



SCOTT-EDIL PHARMACIA LTD.

**56, E.P.I.P Phase -I, Jharmajri, Baddi, Distt.
Solan-173205 (HP) , India**

Summary of Product Characteristics (SPC)

1. Name of the medicinal product

ACICLOVIR CREAM (Aciclovir Cream BP 5% w/w)

1.1 International Non-Proprietary Name (INN)

Aciclovir BP

1.2 Strength

5% w/w

1.3 Pharmaceutical form

Ointment

2. Qualitative and quantitative composition

Composition:

Aciclovir BP 5% w/w

In a Cream base q.s.

3. Pharmaceutical form

Ointment

4. Clinical particulars

4.1 Therapeutic indications

For the treatment of herpes simplex virus infections of the lips and face (herpes labialis). Immunocompromised Patients

Aciclovir cream is not recommended for use in immunocompromised patients. Such patients must be advised to consult a physician concerning the treatment of any infection.

4.2 Posology and method of administration

Route of administration - Topical

Adults and children

Treatment should be initiated as soon as possible after the start of the infection, ideally during the prodromal period or when the lesions first appear. Treatment can also be started during the later (papule or blister) stages.

A thin film of cream should be applied to the infected and immediately adjacent skin areas 5 times daily at 4-hour intervals during the day omitting the night time application.

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MODULE-1**



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Treatment should be continued for 4 days. If healing has not occurred, treatment may be continued for up to 10 days. If lesions are still present after 10 days, users should be advised to consult a doctor.

Patients should wash their hands before and after applying the cream and avoid unnecessary rubbing of the lesions or touching with a towel, to avoid aggravating or transferring the infection.

Elderly

No special requirements

4.3 Contraindications

Hypersensitivity to aciclovir, valaciclovir, propylene glycol to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Only recommended for use on cold sores on the lips and face.

People with particularly severe recurrent herpes labialis should be encouraged to seek medical advice.

Not to be applied to mucous membranes such as inside the mouth or vagina, or on the eye. Particular care should be taken to avoid contact with the eye.

Not for use for the treatment of genital herpes or ocular herpes infections.
Not recommended for use by patients who know they are immunocompromised e.g. by HIV infection, bone marrow transplant or cancer treatment, except on the advice of a doctor. Such individuals should be encouraged to consult a physician concerning the treatment of an infection.

Cold sore sufferers should be advised to avoid transmitting the virus, particularly when active lesions are present.

The excipient propylene glycol can cause skin irritations and the excipient cetyl alcohol can cause local skin reactions (e.g. contact dermatitis)

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid increases the mean half-life and area under the plasma concentration curve of systemically administered aciclovir. Other drugs affecting renal physiology could potentially influence the pharmacokinetics of aciclovir. However this is likely to be of little relevance to the cutaneous application of aciclovir.

No interactions with other drugs have been described for topical Acyclovir.

4.6 Pregnancy and lactation

Pregnancy

No specific studies of topical aciclovir have been carried out in pregnant women or nursing mothers.

So far, no relevant plasma levels have been measured and no systemic effects have been observed.

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A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of aciclovir. The birth defects described amongst aciclovir exposed subjects have not shown any uniqueness or consistent pattern to suggest a common cause.

In internationally accepted standard tests the systemic administration of Aciclovir 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.

Foetal abnormalities were observed in non-standard tests in rats, but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain.

Use of the cream should be considered only when the potential benefit outweighs the possibility of unknown risks however the systemic exposure to aciclovir from topical application of aciclovir cream is very low.

Fertility

Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses greatly in excess of those employed therapeutically. Two generation studies in mice did not reveal any effect of orally administered aciclovir on fertility.

There is no experience of the effect of aciclovir tablets on human female fertility.

Aciclovir tablets have been shown to have no definite effect upon sperm count, morphology or motility in man.

Lactation

Following oral administration of 200 mg aciclovir five times a day, aciclovir has been detected in breast milk at concentrations ranging from 0.6 to 4.1 times the corresponding plasma levels. These levels would potentially expose breast fed infants to aciclovir doses of up to 0.3 mg/kg/day. The dosage received by a nursing infant following maternal use of aciclovir cream would be expected to be insignificant.

4.7 Effects on ability to drive and use machines

The medicinal product has no influence on the ability to drive or operate machinery.

4.8 Undesirable effects

The following convention has been used for the classification of undesirable effects in terms of frequency:-

Very common $\geq 1/10$, common $\geq 1/100$ and $< 1/10$, uncommon $\geq 1/1000$ and $< 1/100$, rare $\geq 1/10,000$ and $< 1/1000$, very rare $< 1/10,000$.

Skin and subcutaneous tissue disorders

Uncommon

- Itching

- Transient burning or stinging following application of aciclovir cream

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- Mild drying or flaking of the skin
- 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 base rather than aciclovir.
- Immune system disorders
- Very rare
- Immediate hypersensitivity reactions including angioedema and urticaria.

4.9 Overdose

Overdose is unlikely to occur, if the cream is applied locally and as indicated. There are no reports concerning an overdose of aciclovir cream.

No unwanted effects would be expected if the entire contents of a 2.0g tube of the cream were ingested. Doses of 800 mg five times daily (4 g per day), have administered without adverse effects. Single intravenous doses of up to 80 mg/kg have been inadvertently administered without adverse effects. Aciclovir is dialysable.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals, ATC code: D06BB03

Aciclovir is an antiviral agent which is highly active in vitro against herpes simplex virus (HSV) types 1 and 2 toxicity to mammalian host cells is low.

