Public Assessment Report

Scientific discussion

Aciclovir Apotex 200 mg and 800 mg tablets

(aciclovir)

NL/H/3711/001-002/DC

Date: 14 November 2017

This module reflects the scientific discussion for the approval of Aciclovir Apotex 200 mg and 800 mg tablets. The procedure was finalised on 7 June 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**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<td>CMS</td>
<td>Concerned Member State</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>ERA</td>
<td>Environmental Risk Assessment</td>
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<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PL</td>
<td>Package Leaflet</td>
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<td>RH</td>
<td>Relative Humidity</td>
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<td>RMP</td>
<td>Risk Management Plan</td>
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<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Aciclovir Apotex 200 mg and 800 mg tablets from Apotex Europe BV.

Aciclovir Apotex 200 mg tablets is indicated for:
- The product is indicated for the treatment of herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital herpes (excluding neonatal HSV and severe HSV infections in immunocompromised children).
- The suppression (prevention of recurrences) of recurrent herpes simplex infections in immunocompetent patients.
- The prophylaxis of herpes simplex infections in immunocompromised patients.
- The treatment of varicella (chickenpox) and herpes zoster (shingles) infections.

Aciclovir Apotex 800 tablets is indicated for the treatment of varicella (chickenpox) and herpes zoster (shingles) infections (excluding neonatal HSV and severe HSV infections in immunocompromised children).

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 Zovirax 200 mg and 800 mg tablets which has been registered in the EEA by GlaxoSmithKline B.V. since 13 June 1984 and 24 July 1992. In the Netherlands, the marketing authorisations of Zovirax tablets have been withdrawn.

The concerned member states (CMS) involved in this procedure were Belgium, Spain and Luxembourg.

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

II. QUALITY ASPECTS

II.1 Introduction

Aciclovir Apotex is tablets in two strengths.
- The 200 mg strength is a white, round, biconvex tablet, with embossment “200” on one side.
- The 800 mg strength is a white, elongated, biconvex tablet with a score line on one side.

Each tablet contains as active substance 200 mg or 800 mg of aciclovir.

The tablets are packed in PVC/Aluminium blisters.

The excipients are povidone K30 (E1201), sodium starch glycolate type A (E468), microcrystalline cellulose (E460) and magnesium stearate (E470b).

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is aciclovir, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Aciclovir is a white or almost white crystalline powder. It is slightly soluble in water, very slightly soluble in ethanol (96%), practically insoluble in heptane. Aciclovir dissolves in dilute solutions of mineral acids and alkali hydroxides. It does not contain any stereogenic center and is consistently isolated as the common commercial 2/3 hydrate polymorph.

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. Compared to the CEP it has additional tests for particle size and microbiology. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

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

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies consist of optimising the order of addition of microcrystalline cellulose and the amount of magnesium stearate as well as the development of a suitable dissolution method for release and comparative dissolution testing. The score line of the 800 mg strength tablets complies with the requirements of the Ph.Eur. tablets monograph. The tablet can be divided into equal halves. The pharmaceutical development of the product has been adequately performed.

The test batches used in the bioequivalence studies are manufactured according to the final manufacturing process. Similar comparative dissolution profiles in 0.1M HCl, pH 4.5, and 6.8 are provided for the test and reference batches equivalent to those used in the bioequivalence study. The choice of manufacturing process is justified by the adequate validation. The choices of the packaging are justified by the results of the stability studies.

Manufacturing process
The tablets are manufactured by a wet granulation process followed by drying, homogenisation with the disintegrant and lubricant, tabletting and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for on one full production scale batch and two pilot scale batches of common blend. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with their corresponding Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, friability, uniformity of dosage units, identity, related substances, assay, dissolution, residual solvents and microbiological quality. The release and shelf-life requirements 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 two batches from the proposed production site have been provided, demonstrating compliance with the specification.
Stability of drug product
Stability data on the product has been provided 15 batches stored at 25°C/60% RH (6 to 48 months), 30°C/65% RH (9 months) and 40°C/75% RH (3 to 6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed Alu/PVC blisters.
Under long term and intermediate storage conditions the drug product complies with the proposed specification, remains stable and no upward or downward trend for any of the tested parameters is observed. Under accelerated conditions the dissolution values of the 200 mg strength do not comply with the proposed acceptance limit. Therefore the proposed storage condition for both strengths of “Store below 30°C” is justified. The tablets are photostable. On the basis of the data submitted, a shelf-life was granted of 12 months for both the 200 mg strength and 800 mg strength tablet.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects
Based on the submitted dossier, the member states consider that Aciclovir Apotex 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 Aciclovir Apotex 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 Zovirax 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
Aciclovir 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 two bioequivalence studies, which are discussed below.
IV.2 Pharmacokinetics

Bioequivalence studies
The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Aciclovir Apotex 200 mg and 800 mg tablets (Apotex Europe BV, The Netherlands) is compared with the pharmacokinetic profile of the reference product Zovirax 200 mg (Glaxo Operations UK Ltd., United Kingdom or Glaxo Wellcome S.A., Spain) and 800 mg tablets (GlaxoSmithKline Ltd., United Kingdom).

