ACIVIR DT Tablets (Aciclovir)

Composition

ACIVIR-200 DT

Each dispersible tablet contains

Aciclovir, BP ..... 200 mg

(in a flavoured base)

ACIVIR-400 DT

Each dispersible tablet contains

Aciclovir, BP ..... 400 mg

(in a flavoured base)

ACIVIR-800 DT

Each dispersible tablet contains

Aciclovir, BP ..... 800 mg

(in a flavoured base)

Dosage Form

Dispersible tablet

Pharmacology

Pharmacodynamics

Aciclovir is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against human herpes viruses, including herpes simplex virus (HSV) types 1 and 2, varicella zoster virus (VZV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV). In cell culture, aciclovir has the greatest antiviral activity against HSV-1, followed (in decreasing order of potency) by HSV-2, VZV, EBV and CMV.

The inhibitory activity of aciclovir for HSV 1 and HSV 2, VZV, EBV and CMV is highly selective. The enzyme thymidine kinase (TK) of normal, non-infected cells does not use aciclovir effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV, VZV and EBV converts aciclovir to aciclovir monophosphate, a nucleoside analogue, which is further converted to the diphosphate and finally to the triphosphate by cellular enzymes. Aciclovir triphosphate interferes with the viral DNA polymerase and inhibits viral DNA replication, with

resultant chain termination following its incorporation into the viral DNA.

Prolonged or repeated courses of aciclovir in severely immune compromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued aciclovir treatment.

Most of the clinical isolates with reduced sensitivity have been relatively deficient in viral TK; however, strains with altered viral TK or viral DNA polymerase have also been reported. In vitro exposure of HSV isolates to aciclovir can also lead to the emergence of less sensitive strains. The relationship between the *in vitro*-determined sensitivity of HSV isolates and clinical response to aciclovir therapy is not clear.

All patients should be cautioned to ensure they avoid the potential of virus transmission, particularly when active lesions are present.

Pharmacokinetics

Aciclovir is only partially absorbed from the gut. Mean steady-state peak plasma concentrations (C_{ssmax}) following doses of 200 mg administered 4-hourly were 3.1 µMol (0.7 µg/ml) and equivalent trough plasma levels (C_{ssmin}) were 1.8 µMol (0.4 µg/ml). Corresponding Cssmax levels following doses of 400 mg and 800 mg administered four-hourly were 5.3 µMol (1.2 µg/ml) and 8 µMol (1.8 µg/ml), respectively, and equivalent C_{ssmin} levels were 2.7 µMol (0.6 µg/ml) and 4 µMol (0.9 µg/ml).

In adults, the terminal plasma half of aciclovir after administration of intravenous aciclovir is about 2.9 hours. Most of the drug is excreted unchanged by the kidneys. Renal clearance of aciclovir is substantially greater than creatinine clearance, indicating that tubular secretion in addition to glomerular filtration contributes to the renal elimination of the drug. 9-Carboxymethox--methylguanine is the only significant metabolite of aciclovir and accounts for approximately 10–15% of the administered dose recovered from the urine. When aciclovir is given 1 hour after 1 g of probenecid the terminal half life and the area under the plasma concentrations-time cure is extended by 18% and 40%, respectively.

In adults, mean C_{ssmax} levels following a 1-hour infusion of 2.5 mg/kg, 5 mg/kg and 10 mg/kg were 22.7 µMol (5.1 µg/ml), 43.6 µMol (9.8 µg/ml) and 92 µMol (20.7 µg/ml), respectively. The corresponding C_{ssmin} levels 7 hours later were 2.2 µMol (0.5 µg/ml), 3.1 µMol (0.7 µg/ml) and 10.2 µMol (2.3 µg/ml), respectively. In children over 1 year of age, similar mean C_{ssmax} and C_{ssmin} levels were observed when a dose of 250 mg/m^2 was substituted for 5 mg/kg and a dose of 500 mg/m^2 was substituted by 10 mg/kg. In neonates and young infants (0–3 months of age) treated with doses of 10 mg/kg administered by infusion over a 1-hour period every 8 hours, the C_{ssmax} was found to be 61.2 µMol (13.8 µg/ml) and the C_{ssmin} to be 0.1 µMol (2.3 µg/ml). The terminal plasma half-life in these patients was 3.8 hours.

In the elderly, total body clearance falls with increasing age associated with decreases in creatinine clearance although there is little change in the terminal plasma half-life.

In patients with chronic renal impairment, the mean terminal half-life was found to be 19.5 hours. The mean aciclovir half-life during haemodialysis was 5.7 hours. Plasma aciclovir levels dropped approximately 60% during dialysis.

Cerebrospinal fluid levels are approximately 50% of corresponding plasma levels. Plasma proteins binding is relatively low (9–33%) and drug interactions involving binding site displacement are not anticipated.

Studies have shown no apparent changes in the pharmacokinetic behaviour of aciclovir or zidovudine when both are administered simultaneously to HIV-infected patients.

