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Public Assessment Report

Scientific discussion

Aciclovir Pharmconsul 50 mg/g
Aciclovir

National procedure

Date: 15.11.2024

This module reflects the scientific discussion for the approval of Aciclovir Pharmconsul 50 mg/g. The procedure was finalised at 07.11.2024. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the State Institute for Drug Control, Slovakia, has granted a marketing authorisation for Aciclovir Pharmconsul 50 mg/g, cream, from Pharmconsul s. r. o., Praha, Czech Republic.

The product is indicated for adults, adolescents and children for the treatment of Herpes simplex virus infections manifesting as cold sores on the lips and face.
A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) hybrid application of Directive 2001/83/EC."

II. QUALITY ASPECTS

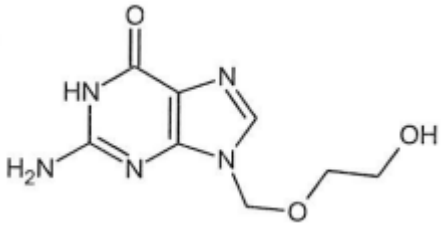
II.1 Introduction

The dosage form of the drug product is a cream which contains aciclovir as active substance in amount of 50 mg/g.
All excipients used in the formulation comply with the European Pharmacopoeia.
Aciclovir Pharmconsul 50 mg/g, cream is packed in laminated tube with HDPE screw cap. The approved package size is 10 g. The microbiological quality control is accepted as it follows the requirements of Ph. Eur. 5.1.4.

II.2 Drug Substance

The active substance is aciclovir.
Chemical name: 2-Amino-9-[(2-hydroxyethoxy)methyl]-1,9,-dihydro-6H-purin-6-one.

Structural Formula:

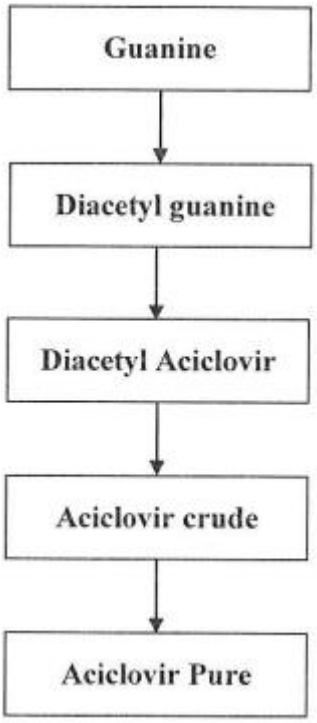


Molecular Formula: $C_8H_{11}N_5O_3$

Aciclovir is white or almost white crystalline powder, slightly soluble in water. It dissolves in diluted solutions of mineral acid and alkali hydroxides.
Aciclovir produced by Mylan Laboratories Limited is the crystalline form.
There are no chiral centers in Aciclovir and hence no stereo isomers and present. Since Aciclovir is optically inactive, no optical isomers are present.

Manufacturing process:

- Flow diagram



Mylan Laboratories Limited is the holder of CEP certificate (CEP 1998-029) for aciclovir .

Stability test was performed at Mylan Laboratories Limited, Unit-7.
There is no significant change in the impurity profile and other physical and chemical parameters at the end of 6 months.
The product meets its pre-determined specifications at the end of 60 months without any significant change in the impurity profile and other physical and chemical parameters. Based on the available stability data, a re-test period of five years is established to the drug substance.

The specification and analytical procedures of aciclovir are in compliance with the Ph. Eur. monograph for aciclovir and general requirements of Ph. Eur.
The requirements included in the specification of aciclovir guarantee appropriate quality for preparation of the drug product.

II.3 Medicinal Product

Pharmaceutical development
The aim of formulation development was to formulate Aciclovir cream 5% w/w, that is robust, stable and equivalent to Zovirax cream 5% w/w marketed by GlaxoSmithKline, which is used as reference product for comparison and developmental studies. Product development was carried out with Aciclovir cream 5 % w/w. All the critical process parameters identified at development stage were confirmed and proved that the process is capable of producing a drug product of the required quality with the proposed process and product parameters.

Excipients selected are common excipients used in cream formulation of the innovator product. The active substance was studied for compatibility with the chosen excipients. The results indicated that there was no interaction between the active substance and chosen excipients and thus the product was found to be stable and compatible with excipients under the conditions of stability.

Composition of the drug product

Ingredients	Specifications	Functions of components
Cetostearyl alcohol	Ph.Eur.	Cream base
Sodium laurylsulfate	Ph.Eur.	Surfactant
White soft paraffin	Ph.Eur.	Cream base
Liquid Paraffin	Ph.Eur.	Emollient
Propylene glycol	Ph.Eur.	Solvent
Purified water	Ph Eur.	Solvent
Sorbitan monostearate	Ph.Eur.	Surfactant
Aciclovir	Ph.Eur.	Active substance

Manufacturing Process

The manufacturing process consists of the following steps:

- Aqueous phase preparation
- Oil phase preparation
- Manufacturing of cream preparation
- Homogenization
- Filling and packaging

Stability

Long-term stability studies were carried out on the finalised formulation packed in a laminated tube with a plastic screw cap. Based on the long-term stability data it can be concluded that the product is stable for 36 months which corresponds to the shelf life of the finished product. Shelf life after first opening is 15 days which is based on the data obtained in the in-use stability study. The approved storage conditions are: Store below 25°C. Do not refrigerate.

