COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Aciclovir Accord 200 mg, 400 mg and 800 mg tablets
(aciclovir)

NL/H/5379/001-003/DC

Date: 24 June 2025

This module reflects the scientific discussion for the approval of Aciclovir Accord 200 mg, 400 mg and 800 mg tablets. The procedure was finalised on 10 April 2024. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Aciclovir Accord 200 mg, 400 mg and 800 mg tablets, from Accord Healthcare B.V.

200 mg and 400 mg tablets
The product is indicated for the treatment of infections of the skin and mucous membranes caused by the *herpes simplex* virus, including primary and recurrent genital herpes (apart from *herpes simplex* virus infections in neonates and severe *herpes simplex* virus infections in immunocompromised children).

The product is indicated for the suppression of recurrent infections (recurrence prevention) caused by the *herpes simplex* virus in immunocompetent patients.

The product is indicated for the prevention of infections caused by the *herpes simplex* virus in immunocompromised patients.

The product is indicated for the treatment of infections caused by the *varicella zoster* virus (chickenpox) and the *herpes zoster* virus (shingles).

800 mg tablets
Therapy of *herpes zoster* and *varicella* infections.
Prophylaxis of *herpes zoster* and *varicella zoster* in severely immunocompromised individuals.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Zovirax 200 mg, 400 mg and 800 mg tablets which has been registered in Austria by GlaxoSmithKline Pharma GmbH since 1985 (original product).

The concerned member states (CMS) involved in this procedure were Austria, Bulgaria (200 mg and 400 mg only), Croatia, Lithuania, Latvia and Poland.

II. QUALITY ASPECTS

II.1 Introduction

The three strengths can be distinguished by debossing of the tablets.

Aciclovir Accord 200 mg is a white to off-white, round, flat bevelled-edged tablet. It is debossed on one side with “LG1” and plain on the other side. The tablet contains as active substance 200 mg of aciclovir.

Aciclovir Accord 400 mg is a white to off-white, round, flat bevelled-edged tablet. It is debossed on one side with “LG” above and “2” below a break-line and plain on the other side. The tablets contains as active substance 400 mg aciclovir.

Aciclovir Accord 800 mg is a white to off-white, oval, biconvex tablet. It is debossed on one side with “LG” and “3” either side of a break-line and plain on the other side. The tablet contains as active substance 800 mg of aciclovir.

The excipients are: microcrystalline cellulose (PH 101) (E 460), sodium starch glycollate (Type A), povidone K25 (E1201), colloidal anhydrous silica, and magnesium stearate (E470b)

The three tablet strengths are dose proportional.

The tablets are packed in polyvinyl chloride/aluminium (PVC/Al) blister packs. The blisters are packed in carton.

II.2 Drug Substance

The active substance is aciclovir, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, crystalline powder and is slightly soluble in water. Aciclovir has no chiral centre and six polymorphic forms. For this product one polymorphic form is consistently produced.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph. Eur.

Manufacturing process

A CEP has been submitted; therefore, no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph. Eur. with additional requirements for microbial contamination and particle size. Batch analytical data demonstrating compliance with this specification have been provided for three full scale 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 development of the product has been described, the choice of excipients is justified and their functions explained. The choices of packaging and manufacturing process are adequately justified based on the dosage form. Comparative dissolution at three pHs has been studied in support of bioequivalence and the biowaiver of strengths. The QC dissolution method is acceptable and the discriminatory power has been demonstrated.
The optimal composition and manufacturing process parameters have been adequately investigated. The 400 mg and 800 mg tablets have a break-line. The pharmaceutical development of the product has been generally performed in an adequate manner.