Indications

ACIVIR DT is indicated for the treatment of *Herpes simplex* virus infections of the skin and mucous membrane, including initial and recurrent genital herpes, suppression of recurrent *Herpes simplex* infections in immune-competent patients; prophylaxis of *Herpes simplex* infection in immunocompromised patients; VZV infections (chickenpox) and *Herpes zoster* (shingles) infections; and management of severely immunocompromised patients, namely those with HIV disease (CD4+ counts <200/mm^3, including patients with AIDS or severe ARC), or after bone marrow transplantation.

Dosage and Administration

Treatment of Herpes Simplex

Herpes Labialis

For the treatment of herpes labialis, 200 mg **ACIVIR DT** should be taken five times daily for a period of 5 days.

Genital Herpes

Treatment of Initial Genital Herpes

For the initial episodes of genital herpes, 200 mg of **ACIVIR DT** should be given every 4 hours, five times daily for a period of 10 days.

Treatment of Recurrent Episodes

Episodic Therapy

For the episodic treatment, 200 mg of **ACIVIR DT** should be given every 4 hours, five times daily for a period of 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Suppressive Therapy

In Immunocompetent Patients

For the suppression of recurrent genital herpes in immunocompetent patients, 400 mg of **ACIVIR DT** should be given twice daily for up to 12 months, followed by re-evaluation.

Alternative regimens have included doses ranging from 200 mg three times daily to 200 mg five times daily.

The frequency and severity of episodes of untreated genital herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of therapy with **ACIVIR DT**.

In HIV-infected patients

For management of immunocompromised patients, 800 mg **ACIVIR DT** should be taken four times daily at approximately 6-hourly intervals.

In patients with advanced HIV disease, the study treatment was 12 months, but it is likely that these patients would continue to benefit from a longer duration of treatment.

Treatment of VZV Infections

Chickenpox

Paediatric Dosage

For treatment of chickenpox, children over the age of 6 years can be given 800 mg **ACIVIR DT** four times daily, and children between the ages of 2 and 6 years can be given 400 mg **ACIVIR DT** four times daily.

Children below the age of 2 years can be given 200 mg **ACIVIR DT** four times daily. Dosing can be more accurately calculated as 20 mg aciclovir/kg bodyweight (not to exceed 800 mg) four times daily. Treatment should continue for 5 days.

No specific data are available on the treatment of herpes zoster infections in immunocompetent children.

Limited data suggest that for management of severely immunocompromised children, over 2 years of age, the adult dose may be given.

Adults Dosage

For the treatment of chickenpox in adults, 800 mg **ACIVIR DT** should be taken five times daily at approximately 4-hourly intervals, omitting the night-time dose. Treatment should continue for 7 days.

Herpes zoster

For treatment of herpes zoster infections, 800 mg **ACIVIR DT** should be taken five times daily at approximately 4-hourly intervals, omitting the night-time dose. Treatment should continue for 7 days.

Dosing should begin as early as possible after the start of an infection. Treatment yields better results if initiated as soon as possible after onset of the rash.

Indications	**Daily Dosage**	**Duration**
Herpes labialis	200 mg × 5 times	5 days

Genital Herpes ***Initial episodes*** ***Recurrent episodes*** 1. Episodic therapy 1. Suppressive therapy (immunocompetent) 1. Suppressive therapy (HIV-infected patients)	200 mg × 5 times 200 mg × 5 times 200 mg × 4 times or 400 mg × 2 times 800 mg × 4 times	10 days 5 days 1 year 1 year
Chicken pox 1. ***Paediatric*** *Children aged below 2 years (calculated as 20 mg/kg body weight and not exceeding 800 mg)* *Children aged between 2 and 6 years* *Children aged above 6 years* ***b. Adults*** **Herpes zoster (Adults)**	200 mg × 4 times 400 mg × 4 times 800 mg × 4 times 800 mg × 5 times 800 mg × 5 times	5 days 5 days 5 days 7 days 7 days

Directions for Use

Disperse the tablet in a teaspoonful (5 ml) of boiled and cooled water before administration.

Contraindications

ACIVIR DT is contraindicated in patients who develop a hypersensitivity to aciclovir or valaciclovir, or to any of the excipients.

Warnings and Precautions

General

Caution should be exercised when administering aciclovir to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction and/or the risk of reversible central nervous system (CNS) symptoms such as those that have been reported in patients treated with intravenous aciclovir. Adequate hydration should be maintained.

Drug Interactions

No clinically significant interactions have been identified.

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that complete with this mechanism may increase aciclovir plasma concentrations. Probenecid and cimetidine increase the AUC of aciclovir by this mechanism, and

reduce aciclovir renal clearance. Similarly, increases in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolatemofetil, an immunosuppressant agent used in transplant patients, have been shown when the drugs are co-administered. However, no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

Renal Impairment

Dosage adjustment is recommended when administering aciclovir to patients with renal impairment. In the treatment and prophylaxis of herpes simplex infections in patients with impaired renal function, the recommended oral doses will not lead to accumulation of aciclovir above levels that have been established safe by intravenous infusion. However, for patients with severe renal impairment (creatinine clearance less than 10 mL/minute) an adjustment of dosage to 200 mg twice daily at approximately 12-hourly intervals is recommended.

