IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Aciclovir 25mg/ml Concentrate for solution for infusion
ACICLOVIR
PA2299/041/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

This product was initially authorised under procedure number UK/H/1977/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 05/12/2018 under procedure number IE/H/0869/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA2299/041/001
Marketing Authorisation Holder: Baxter Holding BV

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the application for Aciclovir 25 mg/ml Concentrate for solution for infusion in the treatment of the following indications could be approved.

- severe initial genital herpes in the immunocompromised and the non-immunocompromised.
- for the prophylaxis and treatment of Herpes simplex infections in immunocompromised patients.
- shingles (Varicella zoster virus) in immunocompetent patients in whom a serious course of the illness can be anticipated.
- initial and recurrent Varicella zoster infections in immunocompromised patients.
- herpes encephalitis.
- Herpes simplex infections in the neonate and infant up to 3 months of age.

This is an abridged complex application submitted under Article 10(3) of Directive 2001/83/EC as amended (hybrid application). This product is claiming to be generic medicinal product of Zovirax I.V. 250 mg and Zovirax IV 500 mg injection (PL 00003/0159), which was first licensed in the UK to The Wellcome Foundation Ltd on 6th April 1982.

With UK as the RMS in this Decentralised Procedure (UK/H/1977/001/DC), Claris Lifesciences UK Limited applied for the Marketing Authorisation for Aciclovir 25 mg/ml Concentrate for solution for infusion in Estonia, Luthuania, Republic of Ireland and The Netherlands.

Aciclovir is a synthetic acyclic purine nucleoside analogue (ATC J05A B01) with *in vitro* and *in vivo* inhibitory activity against human Herpes viruses, including Herpes simplex virus 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 needs to be phosphorylated to the active compound aciclovir triphosphate, in order to become active against the virus. Aciclovir triphosphate acts as an inhibitor of, and a substrate for, the herpes specified DNA polymerase preventing further viral DNA synthesis.

No new clinical or non-clinical studies were conducted, which is acceptable given that the application was based on being a hybrid medicinal product of the originator product that has been licensed for over 10 years. The product is to be administered as aqueous intravenous solutions containing the same active substance in the same concentration as the currently

authorised reference product. Thus, in accordance with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98Rev 1**), the applicant was not required to submit bioequivalence studies for this application.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within and outside 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.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. Suitable justification has been provided for the non-submission of a Risk Management Plan.

All member states agreed to grant a licence for the above product at the end of the procedure (Day 210 – 19th December 2012). After a subsequent national phase, the UK granted a licence for this product on 25th January 2013 (PL 20568/0029).

II. QUALITY ASPECTS

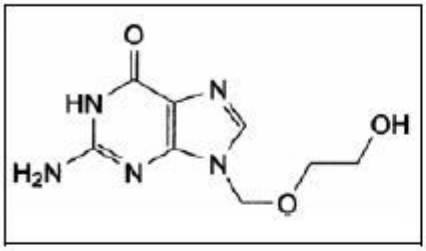
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Aciclovir sodium
Chemical Names: 2-amino-9-[(2-hydroxyethoxy) methyl]-1,9-dihydro-6*H*-purin-6-one

Structure:



Molecular formula: $C_8H_{11}N_5O_3$

Molecular weight: 225.2

Physical form: A white to almost white, crystalline powder.
Solubility: Slightly soluble in water, freely soluble in dimethyl sulphoxide, very slightly soluble in ethanol (96 %). It dissolves in dilute solutions of mineral acids and alkali hydroxides.

Aciclovir sodium is the subject of a European Pharmacopoeia monograph.

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

DRUG PRODUCT

Other Ingredients
Other ingredients consist of the pharmaceutical excipients hydrochloric acid, sodium hydroxide and water for injections.

All excipients comply with the relevant European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for these excipients.

The above excipients do not contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development
The objective of the pharmaceutical development programme was to obtain a stable product containing aciclovir sodium that could be considered a hybrid medicinal product of Zovirax I.V. 250 mg and Zovirax IV 500 mg injection (The Wellcome Foundation Ltd).

Suitable pharmaceutical development data have been provided for this application.

Comparative impurity profiles have been provided for the proposed and originator products.

Manufacture
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Satisfactory process validation data on pilot-scale batches have been provided. The applicant has committed to perform process validation on future commercial-scale batches.

Finished Product Specifications
The finished product specification is satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The finished product is supplied in glass vials with Teflon coated rubber stopper and flip-off seal. The pack sizes are 5, 10, 20 x 10ml and 20 x 20ml.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with relevant guidelines.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf life of 24 months for unopened vials with storage conditions 'Keep this medicine out of the sight and reach of children', 'Do not store this medicine above 25°C' 'Do not refrigerate' and 'Store in the original carton in order to protect from light' are set. These are satisfactory.

After dilution: Chemical and physical in-use stability has been demonstrated for 12 hours at 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.

Bioequivalence/bioavailability
No bioequivalence studies have been submitted and none are required to support an application of this type.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SPC, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the package leaflet contains.

The Marketing Authorisation holder has stated that not all pack sizes may be marketed. They have committed to get the mock-ups approved for unmarketed pack sizes before those packs are commercially marketed.

Marketing Authorisation Application (MAA) Form
The MAA form is pharmaceutically satisfactory.

Expert Report
A pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical point of view.

III. NON-CLINICAL ASPECTS

III.2 NON-CLINICAL ASPECTS
PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY

The pharmacological, pharmacokinetic and toxicological properties aciclovir sodium is well-known.

No new non-clinical data have been supplied with this application and none are required for applications of this type. The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Suitable justification has been provided for the non-submission of an environmental risk assessment.

There are no objections to the approval of this product from a non-clinical point of view.

IV. CLINICAL ASPECTS

III.3 CLINICAL ASPECTS

In accordance with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), a bioequivalence study is not requested if the test product is an aqueous intravenous solution containing the same active substance as the reference product. No bioequivalence study has been submitted with this application and none is required.

No new data have been submitted and none are required for applications of this type.

Pharmacodynamics

No new data have been submitted and none are required for applications of this type.

Clinical efficacy

No new data have been submitted and none are required for applications of this type.

Clinical safety

Aciclovir sodium has an acceptable adverse event profile. No new safety data were supplied or required for this hybrid application. Aciclovir sodium has a well-established side-effect profile and is generally well-tolerated.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling

The SmPC, PIL and labelling are satisfactory from a clinical perspective and consistent with those for the reference product.

Clinical Expert Report

The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Marketing Authorisation Application (MAA) Form

The MAA form is satisfactory from a clinical perspective.

Clinical Conclusion

There are no objections to the approval of this product from a clinical point of view.

V. OVERALL CONCLUSIONS

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Aciclovir 25 mg/ml Concentrate for solution for infusion 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 non-clinical data were submitted and none are required for applications of this type.

EFFICACY

No new efficacy data were submitted and none are required for applications of this type. As the safety profile of aciclovir sodium is well-known, no additional data were required.

SAFETY

No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory.

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 aciclovir sodium is considered to have demonstrated the therapeutic value of the compound. The benefit-risk balance is therefore considered to be positive.

VI. REVISION DATE

25/02/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/1977/1/DC to IE/H/0869/1/DC			