Bundesinstitut für Arzneimittel
und Medizinprodukte

Decentralised Procedure

Public Assessment Report

Aciclovir Agila 25mg/ml Pulver zur Herstellung einer Infusionslösung (Aciclovir Sodium Dihydrate)

DE/H/3554/001/DC

Applicant:
Agila Specialties UK Limited
New Bridge Street House
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London, EC4V 6BJ
United Kingdom

Reference Member State	DE

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Aciclovir Agila 25mg/ml Pulver zur Herstellung einer Infusionslösung
Name of the drug substance (INN name):	Aciclovir Sodium Dihydrate
Pharmaco-therapeutic group (ATC Code):	J05AB01
Pharmaceutical form(s) and strength(s):	Powder for solution for infusion, 25mg/ml
Reference Number(s) for the Decentralised Procedure	DE/H/3554/001/DC
Reference Member State:	DE
Concerned Member States:	AT; BE; DK; ES; FI; FR; IT; PL; SE; UK
Applicant (name and address)	Agila Specialties UK Limited New Bridge Street House 30-34 New Bridge Street London, EC4V 6BJ United Kingdom

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for Aciclovir Agila 25 mg/ml powder for solution for infusion in the treatment of

- Herpes simplex infections in immunocompromised patients and severe initial genital herpes in the non-immunocompromised;
- Herpes simplex infections in immunocompromised patients;
    - *Varicella zoster* infections;
- herpes encephalitis;
- Herpes simplex infections in the neonate and infant up to 3 months of age.

is approved.

II EXECUTIVE SUMMARY

II.1 Problem statement

This decentralised application concerns a generic version of aciclovir, under the trade name Aciclovir Agila 25mg/ml powder for solution for infusion.
With Germany as the Reference Member State in this Decentralized Procedure, Agila Speciality UK Limited is applying for the Marketing Authorisations for Aciclovir Agila 25mg/ml powder for solution for infusion in AT, BE, ES, FI, SE, FR, UK, DK, IT and PL.

II.2 About the product

Aciclovir is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against human herpes viruses, including Herpes simplex virus (HSV) types 1 and 2 and Varicella zoster virus (VZV), Epstein Barr virus (EBV) and Cytomegalovirus (CMV). In cell culture aciclovir has the greatest antiviral activity against HSV-1, followed (in decreasing order of potency) by HSV-2, VZV, EBV, and CMV.
The inhibitory activity of aciclovir for HSV-1, HSV-2, VZV and EBV is highly selective. The enzyme thymidine kinase (TK) of normal, uninfected cells does not use aciclovir effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV, VZV and EBV converts aciclovir to Aciclovir monophosphate, a nucleoside analogue, which is further converted to the diphosphate and finally to the triphosphate by cellular enzymes. Aciclovir triphosphate interferes with the viral DNA polymerase and inhibits viral DNA replication with resultant chain termination following its incorporation into the viral DNA.
The drug product is a powder for solution for intravenous infusion packaged in 10 ml or 20 ml glass vials with bromobutyl stoppers and aluminium seal containing Aciclovir in a concentration of 25 mg/ml.

II.3 General comments on the submitted dossier

This is an application according to Article 10(1) of 2001/83/EC as amended, for Aciclovir 25mg/mL Powder for Solution for Infusion [10mL & 20mL] referring to the reference medicinal product ”Zovirax I.V. [250mg & 500mg]”, approved on the 6th of April 1982 for The Wellcome Foundation Ltd., trading as GlaxoSmithKline UK.
As this is a generic application for a parenteral aqueous solution no bioequivalence study is required.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
No clinical or bioequivalence studies have been conducted with the product under review.

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug Substance

The drug substance Aciclovir sodium dihydrate is not official in any of the pharmacopoeia. The quality of the drug substance is described via an Active Substance Master File. Letters of access and written confirmations are given. The manufacturing process of the drug substance (including synthesis, purification, amounts of raw materials and yields) is adequately described. The structure of the substance is sufficiently characterised. Potential impurities (related substances, residual solvents, etc.) arising from the manufacturing process are identified. The drug substance specification provided complies with the Ph. Eur. monograph "Aciclovir" except for any single unknown impurity. Additional requirements for residual solvents are set. Batch analysis results showing the compliance with the drug substance specification are given. Based on the provided stability results over 6 months at accelerated and over 18 months at normal conditions the proposed re-test period of 2 years without storage precaution is justified.

