Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Apovir Cream (Acyclovir Cream 5%w/w)

2. Qualitative and quantitative composition

Each 1.0 gram contains Acyclovir BP 5.0% w/w
Excipients with known effect:
Propylene glycol 10% w/w
Cetostearyl alcohol 5.5 % w/w
Chlorocresol BP 0.16 % w/w

3. Pharmaceutical form

Topical Cream

White coloured , homogeneous cream, non- gritty and non-greasy on application to the skin

4. Clinical particulars

4.1 Therapeutic indications

Apovir Cream is indicated for the treatment of Herpes Simplex virus infections of the skin including initial and recurrent genital herpes and herpes labialis.
Route of administration: topical.
Do not use in eyes.

4.2 Posology and method of administration

Adults and Children: Apovir Cream should be applied five times daily at approximately four hourly intervals, omitting the night time application.
Apovir Cream should be applied to the lesions or impending lesions as soon as possible, preferably during the early stages (prodrome or erythema). Treatment can also be started during the later (papule or blister) stages.
Treatment should be continued for at least 4 days for herpes labialis and for 5 days for genital herpes. If healing has not occurred then treatment may be continued for up to an additional 5 days.
Use in the elderly: No special comment

4.3 Contraindications

Apovir Cream is contraindicated in patients known to be hypersensitive to aciclovir, valaciclovir, propylene glycol or any of the excipients of Apovir Cream listed in section 6.1.

4.4 Special warnings and precautions for use

Apovir Cream is not recommended for application to mucous membranes such as in the mouth, eye or vagina, as it may be irritant.
Particular care should be taken to avoid accidental introduction into the eye.
In severely immunocompromised patients (eg AIDS patients or bone marrow transplant recipients) oral Apovir dosing should be considered. Such patients should be encouraged to consult a physician concerning the treatment of any infection.
Apovir Cream contains a specially formulated base and should not be diluted or used as a base for the incorporation of other medicaments.
Excipients
The excipient cetostearyl alcohol can cause local skin reactions (e.g. contact dermatitis).
This medicine contains 100 mg of propylene glycol per gram of product. Propylene glycol may cause skin irritation.
Do not use this medicine in neonates with open wounds or large areas of broken or damaged skin (such as burns).

4.5 Interaction with other medicinal products and other forms of interaction

No clinically significant interactions have been identified.

4.6 Fertility, pregnancy, and lactation

Pregnancy:
A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of Apovir. The registry findings have not shown an increase in the number of birth defects amongst aciclovir exposed subjects compared with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause. Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rabbits, rats or mice.
In a non-standard test in rats, foetal abnormalities were observed but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain.
The use of Apovir Cream should be considered only when the potential benefits outweigh the possibility of unknown risks however the systemic exposure to aciclovir from topical application of Apovir Cream is very low.
Teratogenicity:
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure to indicate little relevance to clinical use (see section 5.3)
Breast-feeding:
Limited human data show that the drug does pass into breast milk following systemic administration. However, the dosage received by a nursing infant following maternal use of Apovir Cream would be insignificant.
Fertility:

There is no information on the effect of aciclovir on human female fertility.
In a study of 20 male patients with normal sperm count, oral aciclovir administered at doses of up to 1g per day for up to six months has been shown to have no clinically significant effect on sperm count, motility or morphology.
See Clinical Studies in section 5.2

4.7 Effects on ability to drive and use machines.
Not applicable

4.8 Undesirable effects
The following convention has been used for the classification of undesirable effects in terms of frequency: very common ≥1/10, common ≥1/100 and <1/10, uncommon ≥1/1000 and <1/100, rare ≥1/10,000 and <1/1000, very rare <1/10,000.
Immune system disorders:
Very rare
• Immediate hypersensitivity reactions including angioedema and urticaria.
Skin and subcutaneous tissue disorders:
Uncommon
• Transient burning or stinging following application of Zovirax Cream
• Mild drying or flaking of the skin
• Itching
Rare
• Erythema
• Contact dermatitis following application. Where sensitivity tests have been conducted, the reactive substances have most often been shown to be components of the cream rather than aciclovir.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose
No untoward effects would be expected if the entire contents of a 10 gram tube of Apovir Cream containing 500 mg of aciclovir were ingested orally. However the accidental, repeated overdose of oral aciclovir, over several days has resulted in gastrointestinal effects (nausea and vomiting) and neurological effects (headache and confusion). Aciclovir is dialysable by haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Aciclovir is an antiviral agent which is highly active *in vitro* against herpes simplex virus (HSV) types I and II and varicella zoster virus. Toxicity to mammalian host cells is low.
Aciclovir is phosphorylated after entry into herpes infected cells to the active compound aciclovir triphosphate. The first step in this process is dependent on the presence of the HSV-coded thymidine kinase. Aciclovir triphosphate acts as an inhibitor of, and substrate for, the herpes-specified DNA polymerase, preventing further viral DNA synthesis without affecting normal cellular processes
In two large, double blind, randomised clinical studies involving 1,385 subjects treated over 4 days for recurrent herpes labialis, Apovir Cream 5% was compared to vehicle cream. In these studies, time from start of treatment to healing was 4.6 days using Apovir Cream and 5.0 days using vehicle cream ($p<0.001$). Duration of pain was 3.0 days after start of treatment in the Apovir Cream group and 3.4 days in the vehicle group ($p=0.002$). Overall, approximately 60% of patients started treatment at an early lesion stage (prodrome or erythema) and 40% at a late stage (papule or blister). The results were similar in both groups of patients

5.2 Pharmacokinetic properties

Pharmacology studies have shown only minimal systemic absorption of aciclovir following repeated topical administration of Apovir Cream

5.3 Preclinical safety data

The results of a wide range of mutagenicity tests *in vitro* and *in vivo* indicate that aciclovir does not pose a genetic risk to man.
Aciclovir was not found to be carcinogenic in long term studies in the rat and the mouse.
Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of aciclovir greatly in excess of those employed therapeutically. Two generation studies in mice did not reveal any effect of orally administered aciclovir on fertility.
Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rats, rabbits or mice.
In a non-standard test in rats, foetal abnormalities were observed, but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose
Maize Starch
Microcrystalline Cellulose
Povidone K30
Purified Talc

Colloidal Anhydrous Silica
Magnesium Stearate
Tab Coat Yellow
Purified Water

6.2 Incompatibilities
None known

6.3 Shelf life
36 months

6.4 Special precautions for storage:
Store in a dry place below 30˚C. Protect from light.

6.5 Nature and contents of container
10 grams cream packed in collapsible Aluminium tubes embossed with batch number, manufacturing date and expiry dates packed in unit box with an insert

6.6 Special precautions for disposal and other handling:
No special requirements.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
National Pharmacy Ltd
Manufacturing site address:
Zain Pharma limited
Plot No: 209/13741, Colchester Park,
Go-Down No.1, 2, 3, Off Mombasa Road,
Behind Nice And Lovely House,
P.O. Box: 100167-00101,
Nairobi, Kenya

8. Marketing authorization number
CTD9338

9. Date of first registration
29/05/2023

10. Date of revision of the text:
14/09/2023

11. Dosimetry:
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable