CLEAN AMENDED PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ACYCLOVIR 25 MG/ML – 10 ML VIAL ACCORD

ACYCLOVIR 25 MG/ML – 20 ML VIAL ACCORD

ACYCLOVIR 25 MG/ML – 40 ML VIAL ACCORD

Concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains acyclovir sodium equivalent to 25 mg acyclovir.

Each vial of 10 ml of solution contains acyclovir sodium corresponding to 250 mg acyclovir.

Each vial of 20 ml of solution contains acyclovir sodium corresponding to 500 mg acyclovir.

Each vial of 40 ml of solution contains acyclovir sodium corresponding to 1 g acyclovir.

Excipient(s) with known effect:

Each ml of solution contains 2.67 mg of sodium (approximately 0.116 mmol).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear, colourless or almost colourless solution, filled in a glass vial.

When examined under suitable conditions of visibility it should be practically free from foreign particles.

The pH value is between 10.7 and 11.7.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- *Herpes simplex* infections in immunocompromised patients:
    a) ACYCLOVIR 25 mg/ml ACCORD is indicated for the treatment of *herpes simplex* infections.

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b) ACYCLOVIR 25 mg/ml ACCORD is indicated for the prophylaxis of *herpes simplex* infections in patients.

- ACYCLOVIR 25 mg/ml ACCORD is indicated in the treatment of *varicella zoster* infections in immuno-compromised patients:
  a) Chickenpox – prophylaxis and therapy of pneumonia complications.
  b) Shingles – only if the lesions are not older than 72 hours
- ACYCLOVIR 25 mg/ml ACCORD is indicated for treatment of *herpes simplex* infections in the neonate.
- ACYCLOVIR 25 mg/ml ACCORD is indicated for the treatment of *herpes simplex* encephalitis.
- ACYCLOVIR 25 mg/ml ACCORD is indicated for the prevention of reactivation of cytomegalovirus infection in seropositive patients following bone marrow transplantation.

4.2 Posology and method of administration

Posology

Dosage in adults

INDICATION	**IMMUNE STATUS**	**DOSAGE**
Herpes simplex infection *(except herpes encephalitis)*	Immunocompromised	5 mg/kg every 8 hours
Varicella zoster infection	Immunocompromised (normal renal function)	10 mg/kg every 8 hours
Herpes simplex encephalitis	Normal or immuno-compromised (normal renal function)	10 mg/kg every 8 hours

Obese patients should be dosed at the recommended adult dose using ideal body weight, rather than actual body weight.

Special populations

Elderly

The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted

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accordingly (see Renal impairment below).

Adequate hydration should be maintained.

Renal Impairment

Caution is advised when administering ACYCLOVIR 25 mg/ml ACCORD to adults and paediatric patients with impaired renal function. The following adjustments in dosage are suggested:

Creatinine clearance (ml/min/1,73m^2)	**Percentage of recommended dose (%)**	**Dosing interval (hours)**
> 50	100 %	8
25-50	100 %	1 2
10-25	100 %	2 4
0-10	50 %	2 4

Dosage for the prevention of cytomegalovirus reactivation following bone marrow transplantation

Adults: 500 mg/m^2 ACYCLOVIR 25 mg/ml ACCORD should be given intravenously 3 times daily at approximately 8-hour intervals. The duration of treatment recommended in bone marrow transplant recipients is from 5 days before, up to 30 days after transplant.

Paediatric population

Dosage in children

The dose of ACYCLOVIR 25 mg/ml ACCORD for children aged between 3 months and 12 years is calculated on the basis of body surface area.

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INDICATION	IMMUNE STATUS	DOSAGE
Herpes simplex (except herpes encephalitis)	Immunocompromised	250 mg/m^2 every 8 hours
Varicella zoster infection	Immunocompromised (normal renal function)	500 mg/m^2 every 8 hours
Herpes simplex encephalitis	Normal (normal renal function)	500 mg/m^2 every 8 hours

Children with impaired renal function require an appropriately modified dose and/or dose interval, according to the degree of impairment as indicated under 'Dosage in renal impairment'.

Children: Limited data suggest that for the prevention of cytomegalovirus reactivation in children over 2 years of age, who have undergone bone marrow transplantation, the adult dose may be given.

Dosage in neonates

The dosage of ACYCLOVIR 25 mg/ml ACCORD in neonates is calculated on the basis of body mass. Neonates with *herpes simplex* infections should be given ACYCLOVIR 25 mg/ml ACCORD in doses of 10 mg/kg every 8 hours.

