**Why is Nevirapine approved?**
In accordance with the EU requirements, Nevirapine prolonged-release tablets has been shown to have comparable quality and clinical characteristics to the reference product Viramune 400 mg prolonged release tablets (Boehringer Ingelheim International GmbH, Germany). Based on this evaluation, the MHRA concluded that the benefits of Nevirapine outweigh the identified risks and recommended Nevirapine for approval.

**What measures are being taken to ensure the safe and effective use of Nevirapine?**
A Risk Management Plan has been developed to ensure that Nevirapine is used as safely as possible. The relevant safety information has been included in the Summary of Product Characteristics and the package leaflet for Nevirapine, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored / reviewed continuously.

**Other information about Nevirapine**
Belgium, Germany, France, Italy, Luxembourg, the Netherlands, Poland, Portugal and the UK agreed to grant a Marketing Authorisation for Nevirapine prolonged-release tablets on 13 June 2016. A Marketing Authorisation was granted in the UK to Generic UK Limited (trading as Mylan) on 12 July 2016.

Following a mutual recognition procedure (UK/H/5652/001/E/001), which concluded on 05 July 2017, Austria, Denmark, Finland, Sweden and Norway agreed to grant a Marketing Authorisation for this product.

The full PAR for Nevirapine follows this summary.

For more information about treatment with Nevirapine read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2017.
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I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Nevirapine 400 mg prolonged-release tablets (PL 04569/1455; UK/H/5652001/DC) could be approved. The product is a Prescription Only Medicine (POM) 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.

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 should be used.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Belgium, Germany, France, Italy, Luxembourg, the Netherlands, Poland and Portugal as Concerned Member States (CMS). The application for Nevirapine prolonged-release tablets was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application, referring to the reference product Viramune 400 mg prolonged-release tablets (Boehringer Ingelheim International GmbH, Germany), which was first authorised in the European Union via the Centralised Procedure on 05 February 1998.

Nevirapine prolonged-release tablets contains the active substance, nevirapine (as anhydrous nevirapine), which is a non-nucleoside reverse transcriptase inhibitor (NNRTI). It binds directly to reverse transcriptase and blocks the RNA-dependent and DNA-dependent polymerase activities by causing disruption of the enzyme’s catalytic site. HIV-2 reverse transcriptase and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ or δ) are not inhibited by nevirapine.

Four (three single dose and one multiple dose) bioequivalence studies were submitted to support this application, comparing the applicant’s test product Nevirapine 400 mg prolonged-release tablets with the reference products Viramune 400mg prolonged release tablets (Boehringer Ingelheim International GmbH, Germany) and Viramune Retardardtabletten 400mg (Boehringer Ingelheim International GmbH, Germany). The bioequivalence studies are stated to have been conducted in accordance with ethical principles outlined in the Declaration of Helsinki, the Committee for Proprietary Medicinal Products (CPMP) Note for Guidance on Good Clinical Practice, the CPMP Note for Guidance on Investigation of Bioavailability and Bioequivalence, and other relevant guidelines.

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that the application was based on the product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The Member States considered that the application could be approved at the end of procedure (Day 210) on 13 June 2016. After a subsequent national phase, a Marketing Authorisation was granted on 12 July 2016 in the UK to Generics UK Limited, trading as Mylan Limited.

Following a mutual recognition procedure (UK/H/5652/001/E/001), which concluded on 05 July 2017, Austria, Denmark, Finland, Sweden and Norway agreed to grant a Marketing Authorisation for this product.
II QUALITY ASPECTS

II.1 Introduction
The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Nevirapine 400 mg prolonged-release tablets are white to off-white, oval-shaped prolonged-release tablets, approximately 19 mm in length and 9 mm in width, debossed with ‘M’ on one side of the tablet and ‘N403’ on the other side. The prolonged-release tablet should not be divided.