Manufacturing process
The product is manufactured using conventional manufacturing techniques. The manufacturing process has been validated according to relevant European guidelines.
Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

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

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, assay, uniformity of dosage unit, loss on drying, disintegration time, dissolution, related substances, and microbial examination tests. The release and shelf-life specification are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from nine full scale batches (three for each strength) from the proposed production site has been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for six full scale batches and six bulk tablets stored at 25°C/ 60% RH (12 months) and 40°C/75% RH (6 months) in accordance with applicable ICH guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of three years for the final product and 12 months for the bulk tablets. No specific storage conditions needed to be included in the SmPC or on the label.

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 Accord 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 Accord is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was 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 was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states agreed that no further clinical studies are required, besides the two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Aciclovir 200 mg and 800 mg tablets (Accord-UK LTD., United Kingdom) was compared with the pharmacokinetic profile of the reference product Zovirax 200 mg and 800 mg (Glaxo Wellcome S.A., Spain).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition at pH 1.2, 4.5 and 6.8. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline. Dissolution similarity to the bio-batch strengths was demonstrated over the physiological pH range (1.2, 4.5 and 6.8). Therefore, the profiles can be considered as similar. As all conditions for the biowaiver criteria are met, a biowaiver for the remaining 400 mg strength has been granted.

Bioequivalence studies

Study 1 – Aciclovir 200 mg under fasted conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, balanced, open label bioequivalence study was carried out under fasted conditions. in 46 healthy male subjects, aged 19 - 44 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 of at least 10 hours. There were two dosing periods, separated by a washout period of four days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36 and 48 after administration of the products.

The design of the study is acceptable.

Aciclovir may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of aciclovir. 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.

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
46 subjects were enrolled in the study. 1 subject discontinued from the study on their own accord in period II. 45 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of aciclovir, 200 mg under fasted conditions.

Treatment N= 45	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	3121 ± 1017	3195 ± 1039	555 ± 215	1.50 (0.75 - 6.00)
Reference	3180 ± 1046	3264 ± 1063	565 ± 213	1.75 (0.75 - 4.00)
***Ratio (90% CI)**	0.98 (0.92 - 1.04)	0.98 (0.92 - 1.04)	0.98 (0.91 - 1.05)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 2 – Aciclovir 800 mg under fasted conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, balanced, open label bioequivalence study was carried out under fasted conditions in 70 healthy male subjects, aged 18 - 44 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 of at least 10 hours. There were two dosing periods, separated by a washout period of four days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 20, 24 and 36 hours after administration of the products.

The design of the study 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
70 subjects were enrolled in the study. 4 subjects discontinued from the study in period II, 3 due to protocol non-compliance and 1 of their own accord. 66 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of aciclovir, 800 mg under fasted conditions.

Treatment N= 45	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	4947 ±1809	5244 ± 1880	861 ± 329	1.75 (0.75 – 5.00)
Reference	4642 ± 1540	5023 ± 1657	816 ± 305	1.63 (0.50 – 4.00)
***Ratio (90% CI)**	1.06 (0.99 – 1.13)	1.04 (0.97 – 1.11)	1.05 (0.97– 1.13)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies 1 and 2:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies 1 and 2 Aciclovir Accord 200 mg and 800 mg are considered bioequivalent with Zovirax 200 mg and 800 mg.

The results of study 1 with 200 mg formulation can be extrapolated to other strength 400 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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

IV.3 Risk Management Plan

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

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	None.
Important potential risks	None.
Missing information	None.

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 two 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 (PL) 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 PL was English.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Aciclovir 200 mg, 400 mg and 800 mg tablets (PL 20416/0243-0245), Aciclvor Apotex 200 mg and 800 mg tablets (NL/H/3711/001-002/DC) and Solifenacin succinate 5 mg and 10 mg film-coated tablets (DK/H/2339/001-002/DC. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content (2) and layout (1) of the leaflet, respectively.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Aciclovir Accord 200 mg, 400 mg and 800 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Zovarix 200 mg, 400 mg and 800 mg tablets are 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 Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 April 2024.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5379/001-3/P/001	Art.61(3): Correct transcriptional error in section 3 of PIL	Yes	15-7-2024	Approved	N/A