Guidelines for acyclovir administration in neonates with renal impairment:

- Creatinine clearance of 20-50 ml/min/1,73 m^2 or serum creatinine 70-100 µmol/l: a dose of 10 mg/kg/12 hours.
- Creatinine clearance of 10-25 ml/min/1,73 m^2 or serum creatinine 110-130 µmol/l with decreasing urine output: a dose of 10 mg/kg/24 hours.
- Renal failure with creatinine clearance of < 10 ml/min/1,73 m^2 or serum creatinine > 130 µmol/l or urine output < 1 ml/kg/hour and peritoneal dialysis: a dose of 5 mg/kg/24 hours.

Method of administration

For intravenous use.

The required dose of ACYCLOVIR 25 mg/ml ACCORD should be administered by slow intravenous infusion over a one-hour period.

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A course of treatment with ACYCLOVIR 25 mg/ml ACCORD usually lasts 5 days, but this may be adjusted according to the patient's condition and response to therapy. Treatment for herpes encephalitis and neonatal herpes simplex infections usually lasts 10 days. The duration of prophylactic administration of ACYCLOVIR 25mg/ml ACCORD is determined by the duration of the period at risk.

For reconstitution of ACYCLOVIR 25mg/ml ACCORD, see section 6.6.

4.3 Contraindications

Hypersensitivity to acyclovir or valacyclovir, or to any of the excipients of ACYCLOVIR 25 mg/ml ACCORD listed in section 6.1.

4.4 Special warnings and precautions for use

Safety of ACYCLOVIR 25mg/ml ACCORD in pregnancy and lactation has not been established (see section 4.6).

Drug reaction with eosinophilia and systemic symptoms (DRESS) and Acute generalised exanthematous pustulosis (AGEP)

Patients need to be advised of the risk of DRESS and AGEP which are considered to be serious cutaneous adverse reactions (SCARs). At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If a patient develops reactions that can be classified as SCARs, treatment with ACYCLOVIR 25 mg/ml ACCORD should be withdrawn immediately and an alternative treatment considered (as appropriate). Treatment with ACYCLOVIR 25 mg/ml ACCORD must not be restarted with the patient at any time.

Use in patients with renal impairment and in elderly patients

Acyclovir, as contained in ACYCLOVIR 25 mg/ml ACCORD, is eliminated by renal clearance, therefore the dose must be reduced in patients with renal impairment (see section 4.2).

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).

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The dose of ACYCLOVIR 25 mg/ml ACCORD must be adjusted in patients with impaired renal function in order to avoid accumulation of acyclovir in the body (see Dosage in renal impairment). In patients receiving ACYCLOVIR 25 mg/ml ACCORD at higher doses (e.g. for herpes encephalitis), specific care regarding renal function should be taken, particularly when patients are dehydrated or have any renal impairment.

Adequate hydration should be maintained in patients given i.v. or high oral doses of acyclovir.

Intravenous doses should be given by infusion over one hour to avoid precipitation of acyclovir in the kidney; rapid or bolus injection should be avoided.

The risk of renal impairment is increased by use with other nephrotoxic medicines. Care is required if administering i.v.acyclovir with other nephrotoxic medicines.

Product contains sodium. This medicinal product contains 2.67 mg sodium per ml of solution equivalent to 0.13 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interactions with other medicines and other forms of interaction

No clinically significant interactions have been identified.

Acyclovir as contained in ACYCLOVIR 25 mg/ml ACCORD is eliminated primarily unchanged in the urine via active renal tubular secretion. Any medicines administered concurrently that compete with this mechanism may increase acyclovir plasma concentrations. Probenecid and cimetidine increase the AUC of acyclovir by this mechanism, and reduces acyclovir renal clearance.

In patients receiving intravenous ACYCLOVIR 25 mg/ml ACCORD, caution is required during concurrent administration with medicines which compete with acyclovir for elimination, because of the potential for increased plasma levels of one or both medicines or their metabolites. 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 the medicines are co-administered.

If lithium is administered with high dose acyclovir IV, the lithium serum concentration should be closely monitored because of the risk of lithium toxicity.

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Care is also required (with monitoring for changes in renal function) if administering intravenous ACYCLOVIR 25 mg/ml ACCORD with medicines which affect other aspects of renal physiology (e.g. ciclosporin, tacrolimus).

4.6 Fertility, pregnancy and lactation

Safety in pregnancy has not been established

Lactation

Following oral administration of 200 mg 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.

Lactating women on ACYCLOVIR 25 mg/ml ACCORD treatment should not breastfeed.