Each prolonged-release tablet contains 400 mg of nevirapine (as anhydrous nevirapine). The product also contains pharmaceutical excipients, namely lactose monohydrate, hypromellose and sodium stearyl fumarate. Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in
1. polyvinylchloride/aluminium blisters, in pack sizes of 14, 30, 30 x 1 (unit dose blister), 60, 90, 100 and 120 prolonged-release tablets.
2. white high-density polyethylene (HDPE) bottles, each with a white opaque polypropylene (PP) screw cap with aluminium induction sealing liner wad and absorbent cotton, in pack sizes of 30, 90, 250 and 500 prolonged-release tablets.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE

Nevirapine
INN: Anhydrous nevirapine
Chemical name: 11-Cyclopropyl-4-methyl-5,11-dihydro-6H-dipyrido [3,2-b:2′,3′-e][1,4]diazepin-6-one

Structure:

![Structure of Nevirapine](image)

Molecular formula: C_{15}H_{14}N_{4}O
Molecular weight: 266.3
Appearance: White or almost white powder.
Solubility: Practically insoluble in water, sparingly soluble or slightly soluble in methylene chloride and slightly soluble in methanol

Anhydrous nevirapine is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, anhydrous nevirapine, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, stable,
Nevirapine 400 mg prolonged-release tablets

A prolonged-release tablet that was bioequivalent to the reference product Viramune 400 mg prolonged release tablets (Boehringer Ingelheim International GmbH, Germany), marketed in the European Union. Suitable pharmaceutical development data have been provided for this application.

Comparative in-vitro dissolution and impurity profiles have been provided for this product and the reference product. The in-vitro dissolution and impurity profiles were satisfactory.

All the excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material, other than calf rennet, is used during the production of lactose monohydrate. Also, the supplier has confirmed that the lactose monohydrate used in the formulation is free from the risk of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated with pilot-scale and full production-scale batches and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on future full-scale production batches.

Control of Finished Product
The finished product specification is acceptable. Test methods have been described and have been validated adequately. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years for the unopened product (product in blisters and HDPE) and 100 days for the product after first opening the HDPE bottle has been accepted. This medicinal product does not require any special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies. The bioequivalence studies are discussed in Section IV, Clinical Aspects.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for this application, from a quality point of view.
III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of nevirapine are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

III.3 Pharmacokinetics
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

III.4 Toxicology
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the product is intended for generic substitution with a product that is already marketed, no increase in environmental exposure to nevirapine is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction.
The clinical pharmacology of nevirapine is well-known. The clinical overview has been written by an appropriately qualified person and is a suitable summary of the clinical aspects of the dossier.

To support the application, the applicant initially submitted the results of single dose, parallel, bioequivalence studies (2 fasting and 1 fed) in healthy volunteers. The design of the studies and the population chosen were acceptable. Inclusion and exclusion criteria were presented and acceptable. The studies used a parallel design in view of the long elimination half-life of nevirapine.

Subsequently, in accordance with the current ‘Guideline on the Pharmacokinetic and Clinical Evaluation of Modified Release Dosage Forms (EMA/CPMP/EWP/280/96 Corr 1)’, the applicant submitted a multiple dose bioequivalence study conducted in HIV infected patients. The design of the study (2 way, cross-over) and the population chosen (HIV infected patients established on treatment with nevirapine 400 mg/day) were acceptable. Nevirapine has significant adverse effects, making multiple dose administration in healthy volunteers inappropriate. In addition, nevirapine has to be given in a 200 mg daily dose initially, to be increased to 400 mg per day after 2 weeks, to reduce the risk of adverse events. As a dose of 400 mg had to be administered to allow evaluation of bioequivalence of the application product, conducting the study in subjects established on treatment with nevirapine 400 mg is appropriate.
With the exception of data from the bioequivalence studies detailed in Section IV.2, Pharmacokinetics below, no new pharmacodynamic or pharmacokinetic data are provided and none are required for this application.

IV.2 Pharmacokinetics
In support of the application, the applicant submitted the following bioequivalence studies:

Study 1
An open-label, randomised, single-period, two-treatment, parallel, balanced, single dose, oral bioequivalence study comparing the pharmacokinetics of the applicant’s test product Nevirapine 400 mg prolonged-release tablets versus the reference product Viramune (Nevirapine) 400 mg prolonged-release tablets (Boehringer Ingelheim International GmbH, Germany) in healthy, adult male subjects under fasting conditions.

