PROFESSIONAL INFORMATION FOR ACITAB DT 200 / 400 / 800 DT

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ACITAB-200 DT (200 mg, dispersible tablets)

ACITAB-400 DT (400 mg, dispersible tablets)

ACITAB-800 DT (800 mg, dispersible tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains acyclovir 200 mg.

Each dispersible tablet contains acyclovir 400 mg.

Each dispersible tablet contains acyclovir 800 mg.

Sugar free

Contains sweetener:

ACITAB-200 DT - Aspartame 5 mg / tablet

ACITAB-400 DT - Aspartame 10 mg / tablet

ACITAB-800 DT - Aspartame 20 mg / table

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Dispersible tablets

ACITAB-200 DT:

White to off-white, circular, flat, bevelled, uncoated tablets with “AC 200” debossed on one face and a central break-line on the other.

ACITAB-400 DT:

White to off-white, circular, flat, bevelled, uncoated tablets with “AC 400” debossed on one face and a central break-line on the other.

ACITAB-800 DT:

White to off-white, capsule-shaped tablets with central break-line on one face and AC embossed on the other face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ACITAB is indicated for:

- Treatment of initial and recurrent herpes simplex infections of the skin and mucous membranes, including initial and recurrent genital herpes simplex virus infections, in both immunocompetent and immunocompromised patients.
- Suppression of recurrent genital herpes simplex infections in immunocompetent patients.
- Prophylaxis of herpes simplex infections in immunocompromised patients.
- Treatment of herpes zoster (shingles) infections if the lesions are not older than 72 hours.
- Treatment of varicella zoster (chickenpox) infection within 24 hours after appearance of the typical chickenpox lesions.
- Reduction of mortality and risk of developing herpes virus infections in certain severely immunocompromised patients, namely those with advanced HIV disease (CD4+ counts < 200/mm^3 including patients with AIDS or ARC) or following bone marrow transplantation. In patients with advanced HIV disease, oral ACITAB has been used in conjunction with oral zidovudine.

- In patients following bone-marrow transplantation oral ACITAB must be preceded by one month's intravenous treatment with acyclovir.

4.2 Posology and method of administration

Posology

ACITAB may be taken with or without meals.

Treatment of initial and recurrent herpes simplex infections of the skin and mucous membranes:

Adults: 200 mg every four hours, five times per day (omitting the night time dose) for 5 days. In severe infections, the duration of treatment may be extended. In severely immunocompromised patients or in patients with impaired gastrointestinal absorption, the dose may be increased to 400 mg five times per day. Alternatively, intravenous administration may be considered. Treatment should be initiated as early as possible after the start of an infection, or in the case of recurrent episodes, treatment should be started during the prodromal period or when the lesions first appear.

Children (immunocompromised):

Two years and older: Adult dosage.

Under two years: Half the adult dose (limited data).

Suppression of recurrent genital herpes simplex infections in immunocompetent patients:

Adults: 200 mg four times per day.

Some patients may be adequately treated with 400 mg twice a day, while 200 mg three times per day or even twice a day may also be suitable for some patients. Therapy should be periodically interrupted to reassess the condition.

Prophylaxis of herpes simplex infections in immunocompromised patients:

Adults: 200 mg four times per day.

In severely immunocompromised patients or in patients with impaired gastrointestinal absorption, the dose may be increased to 400 mg four times per day or changed to intravenous administration.

The duration of prophylactic ACITAB administration is determined by the duration of the period at risk.

Children:

Two years and older: Adult dosage. Under two years:

Half the adult dose (limited data).

Treatment of Varicella zoster infections:

Adults: 800 mg five times per day (omitting the night time dose) for 7 days.

Intravenous (IV) administration should be considered for severely immunocompromised patients or in patients with impaired gastrointestinal absorption.

Treatment should be initiated as soon as possible after the rash appears.

Adolescents (12 to 18 years): 800 mg four times per day for 5 days.

Children (immunocompromised): 20 mg/kg (not to exceed 800 mg) four times a day for 5 days.

Treatment should be started within 24 hours of the occurrence of rash. In severely immunocompromised children over 2 years of age, the adult dose may be given (limited data).

Severely immunocompromised patients:

Adults: 800 mg four times per day at six hourly intervals.

Bone marrow recipients should receive intravenous (IV) acyclovir 3 times daily for one month prior to receiving oral therapy. Duration of therapy is 6 months and 12 months in patients with advanced HIV disease.

Elderly:

Adequate hydration must be ensured in patients taking high doses of ACITAB. Plasma concentrations of ACITAB are higher in geriatric patients compared to younger patients, in part due to age-related changes in renal function. Dose reductions may be necessary in the elderly with impaired renal function.

Renal function impairment:

Treatment and prophylaxis of herpes simplex infections:

Mild to moderate impairment - No dose adjustment necessary.