Fertility:

There is no information on the effect of ACYCLOVIR 25 mg/ml ACCORD on human female fertility. In a study of 20 male patients with normal sperm count, oral acyclovir administered at doses of up to 1 g per day for up to six months has been shown to have no clinically significant effect on sperm count, motility or morphology.

4.7 Effects on ability to drive and use machines

ACYCLOVIR 25 mg/ml ACCORD is generally used in an in-patient hospital population and information on ability to drive and operate machinery is not usually relevant.

4.8 Undesirable effects

a. Summary of the safety profile

The adverse reactions listed have been observed in controlled and uncontrolled clinical trials in approximately 700 patients who received acyclovir at ~ 5 mg/kg (250 mg/m^2) 3 times daily and approximately 300 patients who received 10 mg/kg (500 mg/m^2) 3 times daily.

b. Tabulated summary of adverse reactions

The following convention has been used for the classification of undesirable effects in terms of frequency.

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Undesirable effects in clinical studies and post marketing		
System Organ Class	**Frequency**	**Adverse reaction**
Blood and lymphatic system disorders	Less frequent	Decreases in haematological indices (anaemia, thrombocytopenia, leucopenia).
Immune system disorders	Less frequent	Anaphylaxis, angioedema.
Psychiatric and nervous system disorders	Less frequent	Headache, dizziness, agitation, confusion, tremor, ataxia, dysarthria, hallucinations, psychotic symptoms, convulsions, somnolence, encephalopathy, coma.
Vascular disorders	Frequent	Phlebitis.
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea.
Gastrointestinal disorders	Frequent	Nausea, vomiting.
	Less frequent	Diarrhoea, abdominal pain.
Hepatobiliary disorders	Frequent	Reversible increases in liver-related enzymes.
	Less frequent	Reversible increases in bilirubin, hepatitis, jaundice.
Skin and subcutaneous tissue disorders	Frequent	Rashes (including photosensitivity), urticaria, pruritus, fevers.
	Less frequent	Accelerated diffuse hair loss.
	Frequency unknown	Drug reaction with eosinophilia and systemic symptoms (DRESS) and Acute generalised exanthematous pustulosis (AGEP) (see section 4.4)
Renal and urinary disorders	Frequent	Increases in blood urea and creatinine levels.
	Less frequent	Renal impairment, acute renal failure.
General disorders and administration site conditions	Less frequent	Fatigue, fever, local inflammatory reactions.

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Description of selected adverse reactions

Severe local inflammatory reactions sometimes leading to ulceration have occurred when ACYCLOVIR 25 mg/ml ACCORD has been inadvertently infused into extravascular tissues.

Rapid increases in blood urea and creatinine levels are believed to be related to peak plasma levels and the state of hydration of the patient. To avoid this effect, ACYCLOVIR 25 mg/ml ACCORD should not be given as an intravenous bolus injection, but by slow infusion over a one-hour period.

Adequate hydration of the patient should be maintained. Renal impairment usually responds rapidly to rehydration of the patient and/or dosage reduction or withdrawal of ACYCLOVIR 25 mg/ml ACCORD.

Progression to acute renal failure, may occur.

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Overdosage of intravenous ACYCLOVIR 25 mg/ml ACCORD has resulted in elevations in serum creatinine, blood urea nitrogen and subsequent renal failure. Neurological effects including confusion, hallucinations, agitation, seizures and coma have been described in association with overdosage. Haemodialysis significantly enhances the removal of acyclovir from the blood and may, therefore, be considered an option in the management of overdose of ACYCLOVIR 25 mg/ml ACCORD. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct acting antivirals, Nucleosides and nucleotides excl. reverse transcriptase inhibitors

ATC code: J05AB01.

Pharmacological classification: A20.2.8 Antiviral agents

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Acyclovir is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against human herpes viruses, including Herpes simplex virus types 1 and 2 and Varicella zoster virus (VZV), Epstein Barr virus (EBV) and Cytomegalovirus (CMV). In cell culture acyclovir 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 acyclovir for HSV-1, HSV-2, VZV and EBV is highly selective. The enzyme thymidine kinase (TK) of normal, uninfected cells does not use acyclovir effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV, VZV and EBV converts acyclovir to acyclovir monophosphate, a nucleoside analogue, which is further converted to the diphosphate and finally to the triphosphate by cellular enzymes. Acyclovir triphosphate interferes with the viral DNA polymerase and inhibits viral DNA replication with resultant chain termination following its incorporation into the viral DNA.

5.2 Pharmacokinetic properties

Distribution

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.