Container Closure System

The cream is packed in a laminated tube with a plastic screw cap. The packaging materials are obtained from reliable, qualified suppliers. Results of stability studies confirm suitability of chosen primary packaging materials.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture, control of the active substance and finished product has been satisfactorily presented. The results of tests indicate satisfactory consistency and uniformity of the drug product characteristics and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinical setting.

The quality of the product is considered acceptable when used in accordance with the conditions defined in the SmPC.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of aciclovir are well known. As aciclovir is a widely used, well-known active substance, the Applicant has not provided

additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Aciclovir Pharmconsul 50 mg/g is intended to substitute other identical products on the market, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

Submitted non-clinical data are adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is a national application according to Article 10 (3) of Directive 2001/83/EC – hybrid application. The clinical overview on the clinical pharmacology, efficacy and safety was adequate. The indications given in the proposed SmPC were in line with the SmPC of the reference product.
Aciclovir is a synthetic purine nucleoside analogue, an antiviral agent which is highly active in vitro against herpes simplex virus (HSV) types I and II and varicella zoster virus.

The pharmacological properties as well as safety and efficacy information were documented and the facts were supported by appropriate literature references.

IV.2 Pharmacokinetics

Pharmacology studies from literature references have shown only minimal systemic absorption of aciclovir following repeated topical administration.
There were no drug interactions reported.
The drug is excreted primarily by the kidney.
All the added inactive agents are well known ingredients and do not have any effect of the pharmacokinetic as well as pharmacological properties of the active ingredient i.e. aciclovir when used in the permissible limits as per the guidelines and pharmacopeia specifications.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Dermatologicals; chemotherapeuticals for topical use; antivirals.
ATC code: D06BB03 – aciclovir.

Aciclovir is an antiviral agent only after it is phosphorylated in infected cells by a viral-induced thymidine kinase. Aciclovir monophosphate is phosphorylated to diphosphate and triphosphate forms by cellular enzymes in the infected host cell where the drug is concentrated. Aciclovir triphosphate inactivates viral deoxyribonucleic acid polymerase. Aciclovir incorporation into the growing viral deoxyribonucleic acid chain causes its termination. The antiviral process has relatively little effect on normal, uninfected cells.

IV.4 Clinical efficacy

The applicant did not present own clinical studies to determine efficacy and safety of aciclovir.

In different clinical trials, Aciclovir 5 % w/w cream compared with placebo and other therapeutic drugs as well as different dosage regimen of aciclovir has been shown to be effective in the treatment of Herpes Simplex virus infections of the skin including initial and recurrent genital herpes and herpes labialis.

IV.5 Clinical safety

Aciclovir was approved for human use in 1981 and is being used as antiviral agent and is on the World Health Organization's List of Essential Medicines.

Aciclovir is well tolerated and has a low incidence of side effects, mostly hypersensitivity and localised actions side effects due to its topical use and less systemic exposure.

Applicant submitted sufficient amount of data from the referenced studies and other products available on the market to support the claim that the safety of the proposed product is acceptable to grant the marketing authorisation.
All relevant safety issues and adverse events has been listed in the proposed SmPC and PIL.

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 Pharmconsul 50 mg/g.

Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risk	None
Missing information	None

Pharmacovigilance Plan
Routine pharmacovigilance was suggested and no additional pharmacovigilance activities were proposed by the Applicant, which was endorsed.

Risk minimisation measures
Routine risk minimisation measures were considered satisfactory to minimise the risks of this medicinal product.

The MAH is responsible for closely monitoring any adverse reaction that may involves a change in the risk/benefit ratio of this medicinal product and will update the Core RMP, and where appropriate the Core SmPC/PIL, to reflect the findings.

IV.7 Discussion on the clinical aspects

Submitted clinical data are adequate to support the indication “cold sores on the lips and face caused by the Herpes simplex virus in the stage of itching, burning or blistering”.

V. USER CONSULTATION

The package leaflet 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 PIL 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.

The test consisted of a pilot test with two participants, followed by two rounds with ten participants each. A questionnaire consisted of 12 questions dealing with the key safety issues. The technical readability, comprehensibility of the text, traceability of information and the applicability were investigated in the test.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk assessment is considered positive.
The dossier is generally well presented and all processes appear to be well controlled. The application is acceptable from the quality perspective.
There are no objections to the dossier of Aciclovir Pharmconsul 50 mg/g from a non-clinical point of view. From the clinical perspective, submitted clinical data are adequate to support the indication.
SmPC, PIL and labelling are satisfactory.