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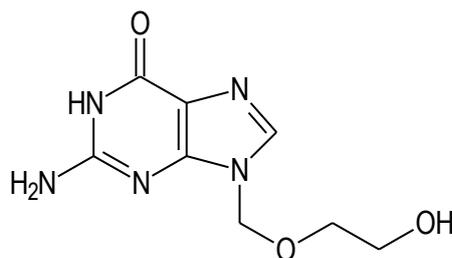
## PRODUCT INFORMATION

### ACICLOVIR SANDOZ® 200MG AND 800MG TABLETS

#### NAME OF THE MEDICINE

Chemical name: 9-[(2-hydroxyethoxy)methyl]guanine

Generic name: aciclovir



Aciclovir

Empirical formula: C<sub>8</sub>H<sub>11</sub>N<sub>5</sub>O<sub>3</sub>

CAS [59 277-89-3]

MW: 225.21

#### DESCRIPTION

Aciclovir is a white to off-white crystalline powder, which is slightly soluble in water.

In addition to Aciclovir - the active ingredient of Aciclovir Sandoz 200mg and 800mg tablets, Aciclovir Sandoz tablets contain the following inactive ingredients: lactose, microcrystalline cellulose, sodium starch glycollate (type A), copovidone, magnesium stearate.

#### PHARMACOLOGY

##### Microbiology

Aciclovir is an antiviral agent which is active *in vitro* against herpes simplex virus (HSV) types 1 and 2 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. 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

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of and substrate for the herpes specified DNA polymerase, preventing further viral DNA synthesis.

### Pharmacokinetics

Aciclovir is only partially and variably absorbed from the gut. Estimated bioavailability following a dose of 200mg is about 20% and decreases to about half of this with an 800mg dose. Mean steady state peak and trough concentrations during dosage of 200mg administered every four hours were 0.49 (range 0.47 to 0.54) microgram/mL and 0.31 (range 0.18 to 0.41) microgram/mL, respectively, and after 800mg every six hours were 1.43 (range 0.66 to 1.8) microgram/mL and 0.55 (range 0.14 to 1.10) microgram/mL, respectively. Both peak and trough levels following repeated doses in adults over 60 years of age are considerably higher than in young adults, apparently because of the reduced renal function in the elderly.

Following oral administration, the mean plasma half-life of aciclovir in volunteers and patients with normal renal function ranges from 2.5 to 3.3 hours. Approximately 60% of the medicine is excreted unchanged by the kidney by glomerular filtration and tubular excretion. When aciclovir is given after probenecid, the terminal half-life and the area under the plasma concentration-time curve are extended. 9-carboxymethoxymethyl-guanine is the major metabolite of aciclovir.

In children aged 0 to 3 months the terminal plasma half-life is approximately 4 hours. However, experience is insufficient at present to recommend therapy for this age group.

Because aciclovir is excreted mainly by the kidneys, its total body clearance in the elderly (> 60 years of age) declines due to decreased renal function. Terminal half-life of aciclovir in the elderly is approximately 4.6 hours. It is important to maintain adequate hydration in elderly patients taking high oral doses. In patients with chronic renal failure, the mean terminal half-life following intravenous administration was found to be  $19.5 \pm 5.9$  (standard deviation) hours. The mean aciclovir half-life during haemodialysis was 5.7 hours. Plasma aciclovir levels dropped approximately 60% during dialysis.

Studies have shown no apparent changes in the pharmacokinetic properties of aciclovir or zidovudine when both are administered simultaneously to human immunodeficiency virus (HIV) infected patients.

Dosage adjustment for aciclovir tablets is recommended in renal impairment (see DOSAGE AND ADMINISTRATION). Plasma protein binding is low (9 to 33%).

## **INDICATIONS**

### Adults

Treatment of first episode (primary or nonprimary) genital herpes and the management of recurrent episodes of genital herpes in certain patients. Treatment of

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acute attacks of herpes zoster (shingles) when the duration of rash is less than 72 hours.

