# AUSTRALIAN PRODUCT INFORMATION – APO-ACICLOVIR (ACICLOVIR)

## 1 NAME OF THE MEDICINE

Aciclovir

## 2 AND 3 QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

Aciclovir is a synthetic acyclic purine nucleoside analogue. It is a white crystalline powder slightly soluble in water and practically insoluble in most organic solvents.

Each tablet contains 200mg or 800mg of acyclovir as the active ingredient.

In addition, each tablet contains the following inactive ingredients: lactose monohydrate(200mg tablet only), magnesium stearate, colloidal anhydrous silica, croscarmellose sodium, –microcrystalline cellulose , brilliant blue FCF (800mg tablet only) and indigo carmine.

Aciclovir 200mg tablets contains sugars as lactose.
Aciclovir tablets are gluten free.

200mg tablets are round, blue flat faced, bevel-edged tablets, engraved “APO” over “200” on one side and the other side plain.

800mg tablets are oval, blue, biconvex tablets, scored. Engraved APO partial bisect 800 on one side, plain in the other side.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

Aciclovir tablets are indicated for use in adult patients for:

- the treatment of first episode (primary or non-primary) genital herpes and the management of recurrent episodes of genital herpes in certain patients;
- the treatment of 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 106/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, central nervous system involvement or inability to take oral medication requires hospitalisation and initiation of more aggressive management.

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

Recurrent Episodes

a) 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 (for example, 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 Section 4.6 Fertility, pregnancy and lactation, refer to effects on fertility, and see Section 5.3 Preclinical safety data, refer to Genotoxicity and Carcinogenicity) 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 Section 4.6 Fertility, pregnancy and lactation, 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 undergone spontaneous change in frequency or severity (see Section 4.2 Dose and method of administration).

b) 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 was 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. The same treatment 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 immune-competent patients with very severe herpes zoster, immune-compromised patients, or in patients with impaired absorption from the gut, consideration should be given to intravenous dosing.

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

## 4.2 DOSE AND METHOD OF ADMINISTRATION

**Treatment of Initial Genital Herpes**
One 200 mg tablet every four (4) hours, while awake, for a total of 5 tablets daily for 10 days (total 50 tablets).

**Chronic Suppressive Therapy for Recurrent Genital Herpes**
One 200 mg tablet 3 times daily for up to 6 months. Many patients will, however, respond satisfactorily to one 200 mg 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 Section 4.1 Therapeutic indications). Therapy should be discontinued at the end of 6 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 Section 4.1 Therapeutic indications)**
One 200 mg tablet every 4 hours, while awake, for a total of 5 tablets daily for 5 days (total 25 tablets). Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

**Treatment of Herpes Zoster in Adults**
800 mg, 5 times daily at approximately 4 hourly intervals, 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 7 days. For herpes zoster ophthalmicus, the recommended duration of therapy is 7 to 10 days. Attention should be given to maintaining adequate hydration in elderly patients.

**Management of Patients with Advanced Symptomatic HIV Disease**
800 mg four times daily at approximately six hourly intervals. 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 2 g daily, followed after 4 weeks by 1 g daily, was used. These doses are above the currently recommended dose of 600 mg daily. The safety and effectiveness of oral aciclovir taken in conjunction with other antiretroviral therapies could not be assessed.

**Patients with acute or chronic renal impairment**

No data are currently available on the kinetics of 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 mL/min/1.73 m2, a 200 mg dose every 12 hours is recommended.

**Herpes Zoster, and in the Management of Patients with Advanced Symptomatic HIV Disease**

For patients with creatinine clearance in the range 10-25 mL/min/1.73 m2, it is recommended to adjust the dosage to 800 mg three times daily (approximately every 8 hours). For patients with creatinine clearance <10 mL/min/1.73 m2, 800 mg twice daily (approximately every 12 hours).

**Dosage in the elderly**

The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly (see above). Adequate hydration of elderly patients taking high oral doses of aciclovir should be maintained.

## 4.3 CONTRAINDICATIONS

Aciclovir tablets are contraindicated in patients known to be hypersensitive to aciclovir or valaciclovir.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**Hydration status**

Care should be taken to maintain adequate hydration in patients receiving high oral doses of aciclovir.

**Development of resistant strains**

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 immune-compromised as well as immuno-competent patients receiving aciclovir for Herpes simplex infections. Therefore the potential for the development of resistant HSV strains in patients treated with aciclovir should be borne in mind. The relationship between the level of *in vitro* sensitivity of herpes viruses to aciclovir and clinical response to therapy has not been adequately established.

**Other conditions**

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 drugs or are receiving concomitantly interferon or intrathecal methotrexate. Animal studies indicate that at high doses aciclovir is cytotoxic.

### Use in renal impairment and in elderly patients

Aciclovir is eliminated by renal clearance, therefore the dose must be reduced in patients with renal impairment (see Section 4.2 Dosage and administration). 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 Section 4.8 Adverse effects (undesirable effects)). The dosage should be adjusted in patients with renal impairment (see Section 4.2 Dosage and administration).

### Paediatric use

Safety and effectiveness in children have not been established.