Each subject was administered a single dose (one 400 mg tablet) of either treatment with 240 ml of water, after at least a 10-hour overnight fast. Subjects were instructed not to chew or crush the tablet but to consume whole. Blood samples were collected before, up to and including 360 hours after administration. The pharmacokinetic results are presented below.

Results:

Table 1: Summary of Pharmacokinetic Data for Nevirapine

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Arithmetic mean</th>
<th>Standard deviation</th>
<th>Coeff of Variation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₂₄ (ng.hr/mL)</td>
<td>36088.843</td>
<td>12325.904</td>
<td>34.154</td>
</tr>
<tr>
<td>AUC₂₄-3₆₀ (ng.hr/mL)</td>
<td>236291.733</td>
<td>118268.315</td>
<td>50.052</td>
</tr>
<tr>
<td>AUC₅ (ng.hr/mL)</td>
<td>272075.325</td>
<td>127489.944</td>
<td>46.858</td>
</tr>
<tr>
<td>AUC₅ (ng.hr/mL)</td>
<td>285050.018</td>
<td>134902.873</td>
<td>47.326</td>
</tr>
<tr>
<td>Cₘₐₓ (ng/mL)</td>
<td>2480.769</td>
<td>1092.670</td>
<td>44.046</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Arithmetic mean</th>
<th>Standard deviation</th>
<th>Coeff of Variation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₂₄ (ng.hr/mL)</td>
<td>36061.544</td>
<td>13471.822</td>
<td>37.358</td>
</tr>
<tr>
<td>AUC₂₄-3₆₀ (ng.hr/mL)</td>
<td>216423.373</td>
<td>117176.287</td>
<td>54.142</td>
</tr>
<tr>
<td>AUC₅ (ng.hr/mL)</td>
<td>252102.496</td>
<td>128149.330</td>
<td>50.832</td>
</tr>
<tr>
<td>AUC₅ (ng.hr/mL)</td>
<td>260581.554</td>
<td>133167.773</td>
<td>51.104</td>
</tr>
<tr>
<td>Cₘₐ₇ (ng/mL)</td>
<td>2500.441</td>
<td>1116.090</td>
<td>44.636</td>
</tr>
</tbody>
</table>

Cₘₐₓ Peak plasma concentration
AUC₂₄ Area under the plasma concentration curve from zero to 24 hours
AUC₂₄-3₆₀ Area under the plasma concentration curve from 24 hours to 360 hours
AUC₅ Area under the plasma concentration curve from administration to last measured time point.
AUC₅ Area under the plasma concentration curve extrapolated to infinity
Table 2: Ratio and 90% Confidence Interval of Test versus Reference for Nevirapine

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Geometric mean (Test)</th>
<th>Geometric mean (Reference)</th>
<th>Ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;24&lt;/sub&gt; (ng.hr/mL)</td>
<td>33659.959</td>
<td>34068.419</td>
<td>98.80</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;24-360&lt;/sub&gt; (ng.hr/mL)</td>
<td>185652.241</td>
<td>205276.417</td>
<td>90.44</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;r&lt;/sub&gt; (ng.hr/mL)</td>
<td>220520.722</td>
<td>240852.731</td>
<td>91.56</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;c&lt;/sub&gt; (ng.hr/mL)</td>
<td>227807.076</td>
<td>251641.168</td>
<td>90.53</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>2255.205</td>
<td>2259.542</td>
<td>99.81</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>90% Confidence Intervals</th>
<th>Inter-Subject CV (%)</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;24&lt;/sub&gt; (ng.hr/mL)</td>
<td>(87.39%; 111.70%)</td>
<td>37.811</td>
<td>0.9115</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;24-360&lt;/sub&gt; (ng.hr/mL)</td>
<td>(74.43%; 109.90%)</td>
<td>63.328</td>
<td>0.5049</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;r&lt;/sub&gt; (ng.hr/mL)</td>
<td>(76.44%; 109.67%)</td>
<td>57.915</td>
<td>0.6522</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;c&lt;/sub&gt; (ng.hr/mL)</td>
<td>(75.51%; 108.53%)</td>
<td>58.246</td>
<td>0.6484</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>(85.56%; 116.43%)</td>
<td>48.413</td>
<td>0.7711</td>
</tr>
</tbody>
</table>

C<sub>max</sub> Peak plasma concentration
AUC<sub>24</sub> Area under the plasma concentration curve from zero to 24 hours
AUC<sub>24-360</sub> Area under the plasma concentration curve from 24 hours to 360 hours
AUC<sub>r</sub> Area under the plasma concentration curve from administration to last measured time point.
AUC<sub>c</sub> Area under the plasma concentration curve extrapolated to infinity
CV Coefficient of variation

Conclusion of Study 1
The 90% confidence intervals of the test/reference ratio for C<sub>max</sub> lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr-*)’. However, the 90% confidence intervals of the test/reference ratio for AUC (that is, AUC<sub>r</sub>, AUC<sub>24</sub>, AUC<sub>24-360</sub> and AUC<sub>c</sub>) values lie outside the acceptable limits of 80.00% to 125.00%. Thus, the data from this study failed to demonstrate bioequivalence between the applicant’s test product and the reference product Viramune 400 mg prolonged-release tablets (Boehringer Ingelheim International GmbH, Germany) under fasting conditions.

Based on the data obtained (including CV%) from this study and the single dose fed study (Study 3) summarised below, the applicant performed a revised sample size calculation and concluded that a larger sample size was required to demonstrate bioequivalence with the reference product. Subsequently, the applicant performed a second single dose fasting bioequivalence study using a larger sample size. A summary of the second single dose, fasting study is provided below.

Study 2
An open-label, randomised, single-period, two-treatment, parallel, balanced, single dose, oral bioequivalence study comparing the pharmacokinetics of the applicant’s test product Nevirapine 400 mg prolonged-release tablets versus the reference product Viramune (Nevirapine) 400 mg prolonged-release Tablets (Boehringer Ingelheim International GmbH, Germany) in healthy male adult humans under fasting conditions.

Each subject was administered a single dose (one 400 mg tablet) of either treatment with 240 ml of water, after at least a 10-hour overnight fast. Subjects were instructed not to chew or crush the tablet but to consume whole. Blood samples were collected before, up to and including 360 hours after administration. The pharmacokinetic results are presented below.
Results:
As per guideline, one subject was excluded from pharmacokinetic and statistical analysis due to high pre-dose concentrations of nevirapine (that is, $C_{\text{max}} > 5\%$). Despite a thorough analysis, no entirely plausible explanation was provided for the high pre-dose concentrations of nevirapine, however the evaluation did not identify any systematic flaws in the bioanalytical method that would suggest the results of the study are invalid. A summary of the pharmacokinetics results excluding the data for this patient is provided below.

Table 3: Log transformed pharmacokinetic parameters for nevirapine (excluding data for one subject with high pre-dose concentrations ($C_{\text{max}} > 5\%$))