The management of patients with advanced symptomatic HIV disease (CD4+ counts <150 x 10<sup>6</sup>/L)

### Genital herpes

*Initial episodes.* The duration of viral shedding is reduced very significantly; the duration of pain and time to healing are also reduced. The promptness of initiation of therapy and/or the patient's prior exposure to *Herpes simplex* virus may influence the degree of benefit from therapy.

Intravenous aciclovir should be considered in patients in whom prostration, CNS involvement or inability to take oral medication requires hospitalisation and initiation of more aggressive management.

Aciclovir does not prevent the establishment of latency in initial episodes.

*Recurrent episodes. Suppression.* In patients with frequent recurrences, suppressive therapy prevents or reduces the frequency and/or severity of recurrences in a high proportion of patients. Abortive episodes (prodromal symptoms without vesicle formation) and occasional breakthrough episodes may, however, continue to occur during suppressive therapy.

Suppressive therapy is not considered appropriate for patients in whom attacks are mild, last for short periods and/or occur infrequently (e.g. less frequently than once a month).

Aciclovir is effective only during the period of intake and has no residual beneficial effect. It does not eradicate the body viral pool. Following cessation of therapy, the time to onset of recurrences, their frequency, severity and duration remain generally unaffected. Some patients may experience increased severity of the first episode following cessation of therapy.

The risk of inducing viral resistance and of potential long-term adverse effects (see PRECAUTIONS, Carcinogenesis, mutagenesis and impairment of fertility) should be weighed carefully before initiating suppressive therapy.

Asymptomatic cases of genital herpes are known to shed the virus with a high frequency. However, at present only limited data are available on the extent and frequency of viral shedding in patients receiving suppressive therapy. Therefore, if therapy with Aciclovir tablets is being used in the prenatal period (see PRECAUTIONS, Use in pregnancy), it should not be assumed that viral shedding has ceased. Pregnancy should be managed according to considerations normally applicable to patients with genital herpes.

In view of the complex and variable natural history of genital herpes, suppressive therapy should be interrupted periodically to ascertain whether the disease has

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undergone spontaneous change in frequency or severity (see DOSAGE AND ADMINISTRATION).

*Intermittent treatment.* For certain patients, intermittent short-term treatment of recurrences is effective. Although the average patient would derive limited benefits from such treatment, a minority of patients who have experienced severe, prolonged recurrent episodes or recurrences complicated by eczema, burns or immunosuppression may experience more appreciable benefits. In those patients, intermittent treatment may be more appropriate than suppressive therapy when recurrences are infrequent.

### Herpes zoster

In controlled trials aciclovir tablets were shown to reduce acute pain and rash progression in adult patients of all ages with *Herpes zoster* in whom the duration of rash was less than 72 hours. Aciclovir tablets appeared to be relatively less effective in younger adults, in whom *Herpes zoster* is generally a milder disease.

In ophthalmic zoster, oral aciclovir has been shown to reduce the incidence of stromal keratitis and both the incidence and severity of anterior uveitis, but not other ocular complications or acute pain.

*Note.* In immunocompetent patients with very severe *Herpes zoster*, immunocompromised patients, or in patients with impaired absorption from the gut, consideration should be given to intravenous dosing.

### Advanced symptomatic HIV disease

Studies have shown that oral aciclovir reduced mortality in patients with advanced HIV disease (CD4+ counts < 150 x 10<sup>6</sup>/L). In addition, oral aciclovir provided effective prophylaxis for herpes virus disease. No significant effect was seen on the prophylaxis of cytomegalovirus (CMV) disease or Epstein-Barr virus (EBV) disease.

## **CONTRAINDICATIONS**

Known hypersensitivity to aciclovir and valaciclovir or to any of the excipients.

## **PRECAUTIONS**

### Use with caution in the following circumstances

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. Therefore the potential for the development of resistance HSV strains in patients treated with aciclovir should be borne in mind. Prolonged or repeated courses of aciclovir in severely immuno-compromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to

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continued aciclovir treatment. The relationship between the level of *in vitro* sensitivity of herpes viruses to aciclovir and clinical response to therapy has not been adequately established.