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.

Bioequivalence study 1: 800 mg strength under fasting conditions

Design
A single-dose, open-label, laboratory-blind, randomised, two-treatment, two-sequence, two-period cross-over bioequivalence study was carried out under fasted conditions in 42 healthy male (n=30) and female (n=12) subjects, aged 18-53 years. Each subject received a single dose (800 mg) of one of the two aciclovir formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected before dosing and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

The design of the study is acceptable. A single-dose, crossover study under fasting conditions to assess bioequivalence is considered adequate since, according to the SmPC, lamivudine/zidovudine can be taken with or without food. The washout period 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
One subject was withdrawn from the study after period I due to an injury (non drug-related); no pharmacokinetic parameters were reported for this subject. Therefore, 41 subjects were eligible for pharmacokinetic analysis.

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

<table>
<thead>
<tr>
<th>Treatment N=41</th>
<th>AUC_{0-t} ng.h/ml</th>
<th>AUC_{0-\infty} ng.h/ml</th>
<th>C_{\text{max}} ng/ml</th>
<th>(t_{\text{max}}) h</th>
<th>(t_{1/2}) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>3647 ± 1139</td>
<td>3985 ± 1139</td>
<td>694 ± 235</td>
<td>1.33 (0.67 – 3.0)</td>
<td>7.88 ± 2.25</td>
</tr>
<tr>
<td>Reference</td>
<td>4033 ± 1364</td>
<td>4383 ± 1408</td>
<td>760 ± 275</td>
<td>1.67 (0.67 – 3.0)</td>
<td>7.89 ± 1.63</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)

|                | 0.91 (0.84 - 1.00) | 0.93 (0.86 - 1.01) | 0.91 (0.83 - 1.01) | --                   | --               |

\(AUC_{0-\infty}\) 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_{\text{max}} maximum plasma concentration
\(t_{\text{max}}\) time for maximum concentration
\(t_{1/2}\) half-life
CV coefficient of variation

*ln-transformed values
Bioequivalence study II: 200 mg strength under fasting conditions

Design
A single-dose, open-label, laboratory-blind, randomised, two-treatment, two-sequence, two-period cross-over bioequivalence study was carried out under fasted conditions in 44 healthy male (n=21) and female (n=23) subjects, aged 18-55 years. Each subject received a single dose (200 mg) of one of the two aciclovir formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected before dosing and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0 and 24.0 hours after administration of the products.

The design of the study is acceptable. A single-dose, crossover study under fasting conditions to assess bioequivalence is considered adequate since, according to the SmPC, lamivudine/zidovudine can be taken with or without food. The washout period 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
All 44 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_max (median, range)) of aciclovir under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_0-t (ng h/ml)</th>
<th>AUC_0-∞ (ng h/ml)</th>
<th>C_max (ng/ml)</th>
<th>t_max (h)</th>
<th>t1/2 (h)</th>
</tr>
</thead>
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<tr>
<td>Test</td>
<td>2448 ± 859</td>
<td>2560 ± 859</td>
<td>459 ± 180</td>
<td>1.5</td>
<td>6.50 ± 2.07</td>
</tr>
<tr>
<td>Reference</td>
<td>2431 ± 846</td>
<td>2530 ± 833</td>
<td>477 ± 185</td>
<td>1.4</td>
<td>6.69 ± 2.10</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cmax (ng/ml)</th>
<th>t_max (h)</th>
<th>t1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>0.99</td>
<td>1.04</td>
<td>--</td>
</tr>
<tr>
<td>Reference</td>
<td>0.99</td>
<td>1.04</td>
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</table>

*AUC_0-t: area under the plasma concentration-time curve from time zero to t hours
*AUC_0-∞: area under the plasma concentration-time curve from time zero to infinity
*C_max: maximum plasma concentration
*t_max: time for maximum concentration
*t1/2: half-life
*CV: coefficient of variation

Conclusion on bioequivalence studies
The 90% confidence intervals calculated for AUC_0-t, AUC_0-∞ and C_max are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Aciclovir Apotex is considered bioequivalent with Zovirax.

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

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Aciclovir Apotex.
Summary table of safety concerns as approved in RMP:

| Important identified risks | • Use in patients with renal impairment and in elderly patients  
|                           | • Interaction with probenecid, and mycophenolate mofetil  
|                           | • Interaction with theophylline  
| Important potential risks  | • Use in combination with nephrotoxic drugs  
|                           | • Prolonged treatment or repeated courses of aciclovir in severely immune-compromised individuals  
|                           | • Use during breast feeding  
| Missing information       | • Effects on human female fertility  
|                           | • Effects on ability to drive and use machines |

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 Zovirax. 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

The package leaflet has (PL) 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 two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Aciclovir Apotex 200 mg and 800 mg tablets has a proven chemical-pharmaceutical quality and is a generic form of Zovirax 200 mg and 800 mg tablets. Zovirax 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 Aciclovir Apotex with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 June 2017.
# STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

<table>
<thead>
<tr>
<th>Procedure number*</th>
<th>Scope</th>
<th>Product Information affected</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Summary/ Justification for refuse</th>
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