IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Aciclovir 200mg/5ml Oral Suspension
ACICLOVIR
PA22697/001/001

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.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/5752/1-2/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 04/09/2018 under procedure number IE/H/0743/1-2/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA22697/001/001-002
Marketing Authorisation Holder: SYRI Limited, t/a Thame Laboratories

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 UK and Ireland considered that the applications for Aciclovir 200mg/5ml and 400mg/5ml Oral Suspension (PL 39307/0034-0035; UK/H/5752/001-002/DC) could be approved. The products may be referred to as 'Aciclovir Oral Suspension' in this report.

The products are Prescription Only Medicines (POM) and are 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)
- suppression (prevention of recurrences) of recurrent herpes simplex infections in immunocompetent patients
- prophylaxis of herpes simplex infections in immunocompromised patients
- treatment of varicella (chickenpox) and herpes zoster (shingles) infections.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Ireland as Concerned Member State (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Zovirax 200mg/5ml Oral Suspension (GlaxoSmithKline, Ireland) and Zovirax Double Strength 400mg/5ml Suspension (Zovirax), which were authorised in Ireland on 24 March 1986 and 27 February 1991, respectively. The corresponding reference products in the UK are Zovirax 200mg/5ml Oral Suspension (PL 0003/0202; GlaxoSmithKline, UK) and Zovirax Double Strength 400mg/5ml Suspension (PL 00003/0264; GlaxoSmithKline, UK), which were first authorised in the UK on 18 October 1984 and 15 December 1989, respectively.

The active ingredient, aciclovir, is a synthetic acyclic purine nucleoside analogue 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). The enzyme thymidine kinase (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 acts as an inhibitor of, and a substrate for, the herpes specified DNA polymerase preventing further viral DNA synthesis.

No new non-clinical studies were performed, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

A bioequivalence study was submitted to support the applications comparing the applicant's test product Aciclovir Oral Suspension, 400mg/5ml (Syri Limited, trading as Thame Laboratories, UK) and the reference product Zovirax Double Strength 400mg/5ml (GlaxoSmithKline, UK) Suspension under fasting conditions. The applicant has stated that the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. 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.

The UK and Ireland considered that the applications could be approved at the end of procedure (Day 210) on 17 April 2016. After a subsequent national phase, licences were granted in the UK on 13 May 2016 to Syri Limited trading as Thame Laboratories.

II. QUALITY ASPECTS

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II.1 Introduction

The submitted documentation concerning the proposed products is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The products are white to off-white uniform oral suspensions with orange and vanilla odour.

Each 5ml of Aciclovir 200mg/5ml Oral Suspension contains 200mg of aciclovir, as the active substance.

Each 5 ml of Aciclovir 400mg/5ml Oral Suspension contains 400mg of aciclovir, as the active substance.

The products also contain xanthan gum (E415), sorbitol liquid (non-crystallising; E420), methyl parahydroxybenzoate (E218), orange flavour (containing propylene glycol (E1520)), vanilla flavour (containing propylene glycol (E1520)) and purified water. Appropriate justification for the inclusion of each excipient has been provided.

The products are available in Type II amber glass bottles, each with a tamper evident, child resistant, plastic (polypropylene/polyethylene) cap with expanded polyethylene liner. The products are supplied with a dosing device: a double ended white polypropylene plastic spoon with 2.5ml and 5ml measuring ends.

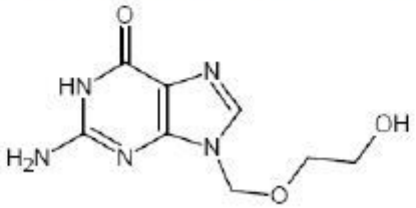
The products are available in a pack size of 100 ml (400mg/5ml strength only) and 125 ml (200mg/5ml strength only).

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with parenteral products.

II.2 DRUG SUBSTANCE

Aciclovir

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



Molecular formula:	$C_8H_{11}N_5O_3$
M_r:	225.2
Appearance:	White or almost white crystalline powder.

7

Solubility:	Slightly soluble in water, very slightly soluble in ethanol (96%), practically insoluble in heptane. It dissolves in dilute solutions of mineral acids and alkali hydroxides.
Polymorphism	Aciclovir does not exhibit polymorphism.

Aciclovir is the subject of a European Pharmacopoeia monograph.

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

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to produce safe, efficacious, stable oral suspensions that were equivalent to the reference products Zovirax 200mg/5ml Oral Suspension (GlaxoSmithKline) and 400mg/5ml Oral Suspension (GlaxoSmithKline). Suitable pharmaceutical development data have been provided for these applications.

With the exception of orange flavour (containing propylene glycol (E1520)) and vanilla flavour (containing propylene glycol (E1520)), all excipients comply with their respective European Pharmacopoeia monographs. Certificates of Analysis have been provided for all excipients, showing compliance with their respective specifications.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full production-scale batches that have shown satisfactory results.

Control of Finished Product

The finished product specifications are acceptable. Test methods have been described that have been validated adequately. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 18 months for the unopened product and 30 days once the product has been opened, with the special storage conditions "Do not store above 25°C. Do not refrigerate or freeze." have been approved.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that Marketing Authorisations are granted for Aciclovir Oral Suspension.

III. NON-CLINICAL ASPECTS

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of aciclovir are well-known, no new non-clinical data have been submitted and none are required.

The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

No new data have been submitted and none are required for applications of this type. Refer to Section III.1 Introduction, above.