Aciclovir is a pharmacologically inactive substance. After penetration into cells which are infected with herpes simplex virus types 1 and (HSV 1 & HSV II) or varicella-zoster virus (VSV), aciclovir is converted into a virostatic agent. The conversion of aciclovir is catalysed by viral HSV- or VZV- thymidine kinase. Human thymidine kinase does not use aciclovir effectively as a substrate, hence the toxicity to mammalian host cells is low.

In the infected cell, aciclovir is phosphorylated by viral thymidine kinase to aciclovir monophosphate, which is further converted by cellular enzymes to aciclovir triphosphate. Aciclovir triphosphate has a greater affinity for viral DNA polymerase than host cell DNA polymerase and therefore selectively interferes with the viral enzyme causing inhibition of viral DNA replication. Aciclovir is also incorporated into viral DNA by viral DNA polymerase, which results in chain termination, as aciclovir lacks a 3'-hydroxyl group, preventing addition of nucleotides by 3',5'-linkage.

In severely immunocompromised patients a longer or repeated treatment with aciclovir can lead to a selection of viral strains with reduced sensitivity. As a result, these patients no longer respond to treatment with Aciclovir. Most of the clinical isolates with reduced

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sensitivity showed a relative lack of virus thymidine kinase. However, strains with changed/different virus thymidine kinase or DNS polymerase were also reported. The in vitro exposition of HSV-isolates can also lead to the development of less sensitive strains. The connection between the in vitro determined sensitivity of HSV-isolates and the clinical response to the treatment with Aciclovir is not clear.

In two large, double blind, randomised clinical studies involving 1,385 subjects treated over 4 days for recurrent herpes labialis, aciclovir cream was compared to vehicle cream. In these studies, time from start of treatment to healing was 4.6 days using aciclovir cream and 5.0 days using vehicle cream ($p<0.001$). Duration of pain was 3.0 days after start of treatment in the aciclovir 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

Absorption and plasma concentrations

Aciclovir penetrates into the skin. The intracutaneous concentration levels are higher than the minimal inhibitory concentration (MIC) in tissue at steady state.

After topical application of aciclovir, no aciclovir plasma concentration could be determined.

As the aciclovir plasma concentrations following topical application are below the limit of detection, no pharmacokinetic studies are available on topical aciclovir. Therefore, the following data is based on the data after oral or intravenous administration.

Plasma protein binding is reported to range between 9 and 33% as a function of dose. The volume of distribution at steady state in adults is $50 \pm 8.71.73 \text{ m}^2$, or 0.7 l/kg .

Two metabolites could be identified in the urine of patients with normal renal function after single dosing with 14C-Aciclovir: 9-carboxymethoxymethylguanine (2-14% of an administered dose) and 8-hydroxy-9-(2-hydroxyethoxymethyl)guanine($<0.2\%$ of a dose). Subjects with normal renal function eliminate 62-91% of an aciclovir dose unchanged and 9-14% as 9-carboxymethoxymethylguanine via the kidneys.

Aciclovir is predominantly eliminated via the kidneys, primarily by glomerular filtration and to a lesser extent by tubular secretion.

In vitro and in vivo studies of aciclovir cream and aciclovir ointment versus oral aciclovir were carried out to determine the bioavailability of aciclovir in human skin. The in vitro studies used human skin biopsates, whilst the bioassays either used human skin grafts on mice or were carried out in the human eye (3 patients).

The following dermal drug concentration gradient emerged for both topical and oral aciclovir: stratum corneum> epidermis>dermis. There was no difference in concentration between cream and ointment.

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The upper layer of the epidermis on average showed a 48-fold higher concentration following topical application of aciclovir ointment or cream 5% than after oral dosing, but the drug concentration in the basal epidermis – the site of herpes virus infection – was 2 to 3 times lower following topical application than after oral dosing.

On the basis of continuous absorption the concentration increased as a function of time (higher drug concentrations being found 48 hours post-topical dose than 24 hours post-topical dose). Thus short dosing intervals appear rational for the special treatment of herpes simplex virus (HSV) infections.

Clinical Studies

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.

5.3 Preclinical safety data

For 24 days, PEG-based aciclovir cream 5 or 10% was applied to the shaved (intact and grazed) skin of guinea-pigs. The treated area corresponded to 10% of the body surface. There were neither systemic nor local toxic symptoms. This is also confirmed by histologic studies and autopsy. According to the test carried out by Draize, who evaluated the allergic sensitising potential of a substance, there were no pathogenic findings.

Studies carried out in swine showed that 5% aciclovir cream in a PEG vehicle caused an only minimal (quantitative) delay in epidermal wound healing.

Rabbits had 1, 3 or 6% aciclovir cream in a white petrolatum vehicle introduced directly into both eyes 5 times daily at 90-minute intervals for 3 weeks. Neither autopsy nor inspection nor histological examination revealed any pathological changes in the rabbit eyes.

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 mouse.

Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported at systemic 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.



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6. Pharmaceutical particulars

6.1 List of excipients

Sr.	Ingredients	Grade
1.	Glyceryl monostearate	BP
2.	Cetostearyl alcohol	BP
3.	Cetomacrogel-1000	BP
4.	Propylene glycol	BP
5.	Methyl hydroxyl benzoate	BP
6.	Propyl hydroxybenzoate	BP
7.	Light liquid paraffin	BP
8.	White Soft paraffin	BP
9.	Purified water	BP

6.2 Incompatibilities

None Known.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

10 g laminated tube packed in a unit carton along with leaflet.

6.6 Special precautions for disposal and other handling

None Known.

7. Manufactured By

Scott-Edil Pharmacia Limited,
56, EPIP, Phase-I, Jharmajri,
Baddi, Distt. Solan- 173205 (H.P)
INDIA

8. Marketed By

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