THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR ACLOHERP 400 (ACICLOVIR 400 MG) TABLETS

Version number 0.1
21 August, 2023

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1. Introduction

ACLOHERP 400 tablets is a generic medicinal product containing the active substance Aciclovir. The originator product is “Zovirax 400 mg tablets” by GlaxoSmithKline. 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 I and II and varicella zoster virus (VZV). The inhibitory activity of aciclovir for HSV I, HSV II and VZV is highly selective. The enzyme thymidine kinase (TK) of normal, uninfected cells does not use aciclovir effectively as a substrate, hence toxicity of mammalian host cells is low; however, TK encoded by HSV and VZV 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. ACLOHERP 400 tablets is approved in Tanzania for use in adults and children (≥2 years).

Product details

Registration number	TAN 23 HM 0288
Brand name	ACLOHERP 400
Generic name, strength, and form	Each uncoated tablet contains Aciclovir 400 mg
ATC classification	Direct acting antivirals, Nucleosides and nucleotides excl. reverse transcriptase inhibitors. ATC code: J05AB01
Distribution category	POM
Country of origin	India
Associated product	ACLOHERP 200
Marketing Authorization Holder	Aurobindo Pharma Limited Plot No.2, Maitrivihar, Ameerpet, Hyderabad, Zip Code: 500 038, Telangana State. India
Local Technical Representative	M/s Generics & Specialities Limited Plot No 478 & 479, Zahara Towers Mindu Street, Upanga, Dar es Salaam

1.1 Assessment procedure

The application for registration of ACLOHERP 400 was submitted on 18/10/2021. The product underwent full assessment. Assessment was completed in 3 (three) rounds of evaluation and the product was registered on 01/06/2023.

1.2 Information for users

Visual description of the finished product	White to off-white, round, biconvex, uncoated tablets debossed with ‘AR and 400’ separated with breakline on one side and plain on the other side
Primary packing material	Clear PVC - Aluminum foil blister pack

Secondary packing materials	Printed carton box
Shelf-life and storage condition	24 months, Do not store above 30 °C.
Route of administration	Oral
Therapeutic indications	Aciclovir Tablets 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). Aciclovir Tablets are indicated for the suppression (prevention of recurrences) of recurrent herpes simplex infections in immunocompetent patients. Aciclovir Tablets are indicated for the prophylaxis of herpes simplex infections in immunocompromised patients. Aciclovir Tablets are indicated for the treatment of varicella (chickenpox) and herpes zoster (shingles) infections (excluding neonatal HSV and severe HSV infections in immunocompromised children).

2. Labelling and product information

Summary of product characteristics
The SmPC included all the relevant information to ensure correct and safe use of the medicine by healthcare providers. The complete SmPC can be accessed here.

Package insert/leaflet
The package insert is confirmed to be derived from the SmPC and contains sufficient data for the end user. Since the product is POM, the package insert contains full prescribing information as per SmPC.

Container labels
The product label information is presented in English. Details in the secondary pack label include:

Brand name: ACLOHERP 400

Composition: Each uncoated tablet contains Aciclovir 400 mg

Pack size: 2x5 tablets

Manufacturing details: batch number, manufacturing date, and expiry date

Storage conditions: Do not store above 30 ^{o}C.

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Refer the pack insert (please read the accompanying instructions before use)

The details of the primary pack include:

Brand name and strength: ACLOHERP 400

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Aurobindo Pharma Limited

The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products. The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.

Mock labels are appended as annex I.

3. Scientific discussion

Quality of Active Pharmaceutical Ingredients

Information on quality of the API was submitted in form of CEP.

General Information

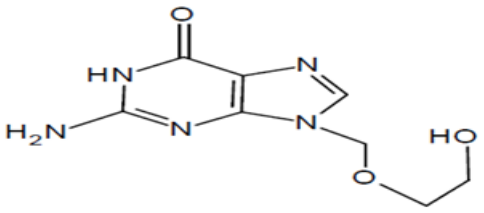
Aciclovir API is compendia in Ph.Eur., BP, USP.

Molecular formula: $C_8H_{11}N_5O_3$

Chemical name:

2-amino-9-[(2-hydroxyethoxy) methyl]-1,9-dihydro-6H-purin-6-one

Structure:



General properties

Aciclovir is a white or almost white, crystalline powder. It is slightly soluble in water, very slightly soluble in alcohol (96%), practically insoluble in heptane. It dissolves in dilute solutions of mineral acids and alkali hydroxides. No polymorphism has been confirmed. Nevertheless, as aciclovir is classified as a BCS class III molecule, which is a high soluble API according to BCS, therefore neither particle size and distribution nor polymorphism are considered to be critical.

Manufacture

Aciclovir API manufacturer is Zhejiang Charioteer Pharmaceutical Co., Limited, Tongyuanxi, Dazhan, Xianju, Zhejiang Province, 317321, P.R. China. The manufacturing complies with GMP requirements as evidenced by the GMP certificates issued by the Zhejiang Food and Drug Administration, China. Aciclovir API is manufactured by chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per Ph. Eur standards and ICHQ3A. The parameters monitored during quality control are: description, identification, appearance of solution, related substances, water content, sulphated ash, assay, and microbial contamination. Compliance to these specifications were established via batch analysis data and stability studies.

<u>Stability and container closure system</u>

The re-test period of Aciclovir API is 60 months when packed inHDPE with storage condition ‘Store in a tightly closed container at temperature not exceeding 25°C’.