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>T/R Ratio</th>
<th>Geo LSM of Reference</th>
<th>Geo LSM of Test</th>
<th>90% CI Lower</th>
<th>90% CI Upper</th>
<th>ISCV</th>
<th>Power</th>
<th>BE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>96.81%</td>
<td>2413.1866</td>
<td>2336.2470</td>
<td>86.48%</td>
<td>108.37%</td>
<td>39.6%</td>
<td>94.6%</td>
<td>YES</td>
</tr>
<tr>
<td>$\text{AUC}_{0-4}$</td>
<td>95.66%</td>
<td>265689.4994</td>
<td>254146.3371</td>
<td>83.33%</td>
<td>109.80%</td>
<td>49.4%</td>
<td>84.6%</td>
<td>YES</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$</td>
<td>97.97%</td>
<td>290027.8937</td>
<td>284143.3119</td>
<td>86.22%</td>
<td>111.32%</td>
<td>45.2%</td>
<td>89.1%</td>
<td>YES</td>
</tr>
<tr>
<td>$\text{AUC}_{24}$</td>
<td>98.35%</td>
<td>32284.2366</td>
<td>31752.7113</td>
<td>90.04%</td>
<td>107.44%</td>
<td>30.6%</td>
<td>99.4%</td>
<td>YES</td>
</tr>
<tr>
<td>$\text{AUC}_{24-360}$</td>
<td>96.56%</td>
<td>239989.0931</td>
<td>231742.9863</td>
<td>84.65%</td>
<td>110.15%</td>
<td>46.7%</td>
<td>87.4%</td>
<td>YES</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$ Peak plasma concentration
$\text{AUC}_{0-4}$ Area under the plasma concentration curve from administration to last measured time point.
$\text{AUC}_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinity
$\text{AUC}_{24}$ Area under the plasma concentration curve from zero to 24 hours
$\text{AUC}_{24-360}$ Area under the plasma concentration curve from 24 hours to 360 hours
ISCV Intra-subject coefficient of variation

The applicant performed an additional statistical analysis on the pharmacokinetic data generated for this one subject with high pre-dose concentrations; the overall results were not affected. A summary of these results are provided below in Table 4.

Table 4: Log transformed pharmacokinetic parameters for nevirapine (including data for one subject with high pre-dose concentrations (that is, $C_{\text{max}} > 5\%$))

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>T/R Ratio</th>
<th>Geo LSM of Reference</th>
<th>Geo LSM of Test</th>
<th>90% CI Lower</th>
<th>90% CI Upper</th>
<th>ISCV</th>
<th>Power</th>
<th>BE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>97.04%</td>
<td>2407.4191</td>
<td>2336.2470</td>
<td>86.76%</td>
<td>108.54%</td>
<td>39.5%</td>
<td>94.9%</td>
<td>YES</td>
</tr>
<tr>
<td>$\text{AUC}_{0-4}$</td>
<td>96.29%</td>
<td>263942.9597</td>
<td>254146.3371</td>
<td>83.94%</td>
<td>110.45%</td>
<td>49.3%</td>
<td>84.9%</td>
<td>YES</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$</td>
<td>98.31%</td>
<td>289031.6625</td>
<td>284143.3119</td>
<td>86.50%</td>
<td>111.10%</td>
<td>45.0%</td>
<td>89.5%</td>
<td>YES</td>
</tr>
<tr>
<td>$\text{AUC}_{24}$</td>
<td>98.40%</td>
<td>32268.9659</td>
<td>31752.7113</td>
<td>90.14%</td>
<td>107.41%</td>
<td>30.5%</td>
<td>99.4%</td>
<td>YES</td>
</tr>
<tr>
<td>$\text{AUC}_{24-360}$</td>
<td>96.93%</td>
<td>239070.7316</td>
<td>231742.9863</td>
<td>85.06%</td>
<td>110.47%</td>
<td>46.5%</td>
<td>87.8%</td>
<td>YES</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$ Peak plasma concentration
$\text{AUC}_{0-4}$ Area under the plasma concentration curve from administration to last measured time point.
$\text{AUC}_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinity
$\text{AUC}_{24}$ Area under the plasma concentration curve from zero to 24 hours
$\text{AUC}_{24-360}$ Area under the plasma concentration curve from 24 hours to 360 hours
ISCV Intra-subject coefficient of variation
Conclusion of Study 2
The 90% confidence intervals of the test/reference ratio for AUC (AUC\textsubscript{t}, AUC\textsubscript{0-24}, AUC\textsubscript{24-360} and AUC\textsubscript{i}) and C\textsubscript{max} values lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**’)’. Thus, these data support the claim that the applicant’s test product is bioequivalent to the reference product Viramune 400 mg prolonged release tablets (Boehringer Ingelheim International GmbH, Germany) under fasting conditions.

The larger sample size in this study, which was designed in the same way as the failed Study 1, was sufficient to tighten the confidence intervals such that bioequivalence criteria were met.

