

## PRODUCT INFORMATION

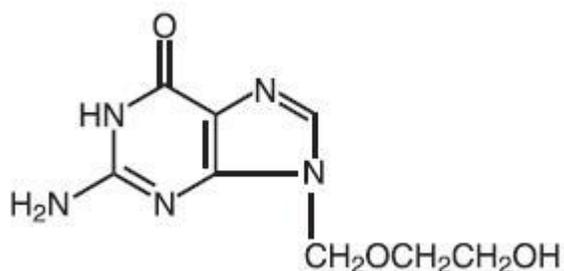
### ZOVIRAX COLD SORE CREAM

#### NAME OF THE MEDICINE

ZOVIRAX Cold Sore Cream contains the active ingredient aciclovir 5%.

Aciclovir is a synthetic acyclic purine nucleoside analogue.

Chemical name: 9-((2-hydroxyethoxy)methyl)-guanine. Molecular formula:  $C_8H_{11}N_5O_3$ . MW: 225. CAS: 59277-89-3. It is a white crystalline powder slightly soluble in water and practically insoluble in most organic solvents. The structural formula is given below:



#### DESCRIPTION

ZOVIRAX Cold Sore Cream is a white to off-white cream, smooth and free from grittiness. Free from lumps and foreign matter. No sign of separation.

ZOVIRAX Cold Sore Cream also contains Propylene glycol, White soft paraffin, Cetostearyl alcohol, Paraffin – liquid, Arlacel 165, Dimeticone 20, Poloxamer, Sodium lauryl sulphate and Water – purified.

#### PHARMACOLOGY

Aciclovir is an antiviral agent which is highly active *in vitro* against herpes simplex virus (HSV) types 1 and 2. Varicella zoster virus (VZV) is considerably less sensitive *in vitro*. Toxicity to mammalian cells is low. 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 PRECAUTIONS). Aciclovir is phosphorylated *after entry into herpes-infected cells* 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 without affecting normal cellular processes.

## **Pharmacokinetics**

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

## **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.

## **INDICATIONS**

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

## **CONTRAINDICATIONS**

ZOVIRAX Cold Sore Cream is contraindicated in patients known to be hypersensitive to aciclovir, valaciclovir, propylene glycol or any other constituents of the cream (see DESCRIPTION).

## **PRECAUTIONS**

Aciclovir cream should only be used on cold sores on the mouth and face. ZOVIRAX Cold Sore Cream is not recommended for application to mucous membranes, such as inside the mouth, or eye and must not be used to treat genital herpes. Particular care should be taken to avoid contact with the eye.

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

Cold sore sufferers should be advised to avoid transmitting the virus, particularly when active lesions are present (e.g. wash hands before and after use – refer to DOSAGE

AND ADMINISTRATION section).

Aciclovir cream is not recommended for use by people who know that they are immunocompromised. Such individuals should be encouraged to consult a doctor concerning the treatment of any infection.

In severely immunocompromised patients (e.g. 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.

### **Effects on Fertility**

Two-generation studies in mice did not reveal any effect of orally administered aciclovir on fertility at doses providing 1,000 times the expected clinical exposure. There is no information on the effect of ZOVIRAX Cold Sore Cream, aciclovir oral formulations or i.v. for infusion on human female fertility. In a study of 20 male patients with normal sperm count, oral aciclovir administered at doses of up to 1 g per day for up to six months has been shown to have no clinically significant effect on sperm count, motility or morphology.

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

Aciclovir has been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.

Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Animal studies show that aciclovir crosses the placenta readily. There have been no adequate and well-controlled studies concerning the safety of aciclovir in pregnant women. Only small amounts of aciclovir are absorbed following application to the skin (less than 0.1% of the applied dose).

A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of ZOVIRAX. The registry findings have not shown

an increase in the number of birth defects amongst ZOVIRAX exposed subjects compared with the general population, and the appearance of 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 following exposure over 1,000 times that expected after clinical use of ZOVIRAX Cold Sore Cream. The clinical relevance of these findings is uncertain.

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

### **Use in Lactation**

Limited human data show that aciclovir does pass into breast milk following systemic administration. However, the dosage received by a nursing infant following maternal use of ZOVIRAX Cold Sore Cream would be negligible.

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 1,000 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 tumorigenicity but in these species the absorption of oral aciclovir is poor and possibly self-limiting.

## **INTERACTIONS WITH OTHER MEDICINES**

No clinically significant interactions have been identified.

## **ADVERSE EFFECTS**

In clinical trials to determine the efficacy of ZOVIRAX Cold Sore Cream the overall incidence of adverse events was 7.7%.

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  $\geq 1/1,000$  and  $< 1/100$ , rare  $\geq 1/10,000$  and  $< 1/1,000$ , very rare  $< 1/10,000$ .

### **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.

### **Immune System Disorders**

#### Very rare

- Immediate hypersensitivity reactions including angioedema

## **DOSAGE AND ADMINISTRATION**

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

A small amount of ZOVIRAX Cold Sore Cream should be applied to the lesions or impending lesions as early as possible after the start of an infection, preferably during the earliest stages (prodrome or erythema).

Zovirax has been shown to be effective at both the early (prodrome or erythema lesion) stage and late (papule or vesicle) stage.

It is recommended that a small amount of cream should be applied at the first sign of a cold sore whether the first sign is a tingle or a blister. The cold sore can still be treated once the blister has appeared.

Treatment should be continued for 4 days.

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

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 10 gram tube of ZOVIRAX Cold Sore Cream containing 500 mg of aciclovir were ingested orally. In the event of a suspected overdose, patients should seek medical advice.

### **Poison Information Centre:**

<b>Australia telephone</b>	<b>131126</b>
<b>New Zealand telephone</b>	<b>0800 764 766</b>

### **PRESENTATION AND STORAGE CONDITIONS**

ZOVIRAX Cold Sore Cream contains aciclovir 5% w/w.

White to off-white cream, smooth and free from grittiness. Free from lumps and foreign matter. No sign of separation.

Tubes of 2 g.  
Pump packs of 2 g.

Store below 25°C.

### **NAME AND ADDRESS OF THE SPONSOR**

GlaxoSmithKline Consumer Healthcare Australia Pty Ltd

82 Hughes Avenue  
Ermington NSW 2115  
AUSTRALIA

## **POISON SCHEDULE OF THE MEDICINE**

Unscheduled

## **DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):**

Zovirax 5% tube (AUST R 150098)	13 February 2008
Zovirax 5% pump pack (AUST R 150099)	13 February 2008

## **DATE OF MOST RECENT AMENDMENT**

October 2017

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