

## PRODUCT INFORMATION

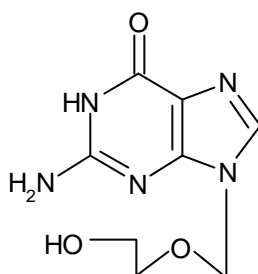
### ZOVIRAX<sup>®</sup> COLD SORE CREAM

**APPROVED NAME:** Aciclovir

**COMPOSITION:** Aciclovir 5% w/w.

#### DESCRIPTION:

Aciclovir is a synthetic acyclic purine nucleoside analogue. Its chemical name is 9-((2-hydroxyethoxy)methyl)guanine. It is a white crystalline powder slightly soluble in water and practically insoluble in most organic solvents. The chemical structure of aciclovir is:



ZOVIRAX Cold Sore Cream is a smooth, white cream containing 50 mg/g (5% w/w) aciclovir in a water miscible base. ZOVIRAX Cold Sore Cream also contains propylene glycol, soft white paraffin, cetostearyl alcohol, liquid paraffin, poloxamer 407, sodium lauryl sulfate, and purified water.

#### PHARMACOLOGY:

##### Microbiology

Aciclovir is an antiviral agent which is active *in vitro* against *Herpes simplex* virus (HSV) types I and II and *Varicella zoster* virus (VZV), the latter being considerably less sensitive. The relationship between the level of *in vitro* sensitivity of herpes viruses to aciclovir and clinical response to therapy has not been adequately established. Development of resistance by HSV to aciclovir has been documented (see **WARNINGS AND PRECAUTIONS**). Aciclovir needs to be phosphorylated to the active compound, aciclovir triphosphate, in order to become active against the virus. Such conversion is very limited in normal cells and in addition cellular DNA polymerase is not very sensitive to the active compound. However, in infected cells HSV or VZV-coded thymidine kinase facilitates the conversion of aciclovir to aciclovir monophosphate which is then converted to aciclovir triphosphate by cellular enzymes. Aciclovir triphosphate acts as an inhibitor of, and substrate for, the herpes-specified DNA polymerase, preventing further viral DNA synthesis.

##### Clinical Trials

Five controlled clinical studies have been carried out investigating ZOVIRAX Cold Sore Cream in the treatment of cold sores. They involved 296 patients (all over 16 years of age and approximately 78% being females) with recurrent herpes labialis who had normal immune function. Therapy was self initiated at the earliest possible time after the onset of first symptoms or signs of their next attack. The patients received either aciclovir or placebo cream which was applied five times daily for five days. Three of the five placebo-controlled trials were investigator assessed, and a statistically significant benefit of ZOVIRAX Cold Sore Cream was demonstrated (time to healing in each study; 4 days versus 6 days; 5.7 days versus 8.3 days; 9 days versus 11 days;  $p < 0.05$  in each study). In one of these three studies there was a significant increase in the number of lesions aborted following aciclovir therapy. The remaining two studies were patient assessed and although healing time for aciclovir-treated lesions was shorter, the difference was not statistically significant, (time to healing in each study: 9 days versus 11 days; 7 days versus 8 days). Overall the results demonstrated that provided therapy was initiated promptly, ZOVIRAX Cold Sore Cream conferred a useful benefit in the treatment of herpes labialis by reducing the duration of lesions.

### **Pharmacokinetics**

Small quantities (less than 0.1% of the applied dose) appear in the urine after application of ZOVIRAX Cold Sore Cream.

### **INDICATIONS:**

ZOVIRAX Cold Sore Cream is indicated for the treatment of *Herpes simplex* virus infections of the lips (herpes labialis).

### **CONTRAINDICATIONS:**

ZOVIRAX Cold Sore Cream is contra-indicated in patients known to be hypersensitive to aciclovir, or any other constituents of the cream (see **DESCRIPTION**).

### **PRECAUTIONS AND WARNINGS:**

ZOVIRAX Cold Sore 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 aciclovir dosing should be used. Such patients should be encouraged to consult a physician concerning the treatment of any infection.

Resistant strains have been isolated *in vitro* and in animals following treatment with aciclovir. HSV strains resistant *in vitro* to aciclovir have also been isolated from immunocompromised as well as immunocompetent patients receiving aciclovir for *Herpes simplex* infections. Development of resistance during treatment with ZOVIRAX Cold Sore Cream is much more common in immunocompromised individuals than those with normal immune function. Therefore the potential for the development of resistant HSV strains in patients treated with

aciclovir should be borne in mind. The relationship between *in vitro* sensitivity of herpes viruses to aciclovir and clinical response to therapy has yet to be established.

