1.3.1.1 Proposed Professional Information

1.5.5.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ACICLOVIR 250 VIATRIS (powder for solution for injection)

ACICLOVIR 500 VIATRIS (powder for solution for injection)

2 QUALITIVE AND QUANTITIVE COMPOSITION

ACICLOVIR 250 VIATRIS: Each 10 ml vial contains aciclovir sodium dihydrate corresponding to aciclovir 250 mg.

ACICLOVIR 500 VIATRIS: Each 20 ml vial contains aciclovir sodium corresponding to aciclovir 500 mg.

ACICLOVIR 250 VIATRIS contains: Sodium 24,5 mg per 10 ml vial.

ACICLOVIR 250 VIATRIS contains: Sodium 98 mg per 20 ml vial.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

ACICLOVIR 250 VIATRIS: *Before reconstitution:* White or almost white freeze-dried powder.

After reconstitution: Clear, colourless solution.

ACICLOVIR 500 VIATRIS: *Before reconstitution:* White or almost white freeze-dried powder.

After reconstitution: Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ACICLOVIR VIATRIS 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.

4.2 Posology and method of administration

Posology

Duration of treatment is normally 5 days.

Refer to section 6.6 for reconstitution of preparations and handling of ACICLOVIR VIATRIS.

Special populations

Herpes simplex encephalitis & neonates herpes simplex infections: Usually 10 days' treatment, considering the patient's condition and response.

Herpes simplex infection: Immunocompromised patients:

*Adults***:** 5 mg/kg - 8 hourly.

*Children***:** 250 mg/m^2 - 8 hourly.

Varicella-zoster: Immunocompromised patients (normal renal function):

*Adults***:** 10 mg/kg - 8 hourly.

*Children***:** 500 mg/m^2 - 8 hourly.

Herpes simplex encephalitis: Normal / immunocompromised patients (normal renal function):

*Adults***:** 10 mg/kg - 8 hourly.

*Children***:** 500 mg/m^2 - 8 hourly.

Herpes simplex infections:

Neonates: 10 mg/kg - 8 hourly.

Severely immunocompromised patients:

Adults:

Bone marrow recipients should receive intravenous (IV) aciclovir 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 ACICLOVIR VIATRIS. Plasma concentrations of ACICLOVIR VIATRIS 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.

Method of administration

Administer by slow intravenous infusion over 1hr.

4.3 Contraindications

Hypersensitivity to ACICLOVIR VIATRIS, valaciclovir or to any components of the formulation (as listed in section 6.1).

4.4 Special warnings and precautions for use

- ACICLOVIR VIATRIS should be administered with caution with renal impairment and doses should be adjusted according to creatinine clearance.
  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 *(see section 4.6)*.
- ACICLOVIR VIATRIS must be given by slow intravenous infusion over a one-hour period (*see section 4.2*).
- Care should be taken to maintain adequate hydration in patients receiving high doses of ACICLOVIR VIATRIS. Renal impairment usually responds rapidly to rehydration of the patient and/or dosage reduction or withdrawal of ACICLOVIR VIATRIS.

Use in Renal Impairment

Aciclovir as contained in ACICLOVIR VIATRIS is eliminated by renal clearance.

In patients with impaired renal function the dosage must be adjusted in order to avoid accumulation of aciclovir as contained in ACICLOVIR VIATRIS in the body *(see section 4.2)*.

For patients who are treated with high doses of ACICLOVIR VIATRIS intravenous infusion,

e.g. because of herpes encephalitis, special attention must be paid to the renal function, particularly in patients who are dehydrated or who have impaired renal function.

Drug reaction with eosinophilia and systemic symptoms (DRESS):

DRESS, which can be life-threatening or fatal, has been reported in associate with aciclovir treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of DRESS appear, aciclovir should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patient has developed DRESS with the use of aciclovir, treatment with aciclovir must not be restarted in this patient at any time.

Use in the Elderly

Elderly patients are likely to have reduced renal function and therefore the need for dose reduction must be considered in this group of patients (*see section 4.2*).

Sodium warning

ACICLOVIR 250 VIATRIS contains 24,5 mg sodium per 10 ml, equivalent to 1,225 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
ACICLOVIR 500 VIATRIS contains 98 mg sodium per 20 ml, equivalent to 4,9 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
ACICLOVIR VIATRIS is sugar free.

4.5 Interaction with other medicines 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 this mechanism or affect renal physiology and may increase ACICLOVIR VIATRIS plasma concentration.

- Probenecid and cimetidine have been shown to decrease the renal excretion and to increase the area under the curve (AUC) of ACICLOVIR VIATRIS.
- Increases in plasma AUCs of ACICLOVIR VIATRIS and of the inactive metabolite of mycophenolate mofetil, have been shown when the medicines are co-administered.
- Monitor for changes in renal function when administering ACICLOVIR VIATRIS with medicines that affect other aspects of renal physiology (e.g. ciclosporin, tacrolimus) (*see section 4.4*).
- No significant increase in toxicity was noted when zidovudine was given together with ACICLOVIR VIATRIS.

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.

4.7 Effects on ability to drive and use machines

As ACICLOVIR VIATRIS may cause dizziness, confusion and hallucinations, patients must be informed that it may affect their mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects

Tabulated list of adverse reactions

Body System	Undesirable effect

	Frequent	Less frequent	Frequency not known
Blood and the lymphatic system disorders:		Anaemia, leukopenia, thrombocytopenia, neutropenia, hypotension.	
Immune system disorders:		Anaphylaxis.	
Central nervous system disorders:		Headaches, fatigue, reversible neurological reactions such as dizziness, confused states, hallucinations, tremors, psychosis, agitation, somnolence, convulsions, and coma (especially in patients with renal impairment in whom the dosage was more than that recommended).	