As aciclovir has been associated with reversible encephalopathic changes, it should be used with caution in patients with underlying neurological abnormalities, significant hypoxia or serious renal, hepatic or electrolyte abnormalities. It should also be used with caution in patients who have manifested neurological reactions to cytotoxic medicines or are receiving interferon or intrathecal methotrexate concomitantly.

Animal studies indicate that at high doses aciclovir is cytotoxic.

#### Impaired renal function

The dosage should be adjusted in patients with renal impairment (see DOSAGE AND ADMINISTRATION). Care should be taken to maintain adequate hydration in patients receiving high oral doses of aciclovir.

#### Use in the elderly

It is important to maintain adequate hydration in elderly patients taking high doses of aciclovir tablets for the treatment of herpes zoster. Aciclovir is eliminated by renal clearance. Therefore the dose must be reduced in patients with renal impairment. Elderly patients are likely to have reduced renal function and therefore the need for dose reduction must be considered in this group of patients. Both elderly patients and patients with renal impairment are at increased risk of developing neurological side effects and should be closely monitored for evidence of these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (see ADVERSE EFFECTS).

#### Carcinogenesis, mutagenesis, impairment of fertility

##### *Mutagenesis*

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

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

##### *Carcinogenesis*

Aciclovir was positive in one of two mouse cell transformation systems *in vitro*. Inoculation of the transformed cells into immunosuppressed 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.

#### *Effects on fertility*

There is no information on the effect of Zovirax 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.

#### Use in pregnancy (Category B3)

Animal studies show that aciclovir crosses the placenta readily. Aciclovir was not teratogenic in the mouse (450mg/kg/day orally), rabbit (50/mg/kg/day subcutaneously and intravenously) or rat (50/mg/kg/day subcutaneously) when dosed throughout the period of major organogenesis. This exposure in the rat resulted in plasma levels 11-fold the mean steady state peak concentration in human doses of 800mg every four hours. In additional studies in which rats were given three subcutaneous doses of aciclovir 100mg/kg on gestation day 10, fetal abnormalities, eg head and tail anomalies, were reported (exposure was 63-fold human levels after 800mg every four hours.)

There have been no adequate and well-controlled studies concerning the safety of aciclovir in pregnant women. It should not be used during pregnancy unless the benefits to the patient clearly outweigh the potential risks to the fetus. If suppressive therapy is used in the perinatal period, it should not be assumed that viral shedding has ceased, or that the risk to fetus/neonate has decreased. Pregnancy should be managed according to consideration normally applicable to patients with genital herpes.

Australian categorisation definition of **Category B3**: Drugs which have 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 fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

#### Use in lactation

Limited human data show that aciclovir does pass into breast milk. Aciclovir should only be administered to breastfeeding mothers if the benefits to the mother outweigh the potential risks to the baby.

#### Paediatric Use

Safety and effectiveness in children have not been established.

#### Effects on the ability to drive and operate machinery

The clinical status of the patient and the adverse event profile of Aciclovir Sandoz should be borne in mind when considering the patient's ability to drive or operate

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machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

## **INTERACTIONS WITH OTHER MEDICINES**

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any medicines administered concurrently that compete with this mechanism may increase aciclovir plasma concentrations. Probenecid and cimetidine increase the AUC of aciclovir by this mechanism and reduce aciclovir renal clearance. However, no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

In patients receiving Aciclovir Sandoz, caution is required during concurrent administration with medicines which compete with aciclovir for elimination, because of the potential for increased plasma levels of one or both medicines or their metabolites. Increase in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant agent used in transplants, have been shown when the medicines are coadministered. However, no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

In patients over 60 years of age, concurrent use of diuretics increases plasma levels of aciclovir very significantly. It is not known whether a similar effect occurs in young adults.

An experimental study on five male subjects indicates that concomitant therapy with aciclovir increases AUC of totally administered theophylline. It is recommended to measure plasma concentrations during concomitant therapy with aciclovir.

In patients receiving zidovudine no significant overall increase in toxicity was associated with the addition of aciclovir. No data are available on interactions between aciclovir and other antiretroviral therapies. Aciclovir should also be used with caution in patients who have manifested neurological reactions to cytotoxic drugs or are receiving concomitantly interferon or intrathecal methotrexate (See **PRECAUTIONS**).