Animal studies indicate that at high doses aciclovir is cytotoxic.

### **Use in Pregnancy** (Category B3)

Animal studies show that aciclovir crosses the placenta readily. Aciclovir was not teratogenic in the mouse (450 mg/kg/day po), rabbit (50 mg/kg/day, sc and iv) or rat (50 mg/kg/day, sc) when dosed throughout the period of major organogenesis. In additional studies in which rats were given 3 sc doses of 100 mg/kg aciclovir on gestation day 10, fetal abnormalities, such as head and tail anomalies, were reported.

There have been no adequate and well controlled studies concerning the safety of aciclovir in pregnant women. Only small amounts are absorbed following application to the skin (less than 0.1% of the applied dose). To date, monitoring of pregnancy outcomes in women who have received both topical and systemic aciclovir has not revealed any evidence of teratogenesis.

ZOVIRAX Cold Sore Cream should not be used during pregnancy unless the benefits to the patients clearly outweigh the potential risks to the foetus.

### **Use in Lactation**

Limited human data show that aciclovir does pass into breast milk following systemic administration. No information is available on levels of aciclovir which may appear in breast milk after administration of ZOVIRAX Cold Sore Cream. Aciclovir should only be administered to nursing mothers if the benefits to the mother outweigh the potential risks to the baby.

### **Mutagenicity**

Aciclovir was clastogenic in Chinese hamster cells *in vivo*, at exposure levels also causing nephrotoxicity (500 and 1000 mg/kg parenteral dose). There was also an increase, though not statistically significant, in chromosomal damage at maximum tolerated doses (100 mg/kg) of aciclovir in rats. No activity was found in a dominant lethal study in mice or in 4 microbial assays. Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro* (positive in human lymphocytes *in vitro* and one locus in mouse lymphoma cells, negative at 2 other loci in mouse lymphoma cells and 3 loci in a Chinese hamster ovary cell line).

The results of mutagenicity tests *in vitro* and *in vivo* suggest that aciclovir is unlikely to pose a genetic threat to man at therapeutic dose levels.

### **Carcinogenicity**

Aciclovir was positive in one of two mouse cell transformation systems *in vitro*. Inoculation of the transformed cells into immune-suppressed mice resulted in tumours. These data are suggestive of an oncogenic potential. However, the validity of this type of study is unclear. Lifetime oral dosing studies in mice and rats gave no evidence of tumourigenicity but in these species the absorption of oral aciclovir is poor and possibly self-limiting.

### **Effects on Fertility**

There is no experience of the effect of ZOVIRAX Cold Sore Cream on human fertility. The results of studies in animals indicate that aciclovir should have no effect on fertility in man at therapeutic doses.

### **DRUG INTERACTIONS:**

None known.



## **ADVERSE EFFECTS:**

In clinical trials to determine the efficacy of ZOVIRAX Cold Sore Cream the overall incidence of adverse events was 7.7%. The most common adverse event reported is flaking skin, with less frequent reports of dry skin, burning or stinging. All these events were considered minor and no patient stopped therapy because of adverse events.

Erythema and itching have been reported in a small proportion of patients. Contact dermatitis has been reported rarely 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.

## **DOSAGE AND ADMINISTRATION:**

ZOVIRAX Cold Sore Cream should be applied five times daily at approximately four hourly intervals omitting the night time application.

ZOVIRAX Cold Sore Cream should be applied to the lesions or impending lesions 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 the lesions first appear.

Treatment should be continued for 5 days.

ZOVIRAX Cold Sore Cream contains a specially formulated base and should not be diluted or used as a base for incorporation of other medicaments.

## **OVERDOSAGE:**

No untoward effects would be expected if the entire contents of a 2 gram tube of ZOVIRAX Cold Sore Cream containing 100 mg of aciclovir were ingested orally. Oral doses of 800 mg aciclovir five times a day (4 grams per day) have been administered for 7 days without adverse effects. Single intravenous doses of up to 80 mg/kg have been inadvertently administered without adverse effects.

Aciclovir can be removed from the circulation by haemodialysis.

## **PRESENTATION:**

ZOVIRAX Cold Sore Cream is available in 2 g tubes (AUST R 55006).

## **STORAGE CONDITIONS AND SHELF-LIFE:**

Store below 25°C. Do not refrigerate.

Shelf-life: 24 months.

**DATE OF TGA APPROVAL:** 26 March 1995

ã **ZOVIRAX** is a trade mark of the Glaxo Wellcome Group of Companies.

Shelf life extension approved by TGA on 12 July 1996.

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