Study 3
An open-label, randomised, single-period, two-treatment, parallel, balanced, single dose, oral bioequivalence study comparing the pharmacokinetics of the applicant’s test product Nevirapine 400 mg prolonged-release tablets (Mylan Laboratories Limited) versus the reference product Viramune (Nevirapine) prolonged-release tablets 400 mg (Boehringer Ingelheim International GmbH, Germany) in healthy subjects, under fed conditions.

After at least a 10-hour fast, the subjects were administered a single dose (one 400 mg tablet) of either the test or the reference product with 240 ml water, 30 minutes after the start of a standardised, high fat, high calorie breakfast. Blood sampling was carried out at before, up to and including 360 hours after administration of treatment. The pharmacokinetic results are presented below.

Results:

Table 5: Bioequivalence evaluation of Nevirapine

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Geometric Mean Ratio Test/Ref (%)</th>
<th>Confidence Intervals</th>
<th>CV %</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\textsubscript{max}</td>
<td>97.82%</td>
<td>88.22% - 108.47%</td>
<td>28.106</td>
</tr>
<tr>
<td>AUC\textsubscript{0-24}</td>
<td>96.65%</td>
<td>87.35% - 106.93%</td>
<td>27.492</td>
</tr>
<tr>
<td>AUC\textsubscript{24-360}</td>
<td>97.07%</td>
<td>83.94% - 112.26%</td>
<td>40.311</td>
</tr>
<tr>
<td>AUC\textsubscript{0-t}</td>
<td>97.07%</td>
<td>85.18% - 110.62%</td>
<td>35.933</td>
</tr>
<tr>
<td>AUC\textsubscript{inf}</td>
<td>97.30%</td>
<td>84.97% - 111.18%</td>
<td>37.061</td>
</tr>
</tbody>
</table>

C\textsubscript{max}  Peak plasma concentration
AUC\textsubscript{0-24}  Area under the plasma concentration curve from zero to 24 hours
AUC\textsubscript{24-360} Area under the plasma concentration curve from 24 hours to 360 hours
AUC\textsubscript{0-t} Area under the plasma concentration curve from administration to last measured time point.
AUC\textsubscript{inf} Area under the plasma concentration curve extrapolated to infinity
CV  Coefficient of variation

Discussion and conclusion of Study 3
The 90% confidence intervals of the test/reference ratio for AUC (AUC\textsubscript{t}, AUC\textsubscript{0-24}, AUC\textsubscript{24-360} and AUC\textsubscript{i}) and C\textsubscript{max} values lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**’)’.

Based on these results, bioequivalence has been demonstrated between the applicant’s product and the reference product, Viramune 400 mg prolonged release tablets (Boehringer Ingelheim International GmbH, Germany), under single dose fed conditions.
Study 4
An open label, randomised, two-period, two-treatment, two-sequence multiple dose two-way, cross-over bioequivalence study in HIV-1 infected patients under fasting conditions to (i) evaluate the pharmacokinetic bioequivalence of the applicant’s test product Nevirapine 400 mg prolonged-release tablets versus the reference product Viramune (Nevirapine) Retardardtabletten 400mg (comparable to Viramune 400 mg prolonged release tablets Boehringer Ingelheim International GmbH) and (ii) monitor safety in the patients.

Patients already receiving and stable on a nevirapine 400mg based regimen (either immediate release or prolonged release for at least 14 days) were eligible. Zidovudine and Lamivudine or Tenofovir and Lamivudine were allowed as antiretroviral therapy (ART).

Patients were confined at the clinical facility from at least 12 hours before dosing until at least 4 hours after the administration of the investigational product (test or reference product) on Day 1 dose in each period. Patients were also confined at the clinical facility from at least 12 hours before dosing on Day 06 until at least 24 hours after dosing on Day 08 in each period. The test or reference product was swallowed whole and was not chewed, crushed or divided.

