For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

HERPEX CREAM

(Aciclovir 5% W/W Cream)

COMPOSITION

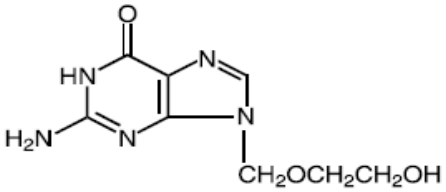
HERPEX - 5%

Aciclovir I.P……..5.0%

In a cream base

DESCRIPTION

Acyclovir is a white, crystalline powder with the molecular formula $C_8H_{11}N_5O_3$ and a molecular weight of 225. The maximum solubility in water at 37°C is 2.5 mg/mL. The pka's of acyclovir are 2.27 and 9.25. The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one; it has the following structural formula:



CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

ATC code: D06BB03

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 dependant 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 the normal cellular processes.

Herpes simplex virus develops resistance to aciclovir by selection of mutants deficient in thymidine kinase which are usually of diminished virulence with reduced infectivity and latency. Resistance is rare in immunocompetent patients on short courses of oral therapy but it is more prevalent in immunocompromised patients who have often received prolonged courses of treatment. Herpes zoster resistance develops by a similar mechanism and has been

reported in immunocompromised patients undergoing prolonged therapy with aciclovir.

PHARMACOKINETICS

Aciclovir is excreted through the kidney by both glomerular filtration and tubular secretion. The terminal or beta-phase half-life is reported to be about 2 to 3 hours for adults without renal impairment. In chronic renal failure this value is increased and may be up to 19.5 hours in anuric patients. During haemodialysis and the half-life is reduced to 5.7 hours, with 60% of a dose of aciclovir being removed in 6 hours. Faecal excretion may account for about 2% of a dose. There is a wide distribution to various tissues, including the CSF where concentrations achieved are about 50% of those achieved in plasma. Protein binding is reported to range from 9-33%. Aciclovir crosses the placenta and is excreted in breast milk in concentrations approximately 3 times higher than those in maternal serum. Absorption of aciclovir is usually slight following topical application to intact skin, although it may be increased by changes in formulation.

INDICATIONS AND USAGE

Herpex Cream is indicated for the treatment of initial and recurrent herpes genitalis; non-life threatening mucocutaneous HSV infections in immunocompromised patients; herpes labialis and blepharitis. Herpex Cream is also applied to the cutaneous lesions in herpes zoster.

CONTRAINDICATIONS

Aciclovir cream is contraindicated in patients known to be hypersensitive to aciclovir, valaciclovir, or any of the excipients of aciclovir cream.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In severely immunocompromised patients (eg AIDS patients or bone marrow transplant recipients) oral Aciclovir dosing should be considered. Such patients should be encouraged to consult a physician concerning the treatment of any infection.

Aciclovir 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. 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. There has been no experience of the effect of Aciclovir Cream on human fertility. Two generation studies in mice did not reveal any effect of (orally administered) Aciclovir on fertility. Aciclovir Tablets have been shown to have no definite effect upon sperm count, morphology or motility in man.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No clinically significant interactions have been identified.

Probenecid increases the mean half-life and area under the plasma concentration curve of systematically administered Aciclovir. However, this is likely to be of little relevance to the topical application of Aciclovir.

PREGNANCY AND LACTATION

Pregnancy

Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rats, rabbits and 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. Experience in humans is limited, so use of Aciclovir 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 aciclovir cream is very low.

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.

A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of aciclovir. 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.

Lactation

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 aciclovir cream or ophthalmic ointment would be insignificant.

ADVERSE EXPERIENCES

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.

Clinical trial data have been used to assign frequency categories to adverse reactions observed during clinical trials with aciclovir 3% ophthalmic ointment. Due to the nature of the adverse events observed, it is not possible to determine unequivocally which events were

related to the administration of the drug and which were related to the disease. Spontaneous reporting data has been used as a basis for allocating frequency for those events observed post-marketing.

Skin and subcutaneous tissue disorders

Uncommon: Transient burning or stinging following application of aciclovir 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.

Immune system disorders

Very rare: Immediate hypersensitivity reactions including angioedema and urticaria.

OVERDOSAGE

No untoward effects would be expected if the entire contents of an Aciclovir Cream 10g tube containing 500mg of Aciclovir were ingested orally. Oral doses of 800mg five times daily (4g/daily), have been administered for seven days without adverse effects. Single intravenous doses of up to 80mg/kg have been inadvertently administered without adverse effects. Aciclovir is dialysable.

DOSAGE AND ADMINISTRATION

Aciclovir Cream should be applied to the lesion or impending lesion as early as possible after the start of an infection. It is particularly important to start treatment of recurrent episodes during the prodromal period or when lesions first appear.

Adults (*including elderly*): Aciclovir Cream should be applied five times daily at approximately four hourly intervals, omitting the night time application. Treatment should be continued for five days. If, after five days, healing is not complete then treatment can be continued for up to an additional five days.

Expiry date: Do not use later than the date of expiry.

Storage: STORE AT A TEMPERATURE NOT EXCEEDING 25°C.

Presentation: HERPEX is available in one aluminium tube of 5g.

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
"Torrent House", Off Ashram Road,
Ahmedabad - 380 009, INDIA.

Revised May 2013