Quality of the Finished Pharmaceutical Product

Formulation

ACLOHERP 400 is a white to off-white, round, biconvex, uncoated tablets debossed with 'AR and 400' separated with breakline on one side and plain on the other side. √

ACLOHERP 400 contains the Aciclovir other ingredients listed here after: cellulose microcrystalline, sodium starch glycolate, povidone, silica colloidal anhydrous, magnesium stearate. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, 8th Edition in terms of function and quantities.

Manufacture

The finished product manufacturers are Aurobindo Pharma Limited - UNIT XV, Plot no-17A, E Bonangi (Village), Parawada (Mandal), Visakhapatnam District, Andhra Pradesh, 531021, India.The compliance of the sites to TMDA GMP standards was confirmed through site inspection on DD/MM/YYYY.

Specifications

The FPP is compendia. The manufacturer controls the quality of the finished product as per USP standards and ICH requirements. The parameters monitored during quality control are: Description, identification by HPLC and UV, average mass, uniformity of dosage units by mass variation, subdivision of tablets (uniformity of mass for split halves), water content, dissolution, organic impurities, assay, and microbiological purity. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on 3(three) batches of the finished product stored at 30 ± 2°C & RH: 75 ± 5% RH for 24 months and 40± 2°C & RH: 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in Clear PVC - Aluminum foil blister pack with storage condition 'Do not store above 30 ^{o}C'.

Safety and efficacy information

The biowaiver was approved based on additional strength.

ACLOHERP 400 fulfilled the criteria for waiving an in-vivo bioequivalence study as per relevant TMDA guidance. Dissolution profiles of ACLOHERP 400 tablets was compared to ACLOHERP 800 tablets. At least 85% of the labelled amount of Aciclovir had dissolved in all three media. Therefore, confirming similarity.

4. Benefit-Risk Assessment and Conclusion

On basis of the data submitted, the current state of knowledge and compliance to Good Manufacturing Practice, the benefit of the product outweighs the risks associated with its use when used in accordance to the summary of product characteristics. ACLOHERP 400 is recommended for registration.

5. Post-approval updates

Variation applications

Reference number	Date submitted	Change requested	Recommendation	Granting date

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

Type of feedback	Impact	Response

Re-registration applications

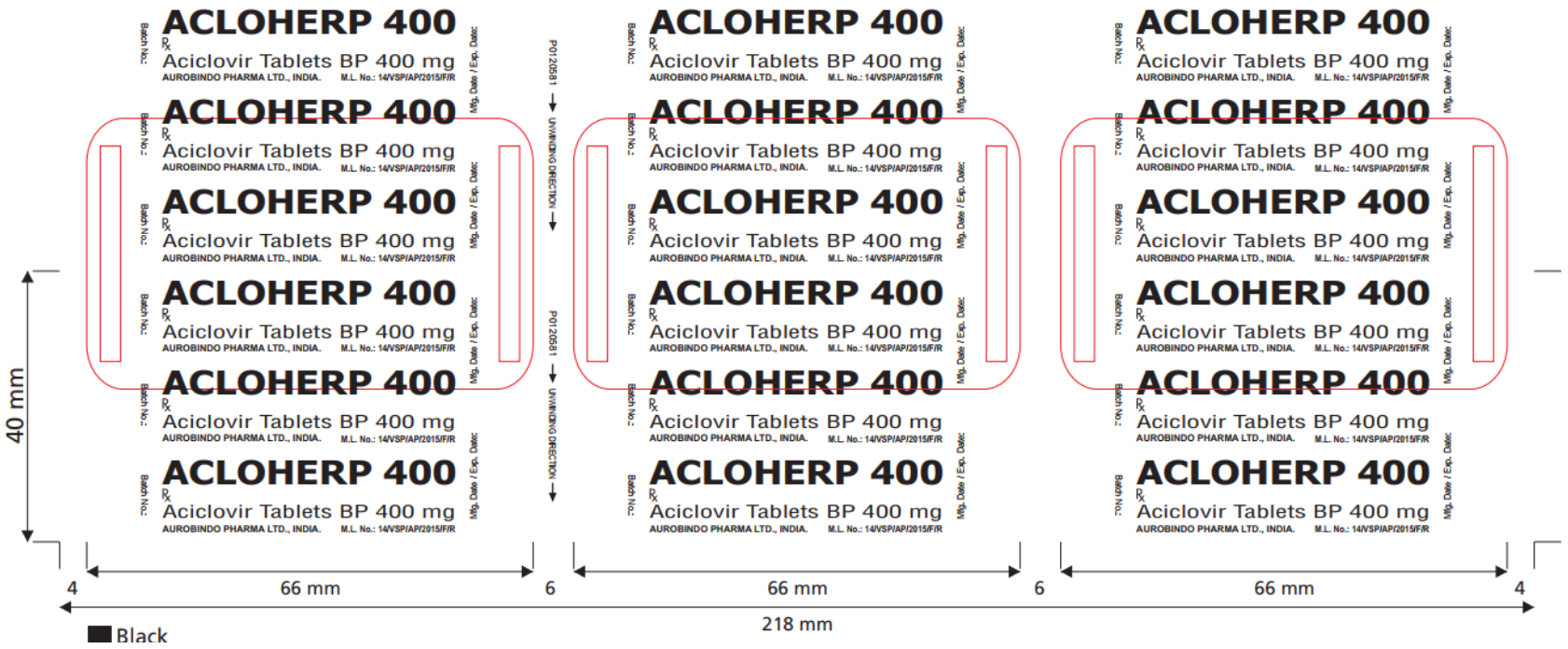
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up labels;

Primary pack label;



Secondary pack label:

Effective date: 03/10/2022