Drug Product

The product is presented as a powder for solution for infusion, which contains Aciclovir sodium dihydrate (corresponding to 25 mg/ml Aciclovir). The product is packaged in 10 or 20 ml glass vials with bromo butyl stoppers and aluminium seal. Compatibility studies after reconstitution and dilution show that the product is compatible up to 24 hours at 25°C with 0.9% Sodium chloride solution, with 5% Dextrose and Sodium lactate solutions. The manufacturing and sterilisation processes including flow chart, in-process controls and critical steps are described in detail. Process validation data for two exhibit batches for each of the packaging sizes including critical process steps and parameters like preparation of the solution, sterile filtration, sterilisation of container/closure, filling steps and lyophilisation are provided. The proposed release and shelf life specifications contain the quality relevant characteristics required for this pharmaceutical form. The descriptions of the in-house methods are satisfactorily. Appropriate validation data for assay, related substances, sterility and LAL testing are provided. Batch analysis results of two pilot batches for each of the packaging sizes are provided showing compliance with the set specifications.
Based on the provided stability results of two pilot batches for each of the packaging sizes stored 12 months at 25°C±2°C/60%±5%RH and 6 months at 40°C±2°C/75%±5%RH a shelf life of 24 months without storage precaution is approved. A photostability study was performed demonstrating that the drug product is not sensitive to light. The reconstitution study supports an in-use shelf life of the reconstituted solution in water for injections and 0.9% sodium chloride of 12 h at 25°C.

III.2 Non-clinical aspects

There are no objections to approval of Aciclovir Agila 25 mg/ml powder for solution for infusion from a non-clinical point of view.

III.3 Clinical aspects

The applicant has not submitted any clinical studies.
According to the regulatory requirements, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, Guideline on the Investigation of Bioequivalence, Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product and the applicant has not submitted any. So it is plausible and acceptable that no clinical or bioequivalence studies have been conducted with the product under review.
All clinical information is provided and is literature based.
No new safety data have been submitted.

Pharmacovigilance system (DDPS)
The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System and asked the RMS to replace the previously submitted DDPS with the new Summary of Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS accepts this substitution.

Risk Management Plan

Summary of safety concerns	
Important identified risks	1. Blood dyscrasias 2. Hypersensitivity reactions Use in patients with renal impairment and in elderly patients 4. Interaction - Probenecid and cimetidine 5. Interaction – Lithium 6. Interaction - Theophylline
Important potential risks	Nephrotoxicity associated with dehydration 2. Nephrotoxicity associated with drugs which affect other aspects of renal physiology (e.g. ciclosporin, tacrolimus)
Important missing information	1. Fertility Effects on ability to drive and use machines

The Applicant has provided an RMP within the new format of GVP module V. The Applicant has generated a list of important safety concerns (i.e. important identified risks, potential risk and missing information) based on information provided in sections 4.3-4.6 of the SmPC with no additional risk minimisation measures and no need for additional pharmacovigilance measures.

Periodic Safety Update Report (PSUR)
The Applicant should provide PSURs only in the case this is required according to the published EURD-List.
The Applicant will comply with any outcome of the PSUR Worksharing procedure for Aciclovir and confirmed that additional safety information contained in the agreed core safety profile (CSP) and currently not included in the product information will be added to the product information via variation procedure.

IV BENEFIT RISK ASSESSMENT

Aciclovir for systemic use is well-established with an acceptable and recognised efficacy and safety profile for indications approved for the reference product. As this is a generic application for a parenteral aqueous solution no bioequivalence study is required.
Based on the review of the data on quality, safety and efficacy, the application for Aciclovir Agila 25 mg/ml powder for solution for infusion in the treatment of

- Herpes simplex infections in immunocompromised patients and severe initial genital herpes in the non-immunocompromised;
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- herpes encephalitis;
- Herpes simplex infections in the neonate and infant up to 3 months of age.

is approved.
For intermediate amendments see current product information.