On Day 1 of each period, patients received a morning dose (400 mg) of either the test or reference product as per the randomization schedule and were monitored for at least 4 hours post dose. The time of administration of the dose on Day 1 of Period I was the reference time for all subsequent doses. At the time of check-out on Day 1 of each period, patients were given sufficient quantity of the test or reference product for administration at other times. Patients were instructed to take the investigational product once daily at the same time as per schedule. A subject diary was provided to record the study drug administration details at home. Patients were requested to take along the remaining investigational product to the subsequent site visit.

On Day 6 and Day 7 of each period, the dose (400 mg) of test or reference product was administered to the patients under the supervision of trained study personnel.

On Day 8 of each period, the dose (400 mg) of test or reference product was administered to the patients, under the supervision of trained study personnel, after at least an 8 hour overnight fast with at least 150 ml water. A standard meal was served at least 4 hours after dosing. Further meals/snacks were served at appropriate times. Water was restricted from at least 1 hour before to at least 1 hour after the morning dose on Day 8 of each period (no fluid was allowed except water given with dosing).

The other drugs (Zidovudine, Lamivudine or Tenofovir) were administered after the water restrictions were completed i.e. after 1 hour after time of dosing). On the next day, patients were crossed over to receive the other investigational product (i.e. Period II started).

Blood samples were collected at pre-dose (0.0 hours) on Day 01, on Day 06 to Day 08 and up and including 24 hours after drug administration on Day 08 of each period. Samples were analysed and a summary of the results are presented below.
Results:

Table 6: Summary of Statistical Analysis of Log-Transformed Data

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>REFERENCE LEAST SQUARE MEAN</th>
<th>TEST LEAST SQUARE MEAN</th>
<th>REFERENCE GEOMETRIC MEAN</th>
<th>TEST GEOMETRIC MEAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmaxss</td>
<td>1.734</td>
<td>1.778</td>
<td>5.666</td>
<td>5.921</td>
</tr>
<tr>
<td>Ctauss</td>
<td>1.398</td>
<td>1.446</td>
<td>4.049</td>
<td>4.247</td>
</tr>
<tr>
<td>Cminss</td>
<td>1.369</td>
<td>1.419</td>
<td>3.933</td>
<td>4.131</td>
</tr>
<tr>
<td>AUCtau</td>
<td>4.708</td>
<td>4.746</td>
<td>110.781</td>
<td>115.078</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>INTRA SUBJECT CV</th>
<th>(TEST/REFERENCE) RATIO</th>
<th>90% CONFIDENCE INTERVAL</th>
<th>POWER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmaxss</td>
<td>19.533%</td>
<td>104.50%</td>
<td>(96.50%,113.16%)</td>
<td>0.9977</td>
</tr>
<tr>
<td>Ctauss</td>
<td>23.151%</td>
<td>104.90%</td>
<td>(95.48%,115.24%)</td>
<td>0.9867</td>
</tr>
<tr>
<td>Cminss</td>
<td>17.685%</td>
<td>105.04%</td>
<td>(97.72%,112.91%)</td>
<td>0.9994</td>
</tr>
<tr>
<td>AUCtau</td>
<td>15.440%</td>
<td>103.88%</td>
<td>(96.60%,111.70%)</td>
<td>0.9992</td>
</tr>
</tbody>
</table>

Data
Cmaxss: Maximum measured plasma concentration at steady state
AUCtau: Area under the concentration curve during a dosage interval at steady state, where tau is the dosing interval for steady state data.
Cminss: Minimum plasma concentration at steady state
Ctau: Concentration at the end of dosing interval at steady state

Safety
Overall, both test and reference formulations were well tolerated.

Discussion and Conclusion of Study 4
There was no washout period between treatment periods, as is appropriate for a study in patients. EU guidance stipulates that, in steady-state studies, the washout period of the previous treatment can overlap with the build-up of the second treatment (direct switching), provided the build-up period is sufficiently long (at least 5 times the terminal half-life). An 8 day build-up is hence acceptable for nevirapine.

The 90% confidence intervals of the test/reference ratio for Cmaxss, AUCtau and Cminss values lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**)’. Statistical analysis has been performed to confirm attainment of steady state levels in both periods for both treatments. Thus, these data support the claim that the applicant’s test product is bioequivalent to the reference product Viramune 400 mg prolonged-release tablets (Boehringer Ingelheim International GmbH, Germany) under multiple dose, fasting (steady-state) conditions.