## **ADVERSE EFFECTS**

Aciclovir tablets appear to be generally very well tolerated. Adverse effects are usually mild. However, the following have been noted:

Reversible neurological reactions, notably dizziness, confusion states, hallucinations, somnolence and convulsions, have occasionally been reported, usually in patients with renal impairment in whom the dosage was in excess of that recommended or with other predisposing factors.

*Short-term administration for genital herpes.* Nausea and/or vomiting and headache were the most frequent adverse effects. Less frequent (< 1%) reactions included diarrhoea, dizziness, anorexia, fatigue, oedema, skin rashes, leg pain, inguinal

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adenopathy, medication taste and sore throat. Occasional changes in hepatic enzymes and changes in haematological parameters were also noted.

*Long-term suppressive therapy for genital herpes.* Nausea and/or vomiting, headache, diarrhoea, vertigo and arthralgia were the most frequent adverse effects. Less frequent adverse effects included skin rash, insomnia, fatigue, fever, palpitation, sore throat, superficial thrombophlebitis, muscle cramps, pars planitis, menstrual abnormalities, lymphadenopathy, irritability, accelerated hair loss, depression and occasional increases in hepatic enzymes.

*Herpes zoster.* The most commonly reported adverse effect was gastrointestinal disturbance. Other reports included aching, chest pain, confusion, constipation, diarrhoea, giddiness, hallucinations, headache, insomnia, nausea, rash, shaking, taste disturbance, tremor, vertigo and malaise, vomiting and mental status alteration. Significantly, the overall incidence of side effects reported was the same in patients on placebo.

*Advanced symptomatic HIV disease.* In patients receiving antiretroviral therapy (mainly oral zidovudine), no significant overall increase in toxicity was associated with the addition of aciclovir. However, moderate increases in anaemia and neutropenia were seen in some studies in patients with advanced HIV disease.

The frequency categories associated with the adverse events below are estimates. For most events, suitable data for estimating incidence were not available. In addition, adverse events may vary in their incidence depending on the indication.

The following convention has been used for the classification of undesirable effects in terms of frequency: very common greater than or equal to 1/10, common greater than or equal to 1/100 and < 1/10, uncommon greater than or equal to 1/1,000 and < 1/100, rare greater than or equal to 1/10,000 and < 1/1,000, very rare < 1/10,000.

*Blood and lymphatic system disorders*

Very rare: anaemia, leucopenia, thrombocytopenia.

*Immune system disorders*

Rare: anaphylaxis.

*Psychiatric and nervous system disorders*

Common: headache, dizziness, confusion, hallucinations, somnolence, convulsions.

Very rare: agitation, tremor, ataxia, dysarthria, psychotic symptoms, encephalopathy, coma.

The above events are reversible and usually reported in patients with renal impairment in whom the dosage was in excess of that recommended, or with other predisposing factors.

*Vascular disorders*

Common: phlebitis.

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*Respiratory, thoracic and mediastinal disorders*

Rare: dyspnoea.

*Gastrointestinal disorders*

Common: nausea, vomiting, diarrhoea, abdominal pain.

*Hepatobiliary disorders*

Rare: reversible rises in bilirubin and liver related enzymes.

Very rare: hepatitis, jaundice.

*Skin and subcutaneous tissue disorders*

Common: pruritus, rashes (including photosensitivity).

Uncommon: urticaria, accelerated diffuse hair loss.

Accelerated diffuse hair loss has been associated with a wide variety of disease processes and medicines; the relationship of the event to aciclovir therapy is uncertain.

Rare: angioedema.

*Renal and urinary disorders*

Rare: increases in blood urea and creatinine.

Very rare: acute renal failure, renal pain.

Renal pain may be associated with renal failure.

*General disorders and administration site conditions*

Common: fatigue, fever.

## **DOSAGE AND ADMINISTRATION**

*Initial genital herpes.* One 200mg tablet every four hours while awake, for a total of 5 tablets daily for ten days (total 50 tablets).