Vascular disorders:	Phlebitis.		
Respiratory, thoracic and mediastinal disorders:		Dyspnoea.	
Gastrointestinal disorders:		Nausea, vomiting, diarrhoea, abdominal pain.	
Hepato-biliary disorders:		Reversible increases in bilirubin and liver enzymes, hepatitis, jaundice.	
Skin and subcutaneous tissue disorders:		Diffuse hair loss, hypersensitivity reactions including rashes, photosensitivity, urticaria, pruritus, angioedema, fevers.	Drug reaction with eosinophilia and systemic symptoms (DRESS) *(see section 4.4)*.
Renal and urinary disorders:		Increases in blood urea and creatinine, acute renal failure.	

Post-marketing side effects:

- **Immune system disorders:** anaphylaxis, angioedema.

- **Psychiatric and nervous system disorders:** headache, dizziness. agitation, confusion, tremor, ataxia, dysarthria, hallucinations, psychotic symptoms, convulsions, somnolence, encephalopathy, coma.
- **Respiratory, thoracic and mediastinal disorders:** dyspnoea
- **Gastrointestinal disorders:** diarrhoea, abdominal pain
- **Hepatobiliary disorders:** reversible increases in bilirubin, hepatitis jaundice
- **Skin and subcutaneous tissue disorders:** accelerated diffuse hair loss. The relationship of accelerated diffuse hair loss to ACICLOVIR VIATRIS therapy is uncertain.
- **Renal and urinary disorders:** renal impairment, acute renal failure, renal pain Renal pain may be associated with renal failure and crystalluria.
- **General disorders and administration site conditions:** fatigue, fever, local inflammatory reactions.

  Severe local inflammatory reactions sometimes leading to ulceration have occurred when ACICLOVIR VIATRIS has been inadvertently infused into extravascular tissues.

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. Healthcare 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

4.9 Overdose

Symptoms:

- In overdose, side effects can be precipitated and/or be of increased severity *(see section 4.8)*.
- Overdose of intravenous ACICLOVIR VIATRIS 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 overdose.

Treatment:

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

Pharmacotherapeutic group: Antivirals for systemic use (Nucleoside and nucleotides excl. reverse transcriptase inhibitors).

ATC code: J05AB01.

Mechanism of action:

Aciclovir 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, aciclovir is taken up into the herpes infected cells and converted via phosphorylation to the active compound, aciclovir triphosphate. Aciclovir 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 aciclovir from the gastro-intestinal tract is poor with a bioavailability ranging from 10 to 30 %. Protein binding is low (9 to 33 %).

Distribution:

Peak aciclovir concentrations are achieved within 2 hours of oral administration.

In patients with normal renal function, the half-life of aciclovir is approximately 2,5 hours. The half-life is increased in patients with chronic renal failure. Metabolism is hepatic with one inactive metabolite accounting for 14,1 % of the excreted aciclovir dose in patients with normal renal function.

Metabolism:

Metabolism is hepatic with one inactive metabolite accounting for 14,1 % of the excreted aciclovir dose in patients with normal renal function.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The other ingredients in ACICLOVIR 250 VIATRIS are: water for injection.

The other ingredients in ACICLOVIR 500 VIATRIS are: Sodium hydroxide; sodium hydroxide solution; and water for injection.

6.2 Incompatibilities

None known.

6.3 Shelf life

ACICLOVIR 250 VIATRIS: 24 months when stored below 25°C before reconstitution.

ACICLOVIR 500 VIATRIS: 36 months when stored below 25°C before reconstitution.

6.4 Special precautions for storage

- *Before reconstitution:* Store at or below 25 °C. Keep containers dry and tightly closed.
- Preferably use the reconstituted solution immediately.
- ACICLOVIR VIATRIS is a single dose vial, discard any unused portion.

6.5 Nature and contents of container

ACICLOVIR 250 VIATRIS: Packs of 5 x 10 ml clear, colourless, Type I glass vials with lyophilisation stoppers made from grey bromobutyl rubber and flip-off aluminium capsules.

ACICLOVIR 500 VIATRIS: Packs of 5 x 20 ml clear, colourless, Type I glass vials with lyophilisation stoppers made from grey bromobutyl rubber and flip-off aluminium capsules.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

ACICLOVIR VIATRIS must be reconstituted by adding 10 ml (250 mg) or 20 ml (500 mg) water for injections to the vial before use. The solution must be further diluted to a

concentration of not more than 7 mg/ml, usually not more than 5 mg/ml aciclovir, with suitable intravenous fluid before use. It may also be dissolved directly in the intravenous fluid, usual amount: 50 ml or more per 250 mg of aciclovir.

Intravenous fluids for dilution:

- Sodium chloride 0,9 % (= 9 mg/ml).
- Glucose 5 % (= 50 mg/ml).
- Sodium chloride 0,45 % and glucose 2,5 % (= 25 mg/ml).

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris South Africa (Pty) Ltd

4 Brewery Street

Isando

Gauteng

1609

8 REGISTRATION NUMBER(S)

ACICLOVIR 250 VIATRIS: 42/20.2.8/0069

ACICLOVIR 500 VIATRIS: 42/20.2.8/0070

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of publication: 26 November 2010

10 DATE OF REVISION OF TEXT

TBA.