Severe impairment (creatinine clearance less than 10 mL / min) - 200 mg every 12 hours.

Treatment of varicella and herpes zoster infections and management of severely immunocompromised patients (usual dose is 800 mg every four hours:

Moderate impairment (creatinine clearance of 10 to 25 mL / min) – 800 mg every 8 hours.

Severe impairment (creatinine clearance of less than 10 mL / min) - 800 mg every 12 hours.

4.3 Contraindications

Hypersensitivity to acyclovir, valacyclovir or to any excipients in ACITAB (see **section 6.1**).

4.4 Special warnings and precautions for use

Severe renal impairment - A dose reduction is required in patients with a creatinine clearance of < 10 mL / minute.

Safety and efficacy in pregnancy have not been established.

Care should be taken to maintain adequate hydration in patients:

- with impaired renal function or
- who are elderly and are receiving high doses of ACITAB.

ACITAB should be administered with caution to patients with renal impairment and doses should be adjusted according to creatinine clearance.

Due to elderly patients being more likely to have reduced renal function the need for dose reduction must be considered in this group of patients.

Elderly patients and patients with renal impairment are at an increased risk of developing neurological side effects and should thus be closely monitored for evidence of these effects. In the reported cases, these reactions may be reversible on discontinuation of treatment (see **section 4.8**).

There is a risk of developing a drug reaction with eosinophilia and systemic symptoms (DRESS) and / or acute generalized exanthematous pustulosis (AGEP) with the use of ACITAB. DRESS and AGEP are considered serious cutaneous adverse reactions (SCARs) which are unpredictable and present a substantial risk to patients. If a patient develops these reactions during ACITAB use, treatment should be withdrawn immediately, and an alternative treatment considered (as appropriate). Treatment with ACITAB or any other acyclovir or valacyclovir containing medicines must not be restarted for the patient at any time.

ACITAB contains aspartame. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

4.5 Interaction with other medicinal products and other forms of interaction

Although no clinically significant interactions have been reported, any medicine which is excreted via renal tubular secretion may compete with and thus interact with ACITAB. Probenecid and cimetidine has been shown to decrease the renal excretion of acyclovir and to increase the area under the curve (AUC) of acyclovir.

Similarly, increases in plasma AUCs of acyclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant medicine used in transplant patients have been shown when these two medicines are co-administered.

There has been a study that indicates that concomitant therapy with acyclovir increases AUC of totally administered theophylline with approximately 50 %. It is recommended to measure plasma concentrations during concomitant therapy with acyclovir.

No significant increase in toxicity was noted when zidovudine was given together with acyclovir.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy in pregnancy have not been established.

Breastfeeding

Safety and efficacy in lactation have not been established.

Following oral administration of a 200 mg dose ACITAB, five times a day, acyclovir 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 acyclovir dosages of up to 0,3 mg / kg / day.

4.7 Effects on ability to drive and use machines

ACITAB can cause dizziness. Therefore, patients should see how ACITAB affects them before driving or operating machinery.

4.8 Undesirable effects

Tabulated summary of adverse reactions

The following adverse reactions have been classified according to the following categories, frequent, less frequent and frequency unknown.

MedDRA system organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	*Less frequent*	Anaemia, leucopenia, thrombocytopenia, neutropenia
Immune system disorders	*Less frequent*	Angioedema, anaphylaxis
Psychiatric and nervous system disorders	*Frequent*	Headaches, dizziness,
	Less frequent	Ataxia, dysarthria, encephalopathy fatigue, reversible neurological reactions such as confusional states, hallucinations, tremors, psychosis, agitation, somnolence, convulsions coma (especially in patients with renal impairment in whom the dosage was in excess of that recommended). *The above effects may be reversible and is usually also reported in patients with renal impairment or with other predisposing factors (see **section 4.4**).*
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Dyspnoea
Gastrointestinal disorders:	*Frequent*	Nausea, vomiting, diarrhoea, abdominal pains.

MedDRA system organ Class	**Frequency**	**Side effects**
Hepatobiliary disorders:	*Less frequent*	Reversible increases in bilirubin and liver enzymes, hepatitis, jaundice.
Skin and subcutaneous tissue disorders:	*Frequent*	pruritus, rashes, photosensitivity urticaria, accelerated diffuse hair loss (The relationship of accelerated diffuse hair loss to ACITAB therapy is uncertain)
	Frequency unknown	Drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) [together these are referred to as serious cutaneous adverse reactions (SCARs) – see **section 4.4**]
Renal and urinary disorders	*Less frequent*	Increases in blood urea and creatinine, acute renal failure, renal pain. (Renal pain may be associated with renal failure and crystalluria.)
General disorders and administration site conditions	*Frequent*	Fatigue, fever.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8 and to Cipla Medpro (Pty) Ltd at drugsafetysa@cipla.com or telephone 080 222 6662 (toll free).