In the treatment of VZV and herpes zoster infections and in the management of severely immunocompromised patients, it is recommended to adjust the dosage to 800 mg twice daily, at approximately 12-hourly intervals, for patients with severe renal impairment (creatinine clearance less than 10 mL/minute) and to 800 mg three times daily, at intervals of approximately 8 hours, for patients with moderate renal impairment (creatinine clearance in the range of 10 to 25 mL/minute).

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. A prospective epidemiologic registry of aciclovir use during pregnancy was established in 1984 and completed in April 1999. There were 749 pregnancies followed in women exposed to systemic aciclovir during the first trimester of pregnancy, resulting in 756 outcomes. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable or definitive conclusions regarding the safety of aciclovir in pregnant women and their developing foetuses. Aciclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation

Following oral administration of 200 mg aciclovir five times a day, aciclovir has been detected in breast milk at concentrations ranging from 0.6 to 4.1 times the corresponding plasma levels. These levels would potentially expose nursing infants to aciclovir dosages of up to 0.3 mg/kg/day. Caution is therefore advised if **ACIVIR DT** is to be administered to a lactating mother.

Paediatric Use

Safety and effectiveness of oral formulations of aciclovir in paediatric patients younger than 2 years of age have not been established.

Geriatric Use

Of 376 subjects who received oral aciclovir in a clinical study of herpes zoster treatment in immunocompetent subjects aged 50 years, 244 were aged 65 years and over while 111 were 75 years and over. No overall differences in effectiveness for time to cessation of new lesion formation or time to healing were reported between geriatric subjects and younger adult subjects. The

duration of pain after healing was longer in patients aged 65 years and over. Nausea, vomiting and dizziness were reported more frequently in elderly subjects. Elderly patients are more likely to have reduced renal function and require dose reduction. Elderly patients are also more likely to have renal or CNS adverse events. With respect to CNS adverse events observed during clinical practice, somnolence, hallucinations, confusion, and coma were reported more frequently in elderly patients

In the elderly, total aciclovir body clearance declines in parallel with creatinine clearance. Adequate hydration of elderly patients taking high oral doses of **ACIVIR DT** should be maintained.

Hydration Status

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

Undesirable Effects

Clinical Trials Experience

Herpes simplex

***Short-Term Administration*:** The most frequent adverse events reported during clinical trials of treatment of genital herpes with aciclovir 200 mg administered orally five times daily every 4 hours for 10 days were nausea and/or vomiting in 8 of 298 patient treatments (2.7%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

***Long-Term Administration*:** The most frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) two times daily for 1 year in 586 patients treated with aciclovir were nausea (4.8%) and diarrhoea (2.4%). The 589 control patients receiving intermittent treatment of recurrences with aciclovir for 1 year reported diarrhoea (2.7%), nausea (2.4%) and headache (2.2%).

Herpes zoster

The most frequent adverse event reported during three clinical trials of the treatment of herpes zoster (shingles) with 800 mg of oral aciclovir, given five times daily for 7 to 10 days, in 323 patients was malaise (11.5%). The 323 placebo recipients reported malaise (11.1%).

Chickenpox

The most frequent adverse event reported during three clinical trials of the treatment of chickenpox with oral aciclovir at doses of 10–20 mg/kg four times daily for 5 to 7 days, or 800 mg four times daily for 5 days in 495 patients was diarrhoea (3.2%). The 498 patients receiving placebo reported diarrhoea (2.2%).

Observed During Clinical Practice

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of aciclovir. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to aciclovir, or a combination of these factors:

General: Anaphylaxis, angio-oedema, fever, headache, pain, peripheral oedema.

Nervous: Aggressive behaviour, agitation, ataxia, coma, confusion, decreased consciousness, delirium, dizziness, dysarthria, encephalopathy, hallucinations, paraesthesia, psychosis, seizure, somnolence, tremors. These symptoms may be marked, particularly in older adults or in patients with renal impairment.

Digestive:Diarrhoea , gastrointestinal distress, nausea.

Haematologic and Lymphatic: Anaemia, leucocytoclastic vasculitis, leucopenia, lymphadenopathy, thrombocytopenia.

Hepatobiliary Tract and Pancreas: Elevated liver function tests, hepatitis, hyperbilirubinaemia, jaundice.

Musculoskeletal: Myalgia.

Skin: Alopecia, erythema multiforme, photosensitive rash, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria.

Special Senses: Visual abnormalities.

Urogenital: Renal failure, renal pain (may be associated with renal failure), elevated blood urea nitrogen, elevated creatinine, haematuria.

Respiratory: Dyspnoea

Overdosage

Aciclovir is only partly absorbed in the gastrointestinal tract. Patients have ingested overdoses of up to 20 g 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.

Patients should be observed closely for signs of toxicity. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered a management option in the event of symptomatic overdose.

Shelf-Life

3 years

Storage and Handling Instructions

Store in a cool, dry place.

Packaging Information

ACIVIR-200 DT: Blister pack of 10 tablets

ACIVIR-400 DT: Blister pack of 5 tablets

ACIVIR-800 DT: Blister pack of 5 tablets

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