There were no new or unexpected safety findings.

Overall conclusion of the bioequivalence studies
The data fulfil the bioequivalence criteria for single and multiple dose studies for modified release products. The applicant’s claim of bioequivalence between the test and reference formulations may be accepted.

IV.3 Pharmacodynamics
The clinical pharmacodynamics properties of nevirapine are well-known. No new pharmacodynamic data were submitted and none are required for an application of this type.
IV.4 Clinical Efficacy
The clinical efficacy of nevirapine is well-known. No new efficacy data are presented or are required for this type of application.

IV.5 Clinical Safety
With the exception of the safety data generated during the bioequivalence studies, no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues arose during the bioequivalence studies.

IV.6 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 prolonged-release tablets.

A summary of safety concerns is listed in the table below:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
<th></th>
</tr>
</thead>
</table>
| Important identified risks | • Skin rash (including severe or life threatening skin reactions, e.g. Steven-Johnson syndrome, toxic epidermal necrolysis)  
• Severe and life threatening hepatotoxicity (including fatal fulminant hepatitis)  
• Granulocytopenia particularly in paediatric population |
| Important potential risks   | N/A |
| Missing information        | • Use in pregnant women |

In addition to routine pharmacovigilance activities, additional pharmacovigilance is planned in the form of the Antiretroviral Pregnancy Registry (APR) to address the concern of “Use in Pregnant Women”. The APR is intended to provide an early signal of potential risks of teratogenicity associated with antiretroviral treatment. This independent registry is a voluntary prospective, exposure-registration, observational study designed to collect and evaluate data on the outcomes of pregnancy exposures to anti-retroviral products.

Routine risk minimisation is planned for all safety concerns which is considered acceptable.

IV.7 Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted, from a clinical point of view.

V. USER CONSULTATION
A 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 language used for the purpose of user testing the pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.
VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Nevirapine prolonged-release tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type. As the pharmacokinetics, pharmacodynamics and toxicology of nevirapine are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence studies, no new data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant’s test product and the reference products Viramune 400 mg prolonged release tablets (Boehringer Ingelheim International GmbH, Germany) under fasting, fed and steady state steady-state conditions.

SAFETY
With the exception of the safety data from the bioequivalence studies, no new data were submitted and none are required for this type of application. As the safety profile of nevirapine is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence studies.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with nevirapine is considered to have demonstrated the therapeutic value of the compound.

The overall benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.
In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:
## Annex 1 - Table of content of the PAR update for MRP and DCP

**Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report**

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To update sections 3, 6.1 and 6.3 of the SmPC following the closure of the Repeat Use Procedure (RUP). Leaflet text is updated, no changes to the leaflet mock up.</td>
<td>UK/H/5652/001/IB/002</td>
<td>SmPC PIL</td>
<td>14 September 2017</td>
<td>13 October 2017</td>
<td>Approval</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Annex 1.1

**Our Reference:** PL 04569/1455 - 0007  
**Product:** Nevirapine Mylan 400 mg prolonged-release tablets  
**Marketing Authorisation Holder:** Generics (UK) Limited  
**Active Ingredient(s):** Anhydrous nevirapine

**Type of Procedure:** Mutual Recognition  
**Submission Type:** Variation  
**Submission Category:** Type IB  
**Submission Complexity:** Standard  
**EU Procedure Number (if applicable):** UK/H/5652/001/IB/002

**Reason:**  
To update sections 3, 6.1 and 6.3 of the SmPC following the closure of the Repeat Use Procedure (RUP). Subsequently the leaflet text is updated, no changes to the leaflet mock up.

**Supporting Evidence**  
Revised SmPC fragments and updated leaflet text (Section 5).

**Evaluation**  
The proposed changes to the SmPC and PIL are acceptable

In accordance with Directive 2010/84/EU, the SmPC and PIL for products granted Marketing Authorisations at a national level are available on the MHRA website.

**Conclusion**  
Approved on 14 October 2017