### Effects on laboratory tests

No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs 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, caution is required during concurrent administration with drugs which compete with aciclovir for elimination, because of the potential for increased plasma levels of one or both drugs 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 drugs are co-administered. 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. 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.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on fertility

There is no information on the effect of acyclovir on human female fertility.

**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 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 humans after doses of 800 mg every 4 hours. In additional studies in which rats were given 3 subcutaneous doses of 100 mg/kg aciclovir on gestation day 10, foetal abnormalities, such as head and tail anomalies, were reported (exposure was 63 fold human levels after 800 mg 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 foetus. If suppressive therapy is used in the perinatal period it should not be assumed that viral shedding has ceased, or that the risk to foetus/neonate has decreased. Pregnancy should be managed according to considerations normally applicable to patients with genital herpes.

**Use in lactation**

Limited human data show that aciclovir does pass into breast milk. Aciclovir should only be administered to nursing mothers if the benefits to the mother outweigh the potential risks to the baby. Caution is therefore advised if aciclovir is to be administered to a nursing woman.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The clinical status of the patient and the adverse event profile of aciclovir should be borne in mind when considering the patient's ability to drive or operate machinery. There have been no studies to investigate the effect of aciclovir on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

**Short-term Administration for Treatment 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 adenopathy, medication taste and sore throat. Occasional changes in liver 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 liver enzymes.

**Treatment of Herpes Zoster**

The most commonly reported adverse effect in clinical trials 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.

**Patients with Advanced Symptomatic HIV Disease**

In patients receiving anti-retroviral 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 ≥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.

**Blood and lymphatic system disorders**

Very rare: Anaemia, leukopenia, 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.

**Respiratory, thoracic and mediastinal disorders**

Rare: Dyspnoea

**Gastrointestinal disorders**

Common: Nausea, vomiting, diarrhoea, abdominal pains

**Hepato-biliary 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

**Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems or contact Apotex Medical Information enquiries/Adverse Drug Reaction Reporting on 1800 195 055.

## 4.9 OVERDOSE

**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 overdoses 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.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

### Mechanism of action

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. 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

No data available.

## 5.2 PHARMACOKINETIC PROPERTIES

### Absorption

Aciclovir is only partially and variably absorbed from the gut. Estimated bioavailability following a dose of 200 mg is about 20%, and decreases to about half of this with an 800 mg dose. Mean steady state peak and trough concentrations during dosage of 200 mg administered four hourly were 0.49 (range 0.47 – 0.54) µg/mL and 0.31 (range 0.18 – 0.41) µg/mL respectively, and after 800 mg six hourly were 1.43 (range 0.66 – 1.8) µg/mL and 0.55 (range 0.14 – 1.10) µg/mL respectively. Both peaks 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.

### Distribution

Plasma protein binding is low (9 to 33%).

### Excretion

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 drug 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-carboxymethoxymethylguanine is the major metabolite of aciclovir and accounts for 10-15% of the dose excreted in the urine following i.v. administration.

In children aged 0-3 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. The 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 ± 5.9 SD 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 HIV infected patients.

Dosage adjustment for aciclovir is recommended in renal impairment (see Section 4.2 Dosage and administration).

## 5.3 PRECLINICAL SAFETY DATA

**Genotoxicity**

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 these 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 tumourogenicity but in these species the absorption of oral aciclovir is poor and possibly self-limiting.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

Refer to section 2 and 3- qualitative and quantitative composition and pharmaceutical form.

## 6.2 INCOMPATIBILITIES

See Section 4.5- Interactions with other medicines and other forms of interactions.

## 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below $25^0$C.

## 6.5 NATURE AND CONTENTS OF CONTAINER

200mg tablets:
Blister pack (clear PVC/PVDC/aluminium silver foil) of 25 or 50 or 90 tablets (AUST R 159140).

800mg tablets:
Blister pack (clear PVC/PVDC/aluminium silver foil) of 35 tablets (AUST R 159141).

Not all strengths, pack sizes and/or pack types may be available.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

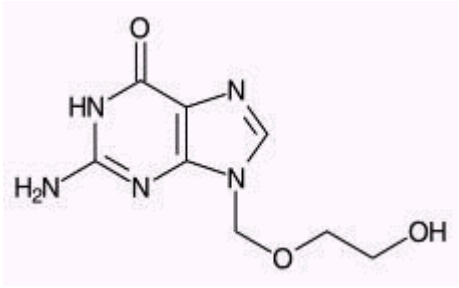
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

**Chemical structure**

Chemical name: 9-((2-hydroxyethoxy) methyl)guanine.

Structural Formula:




Molecular Formula: $C_8H_{11}N_5O_3$

Molecular Weight: 225.2

**CAS number**

59277-89-3

# 7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

# 8 SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

Tel: (02) 8877 8333
Web: www1.apotex.com/au

# 9 DATE OF FIRST APPROVAL

Apo-Aciclovir 200mg and 800mg tablets: 26 Aug 2009

## 10 DATE OF REVISION

08 August 2018.

**Summary table of changes**

| Section Changed | Summary of new information |
|---|---|
| **All** | Reformatted product information |
| **2&3** | Updated to correct IHIN names |
| **9** | Update date as per ARTG start date |