*Chronic suppressive therapy for recurrent genital herpes.* One 200mg tablet three times daily for up to six months. Many patients will, however, respond satisfactorily to one 200mg tablet twice daily. Occasional breakthroughs have been reported in patients receiving 2, 3, 4 or 5 tablets daily. Suppressive therapy is not indicated for all patients with recurrent genital herpes (see INDICATIONS). Therapy should be discontinued at the end of six months to ascertain whether any change has occurred in the natural course of the disease in the particular patient.

*Intermittent therapy for recurrent genital herpes in certain patients* (see INDICATIONS). One 200mg tablet every four hours while awake, for a total of 5 tablets daily for five days (total 25 tablets). Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

*Herpes zoster in adults.* 800mg (1 tablet of Aciclovir Sandoz 800mg) five times daily at intervals of approximately four hours, omitting the night-time dose. Therapy should commence as early as possible after the onset of rash but definitely within 72 hours of the appearance of the rash. Treatment should be continued for seven days.

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For herpes zoster ophthalmicus, the recommended duration of therapy is seven to ten days. Attention should be given to maintaining adequate hydration in elderly patients.

*Advanced symptomatic HIV disease.* 800mg (1 tablet of Aciclovir Sandoz 800mg) four times daily at intervals of approximately six hours. The duration of treatment in the controlled trials was 12 months. Oral aciclovir was given in conjunction with oral zidovudine in most studies, at a range of doses. In a high percentage of the patients in the controlled trials, an initial zidovudine dose of 2g daily followed after four weeks by 1g daily was used. These doses are above the currently recommended dose of 600mg daily. The safety and effectiveness of oral aciclovir taken in conjunction with other antiretroviral therapies could not be assessed.

#### Use in patients with acute or chronic renal impairment

No data are currently available on the kinetics of the oral aciclovir in patients with impaired renal function. However, based on studies with intravenous aciclovir infusion and theoretical considerations, the following dosage adjustments are recommended.

*Genital herpes.* For patients with creatinine clearance  $<10\text{mL/minute}/1.73\text{m}^2$ , a 200mg dose every twelve hours is recommended.

*Herpes zoster and in the management of patients with advanced symptomatic HIV disease.* For patients with creatinine clearance in the range 10 to  $25\text{mL/minute}/1.73\text{m}^2$ , it is recommended to adjust the dosage to 800mg three times daily (approximately every eight hours). For patients with creatinine clearance  $<10\text{mL/minute}/1.73\text{m}^2$ , 800mg twice daily (approximately every twelve hours).

## **OVERDOSAGE**

### Symptoms

Aciclovir is only partly absorbed in the gastrointestinal tract. Patients have ingested overdoses of up to 20g aciclovir on a single occasion, usually without toxic effects. Accidental, repeated overdose of oral aciclovir over several days have been associated with gastrointestinal effects (such as nausea and vomiting) and neurological effects (headache and confusion).

Overdosage of intravenous aciclovir has resulted in elevations of serum creatinine, blood urea nitrogen and subsequent renal failure. Neurological effects including confusion, hallucinations, agitation, seizures and coma have been described in association with intravenous overdosage.

### Treatment

Patients should be observed closely for signs of toxicity. Adequate hydration is essential to reduce the possibility of crystal formation in urine. Haemodialysis significantly enhances the removal of aciclovir from the blood and may therefore, be considered a management option in the event of symptomatic overdose.

Contact the Poison Information Centre on 13 11 26 for advice on the management of an overdose.

## **PRESENTATION AND STORAGE CONDITIONS**

Aciclovir Sandoz 200mg Tablets, are white, round tablets with a break score on one side. Available in blister packs of 25 or 90 tablets.

Aciclovir Sandoz 800mg Tablets, are white, oblong, biconvex tablets with a break score on both sides. Available in blister packs of 35 or 120 tablets.

Store below 25 °C.

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

Sandoz Pty Ltd  
ABN 60 075 449 553  
54 Waterloo Road  
Macquarie Park, NSW 2113  
Australia  
Tel: 1800 634 500

## **POISON SCHEDULE OF THE MEDICINE**

S4 – Prescription only Medicine

**DATE OF FIRST INCUSION ON THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 27/04/1999**

Date of most recent amendment: 25/02/2016