III.3 Pharmacokinetics

No new data have been submitted and none are required for applications of this type. Refer to Section III.1 Introduction, above.

III.4 Toxicology

No new data have been submitted and none are required for applications of this type. Refer to Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion of the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of reference products that have been licensed for over 10 years.

It is recommended that Marketing Authorisations are granted for Aciclovir Oral Suspension, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of aciclovir is well-known.

In accordance with the regulatory requirements CPMP/EWP/QWP/1401/98 Rev 1/Corr**, Guideline on the Investigation of Bioequivalence, the Marketing Authorisation Holder submitted the results from a bioequivalence study to support these generic applications.

With the exception of data from the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

IV.2 Pharmacokinetics

The pharmacokinetic properties of aciclovir are well known.

In support of the applications, a bioequivalence study was submitted. Details of the study are provided below.

A randomised, open-label, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study comparing the pharmacokinetics of the applicant's test product Aciclovir Oral Suspension, 400mg/5ml (Syri Limited, trading as Thame Laboratories, UK) and the reference product Zovirax Double Strength Suspension 400mg/5ml (GlaxoSmithKline UK) in normal, healthy, adult, male and female human subjects under fasting conditions.

The subjects were administered a single dose [800mg (10ml)] of either the test or the reference product with 240±2ml of water, after at least a 10-hour overnight fast. Blood samples were collected before and up to and including 24 hours after each administration. The washout period between the treatment phases was 7 days. The statistical results for primary pharmacokinetic parameters of aciclovir are summarised below:

Table of Geometric Means and 90% Confidence Interval for Aciclovir

Parameters	*Geometric mean		% Ratio	90 % Confidence Interval for	
	Test (A)	Reference(B)	A/B	Lower Limit	Upper Limit
AUC_{0-t}	4811.07	4829.39	99.6207	91.8365	108.0647
C_{max}	894.22	855.31	104.5492	95.7719	114.1309

**Geometric mean was taken as the antilog (exponential) of the Least square mean of the log-transformed data.*

C_{max} maximum plasma concentration
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
Ratios and 90% CI calculated from ln-transformed data

The 90% confidence intervals of the test/reference ratio for C_{max} and AUC_{0-t} values lie within the acceptable limits of 80.00% to 125.00%, in line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**). Thus, the data support the claim that 10 ml of the applicant's 400mg/5ml test product is bioequivalent to the 10 ml of the reference product, Zovirax Double Strength Suspension 400mg/5ml (GlaxoSmithKline UK), under fasting conditions.

As the 200mg/5ml and 400mg/5ml strength suspensions of the test product meet the criteria for a biowaiver specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the results and conclusions from the bioequivalence study with the 400mg/5ml strength suspensions can be extrapolated to the 200mg/5ml strength suspension.

IV.3 Pharmacodynamics

The clinical pharmacodynamic properties of aciclovir are well-known. No new pharmacodynamics data were submitted and none are required for applications of this type.

IV.4 Clinical Efficacy

The clinical efficacy of aciclovir is well-known. No new efficacy data are presented or are required for applications of this type.

IV.5 Clinical Safety

The safety profile of aciclovir is well known. No new safety data have been submitted with these applications and none are required. No new or unexpected safety concerns arose from these applications.

IV.6 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 Oral Suspension.

A summary of safety concerns is listed in the table below:

Summary of safety concerns	
Important identified risks	• Hypersensitivity • Renal impairment (especially in elderly) • Resistance in immuno-compromised patients • Break-through infections in immuno-competent patients • Use in patients with fructose intolerance • Hepatitis • Neurological side effects in elderly patients and patients with renal impairment
Important potential risks	• Safety in lactate
Missing information	• Use in immuno-competent children • Use in chickenpox immuno-competent patients • Effects on fertility • Use in pregnancy

Routine pharmacovigilance and routine risk minimisation activities are acceptable to monitor the safety concerns described in the Risk Management Plan.

IV.7 Discussion of the clinical aspects

It is recommended that Marketing Authorisations are granted for Aciclovir Oral Suspension.

V. USER CONSULTATION

A package leaflet has been evaluated for Aciclovir Oral Suspension via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC as amended. The language used for the purpose of user testing the package leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

V. OVERALL CONCLUSIONS

IV OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The important quality characteristics of Aciclovir Oral Suspension 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 new non-clinical data were submitted and none are required for applications of this type.

EFFICACY

The 90% confidence intervals of the test/reference ratio for C_{max} and AUC_{0-t} values lie within the acceptable limits of 80.00% to 125.00%, in line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**). Thus, the data support the claim that 10 ml

of the applicant's 400mg/5ml test product is bioequivalent to 10 ml of the reference product, Zovirax Double Strength Suspension 400mg/5ml (GlaxoSmithKline UK), under fasting conditions.

As the 200mg/5ml and 400mg/5ml strength suspensions of the test product meet the criteria for a biowaiver specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the results and conclusions from the bioequivalence study with the 400mg/5ml strength suspensions can be extrapolated to the 200mg/5ml strength suspension.

SAFETY

The safety profile of aciclovir is well-known. No new or unexpected safety issues or concerns arose from these applications.

PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference products and in line with current guidance.

BENEFIT/RISK ASSESSMENT

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. aciclovir is a well-known active substance. Extensive clinical experience with aciclovir 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/5752/1-2/DC to IE/H/0743/1-2/DC			