COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Aciclovir Accord 25 mg/ml concentrate for solution for infusion

(aciclovir)

NL/H/4617/001/DC

Date: 18 October 2021

This module reflects the scientific discussion for the approval of Aciclovir Accord 25 mg/ml concentrate for solution for infusion. The procedure was finalised at 19 March 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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
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
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 25 mg/ml concentrate for solution for infusion from Accord Healthcare B.V.

The product is indicated for the treatment and prophylaxis of herpes simplex infections
- in patients undergoing bone marrow transplantations
- during remission-induction therapy of patients with acute leukaemia

The product is also indicated the treatment of
- primary and recurring varicella zoster infections in immunocompromised patients
- severe shingles (recurring varicella zoster infections) in patients with a normal immune response
- severe initial genital herpes
- Herpes simplex encephalitis
- Herpes neonatorum

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Zovirax powder for solution for infusion, 250 mg which has been registered in the Netherlands by GlaxoSmithKline B.V. since 4 January 1983.

The concerned member states (CMS) involved in this procedure were Austria, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Spain, Finland, France, Italy, Lithuania, Norway, Poland, Portugal, Romania, Sweden, and Slovenia.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, as the product is a concentrate for solution for infusion whereas the reference product is a powder for solution for infusion.

II. QUALITY ASPECTS

II.1 Introduction

Aciclovir Accord is a concentrate for solution for infusion.

The product is packed in 10 ml, 20 ml or 50 ml clear glass vials (with filling volumes of 10 ml, 20 ml and 40 ml respectively), rubber stopper and aluminium flip off seal. Each glass vial contains a clear, colorless or almost colorless solution with a pH value between 10.7 and 11.7. Each ml contains aciclovir sodium equivalent to 25 mg aciclovir.

Each vial of concentrate contains aciclovir sodium corresponding to 250 mg (10 ml vial), 500 mg (20 ml vial) or 1 g aciclovir (40 ml vial).

The excipients are sodium hydroxide (for pH adjustment), concentrated hydrochloric acid (for pH adjustment), and water for injection.

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 crystalline white or almost white powder, is slightly soluble in water, very slightly soluble in ethanol and practically insoluble in heptane.

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. It includes additional tests for impurities and residual solvents which are described in the CEP and additional tests for bacterial endotoxins and microbiological contamination. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
The active substance is stable for 60 months 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 excipients are commonly used for this dosage form. Essential similarity with the proposed drug product

and the reference product is demonstrated based on composition and evaluation of parameters as pH, assay, impurities, osmolality after dilution and osmolality of the undiluted concentrates.
The process development studies are presented in sufficient detail. Studies are performed about solubility of the active substance, optimization of pH of the solution, holding times, sterilization method selection, selection of kind of filters, tubing, stoppers, inert gas.
The provided justification and the choice for sterile filtration are considered adequate. Sufficient details about the filtration process and compatibility of the chosen filters with drug product have been provided.
A freeze-thaw study and a photostability study have been performed, showing that freeze-thaw cycles and light exposure do not affect the product's physical and chemical parameters.
The choice of container closure components is discussed, and the reports of closure integrity and delamination studies are included. Closure integrity studies at end of shelf life and extractables/leachables studies in presence of Drug product have been provided as well.

Dilution studies have been performed to substantiate the stability of the solution after dilution in the proposed dilution fluids. The SmPC reflects which plastic materials for administration are compatible (or not) with drug product as per pharmaceutical development. This is critical in view of the high pH of the solution, which could damage some plastic materials.
The results confirm stability up to 24 hours below 25°C. The proposed dilution fluids and instructions for dilution and administration are in line with those of the reference product (after reconstitution). However, as the stability after dilution is different from that of other similar authorized products, a warning is included in the SmPC to avoid medication errors in case of switch between products.

Manufacturing process

The manufacturing process consists of the steps: sterilization of containers and closures, preparation of bulk solution of aciclovir in water, pH adjustment, volume make up, pre-filtration and sterile filtration in line with filling and stoppering the vials. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale batches of each strength in accordance with the relevant European guidelines.

Control of excipients

All the excipients can refer to a Ph.Eur. monograph and are well-known excipients broadly used in similar pharmaceutical forms. 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, identity, assay, related substances, pH, extractable volume, particulate contamination, bacterial endotoxins, sterility, clarity and colour of solution, sodium content . The tests and specification at release and at end of shelf-life are indicated.

The proposed specifications at release and end of shelf life are acceptable. The analytical methods have been adequately described and validated.
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 three batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the finished product has been provided on nine (three per strength) full scale batches stored at 25°C/60% RH (up to 18 months) and 40°C/75% RH (up to 6 months). The batches were stored in the proposed packaging, inverted. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. The results show a trend of increase in the impurities results at accelerated conditions. Additional stability data at 30°C and 75% RH show out of specification results at 9 months for this sum of impurities as well. On basis of the data submitted, a shelf life was granted of 18 months. The labelled storage conditions are "store below 25°C".

Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature (20-25°C). From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. When dilution is carried out under validated aseptic conditions, the product may be stored for a maximum of 24 hours at room temperature, below 25°C.

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 hybrid 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 hybrid 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.

IV.2 Pharmacokinetics

Aciclovir Accord 25 mg/ml concentrate for solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Aciclovir Accord 25 mg/ml concentrate for solution for infusion is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

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 1. Summary table of safety concerns as approved in RMP

Important identified risks	--
Important potential risks	--
Missing information	--

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. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

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 the PL of Zovirax 250 mg powder for solution for infusion (content) and Mycophenolic acid 180 mg and 360 mg gastro-resistant tablets (ES/H/0183/001-002/DC)(design, lay-out and style of writing). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Aciclovir Accord 25 mg/ml concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a hybrid form of Zovirax powder for solution for infusion, 250 mg. Zovirax is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A biowaiver has been granted.

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 19 March 2020.

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