Elimination

In adults, the terminal plasma half-life of acyclovir after administration of acyclovir is about 2,9 hours. Most of the drug is excreted unchanged by the kidney. Renal clearance of acyclovir is substantially greater than creatinine clearance, indicating that tubular secretion, in addition to glomerular filtration, contributes to the renal elimination of the drug. 9-carboxymethoxy-methylguanine is the only significant metabolite of acyclovir and accounts for 10 to 15 % of the dose excreted in the urine.

When acyclovir is given one hour after 1 gram of probenecid, the terminal half-life and the area under the plasma concentration time curve, are extended by 18 % and 40 % respectively.

5.3 Preclinical safety data

Mutagenicity

The results of a wide range of mutagenicity tests *in vitro* and *in vivo* indicate that acyclovir is unlikely to pose a genetic risk to man.

Carcinogenicity

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Acyclovir was not found to be carcinogenic in long-term studies in the rat and the mouse.

Teratogenicity

Systemic administration of acyclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rabbits, rats or mice.

In a non-standard test in rats, foetal abnormalities were observed but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain.

Fertility

Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of acyclovir greatly in excess of those employed therapeutically. Two-generation studies in mice did not reveal any effect of (orally administered) acyclovir on fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH adjustment)

Hydrochloric acid, concentrated (for pH adjustment)

Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

18 months

After dilution: Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature (20 - 25 °C).

From a microbiological point of view the medicine should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

When dilution is carried out under validated aseptic conditions, the medicine may be stored for a maximum of 12 hours at room temperature, below 25 °C.

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6.4 Special precautions for storage

Store at or below 25 °C.

Keep out of reach of children.

Use immediately after reconstitution and discard any excess.

Reconstituted or diluted solution should not be refrigerated.

6.5 Nature and contents of container

10, 20 or 50 ml clear glass vials (with filling volumes of 10, 20 and 40 ml respectively), rubber stopper and aluminium flip off seal.

It is supplied in pack size of 1 vial, 5 vials or 10 vials pack.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

For single use only. Discard any unused solution.

Any unused medicine or waste materials should be disposed of in accordance with local requirements.

From the calculated dose, determine the appropriate number and strength of vials to be used.

Administration:

The required dose of acyclovir should be administered by slow intravenous infusion over a one-hour period.

ACYCLOVIR 25 mg/ml ACCORD may be administered by a controlled-rate infusion pump.

Alternatively, ACYCLOVIR 25 mg/ml ACCORD may be further diluted to give an acyclovir concentration of not greater than 5 mg/ml (0,5 % w/v) for administration by infusion.

Add the required volume of ACYCLOVIR 25 mg/ml ACCORD to the chosen infusion solution, as recommended below, and shake well to ensure adequate mixing occurs.

For children and neonates, where it is advisable to keep the volume of infusion fluid to a minimum, it is recommended that dilution is on the basis of 4 ml of solution (100 mg acyclovir) added to 20 ml of infusion fluid.

For adults, it is recommended that infusion bags containing 100 ml of infusion fluid are used, even when this would give an acyclovir concentration substantially below 0,5 % w/v. Thus one 100 ml infusion bag may be

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used for any dose between 250 mg and 500 mg acyclovir (10 and 20 ml of reconstituted solution) but a second bag must be used for doses between 500 mg and 1000 mg.

When diluted in accordance with the recommended schedules, acyclovir is known to be compatible with the following infusion fluids and stable for up to 24 hours at room temperature (below 25 °C):

Sodium Chloride Intravenous Infusion (0,45 % and 0,9 % w/v)

Sodium Chloride (0,18 % w/v) and Glucose (4% w/v) Intravenous Infusion Sodium Chloride (0,45 % w/v) and Glucose (2,5 % w/v) Intravenous Infusion Compound Sodium Lactate Intravenous Infusion (Hartmann's Solution).

Acyclovir when diluted in accordance with the above schedule will give an acyclovir concentration not greater than 0,5 % w/v.

Since no antimicrobial preservative is included, dilution must be carried out under full aseptic conditions, immediately before use, and any unused solution discarded.

Should any visible turbidity or crystallisation appear in the solution before or during infusion, the preparation should be discarded.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

ACYCLOVIR 25 MG/ML – 10 ML VIAL ACCORD – 55/20.2.8/0369

ACYCLOVIR 25 MG/ML – 20 ML VIAL ACCORD – 55/20.2.8/0370

ACYCLOVIR 25 MG/ML – 40 ML VIAL ACCORD – 55/20.2.8/0371

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION 10 August 2022
10. DATE OF REVISION OF THE TEXT 22 August 2024