4.9 Overdosage

Symptoms of overdose:

ACITAB has a wide therapeutic window, therefore excessive doses of ACITAB are generally well tolerated. Repeated overdoses of oral ACITAB have been associated with gastrointestinal effects (such as nausea and vomiting) and neurological effects (such as headache and confusion).

Treatment of overdose:

Patients should be observed closely for signs of toxicity.

Treatment is symptomatic and supportive. Haemodialysis, if required, significantly enhances the removal of ACITAB from the blood.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

A 20.2.8 Antiviral agents.

Pharmacotherapeutic group

Direct acting antivirals - Nucleosides and nucleotides excl. reverse transcriptase inhibitors.

ATC code

J05AB01

Mechanism of action

Acyclovir is a synthetic purine nucleoside analogue used in the treatment of viral infections caused by Herpes simplex virus (HSV) types I and II, as well as Varicella zoster virus (herpes zoster and

chickenpox). With the aid of HSV thymidine kinase, acyclovir is taken up into the herpes infected cells and converted via phosphorylation to the active compound, acyclovir triphosphate.

Acyclovir triphosphate competitively inhibits herpes specified DNA polymerase, thus preventing further DNA synthesis without affecting normal cellular DNA polymerase.

5.2 Pharmacokinetic properties

Absorption

Absorption of acyclovir from the gastrointestinal tract is poor with a bioavailability ranging from 10 to 20 %. Protein binding is low (9 to 33 %). Peak acyclovir concentrations are achieved within 2 hours of oral administration.

Under fasting conditions, mean peak concentrations (C_{max}) of 0,4 microgram/ml are achieved at approximately 1,6 hours after a 200 mg dose.

Mean peak plasma concentrations (C_{ssmax}) increase to 0,7 microgram/mL (3,1 micromoles) at steady state following doses of 200 mg administered every four hours. A less than proportional increase is observed for C_{ssmax} levels following doses 400 mg and 800 mg administered four-hourly, with values reaching 1,2 and 1,8 microgram/ml (5,3 and 8 micromoles), respectively.

Distribution

The mean volume of distribution of 26 L indicates that acyclovir is distributed within total body water. Apparent values after oral administration (Vd / F) ranged from 2,3 to 17,8 L / kg. Cerebrospinal fluid levels are approximately 50 % of corresponding plasma levels. Plasma protein binding is relatively low (9 to 33 %) and drug interactions involving binding site displacement are not anticipated.

Metabolism

Metabolism is hepatic with one inactive metabolite accounting for 14.1 % of the excreted acyclovir dose in patients with normal renal function.

Acyclovir is predominantly excreted unchanged by the kidney. The only known urinary metabolite is 9-[(carboxymethoxy) methylguanine, and accounts for 10 to15 % of the dose excreted in the urine.

Elimination

Elimination is via the kidneys by both glomerular filtration and tubular secretion.

Approximately 14 % of the total dose is excreted unchanged in the urine with trace amounts excreted via the faeces and lungs.

Mean systemic exposure (AUC0-∞) to acyclovir ranges between 1,9 and 2,2 microgram*h/ml after a 200 mg dose. In adults the terminal plasma half-life after oral administration has been shown to vary between 2,8 and 4,1 hours. Renal clearance of acyclovir (CLr = 14,3 L / h) is substantially greater than creatinine clearance, indicating that tubular secretion, in addition to glomerular filtration, contributes to the renal elimination of the drug. The half-life and total clearance of acyclovir are dependent on renal function. Therefore, dosage adjustment is recommended for renally impaired patients.

Special Patient Populations

In patients with chronic renal failure the mean terminal half-life was found to be 19,5 hours. The mean acyclovir half-life during haemodialysis was 5,7 hours. Plasma acyclovir levels dropped approximately 60 % during dialysis.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame

Colloidal silicon dioxide

Magnesium stearate

Microcrystalline cellulose

Povidone

Purified talc

Sodium starch glycolate

Trusil banana special

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

- Store in a dry place, at or below 25 °C.
- Protect from light.

6.5 Nature and contents of container

ACITAB-200 DT: PVC/Aluminium foil blister packs of 25 tablets packed in a carton. ACITAB-400 DT: PVC/Aluminium foil blister packs of 25, 56, 60 or 70 tablets packed in a carton.

ACITAB-800 DT: PVC/Aluminium foil blister packs of 35 tablets packed in a carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBERS

ACITAB-200 DT: 38/20.2.8/0129

ACITAB-400 DT: 38/20.2.8/0128

ACITAB-800 DT: 38/20.2.8/0130

Namibia: ACITAB-200 DT NS2 11 / 20.2.8 / 0118

ACITAB-400 DT NS2 11 / 20.2.8 / 0124

Botswana: ACITAB-200 DT S2 BOT1101945

ACITAB-400 DT S2 BOT1101946

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of first authorization: July 2005

Date of latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

15 March 2024