SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Apovir Injection 500

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Vial contains:
Acyclovir USP.....500 mg
For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

White coloured lyophilized mass filled in clear vials.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Apovir Injection 500 is indicated for the treatment of Herpes simplex infections in immunocompromised patients and severe initial genital herpes in the non-immunocompromised.

Apovir Injection 500 is indicated for the prophylaxis of Herpes simplex infections in immunocompromised patients.

Apovir Injection 500 is indicated for the treatment of Varicella zoster

infections.

Apovir Injection 500 is indicated for the treatment of herpes

encephalitis.

Apovir Injection 500 is indicated for the treatment of Herpes simplex infections in the neonate and infant up to 3 months of age.

4.2 Posology and method of administration

Route of administration: Slow intravenous infusion over 1 hour.

A course of treatment with Apovir Injection 500 usually lasts 5 days, but this may be adjusted according to the patient's condition and response to therapy. Treatment for herpes encephalitis usually lasts 10 days. Treatment for neonatal herpes infections usually lasts 14 days for mucocutaneous (skin-eye-mouth) infections and 21 days for disseminated or central nervous system disease.

The duration of prophylactic administration of Apovir Injection 500 is determined by the duration of the period at risk.

Dosage in adults:

Patients with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given Apovir Injection 500 in doses of 5 mg/kg body weight every 8 hours provided renal function is not impaired (see Dosage in renal impairment).

Immunocompromised patients with *Varicella zoster* infections or patients with herpes encephalitis should be given Apovir Injection 500 in doses of 10 mg/kg body weight every 8 hours provided renal function is not impaired (see Dosage in renal impairment).

In obese patients dosed with intravenous Acyclovir based on their actual body weight, higher plasma concentrations may be obtained (see 5.2 Pharmacokinetic properties). Consideration should therefore be given to dosage reduction in obese patients and especially in those with renal impairment or the elderly.

Dosage in infants and children: The dose of Apovir Injection 500 for infants and children aged between 3 months and 12 years is calculated on the basis of body surface area.

Infants and children 3 months of age or older with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given Apovir Injection 500 in doses of 250 mg per square metre of body surface area every 8 hours if renal function is not impaired.

In immunocompromised children with *Varicella zoster* infections or children with herpes encephalitis, Apovir Injection 500 should be given in doses of 500 mg per square metre body surface area every 8 hours, if renal function is not impaired.

The dosage of Apovir Injection 500 in neonates and infants up to 3 months of age is calculated on the basis of body weight.

The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 21 days for disseminated and CNS disease, or for 14 days for disease limited to the skin and mucous membranes.

Infants and children with impaired renal function require an appropriately modified dose, according to the degree of impairment (see Dosage in renal impairment).

Dosage in the elderly:

The possibility of renal impairment in the elderly must be considered and dosage should be adjusted accordingly (see *Dosage in renal impairment* below).

Adequate hydration should be maintained.

Dosage in renal impairment:

Caution is advised when administering Apovir Injection 500 to patients with impaired renal function. Adequate hydration should be maintained.

Dosage adjustment for patients with renal impairment is based on creatinine

clearance, in units of ml/min for adults and adolescents and in units of ml/min/1.73m^2 for infants and children less than 13 years of age. The following adjustments in dosage are suggested:

Dosage adjustments in adults and adolescents:

Creatinine Clearance	Dosage
25 to 50 ml/min	The dose recommended above (5 or 10 mg/kg body weight) should be given every 12 hours.
10 to 25 ml/min	The dose recommended above (5 or 10 mg/kg body weight) should be given every 24 hours.
0 (anuric) to 10 ml/min	In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (5 or 10 mg/kg body weight) should be halved and administered every 24 hours. In patients receiving haemodialysis the dose recommended above (5 or 10 mg/kg body weight) should be halved and administered every 24 hours and after dialysis.

Dosage adjustments in infants and children:

Creatinine clearance	Dosage
25–50 mL/min/1.73 m²)	The dose recommended above (250 or 500 mg/m2 body surface area or 20 mg/kg body weight) should be given every 12 hours.
10–25 mL/min/1.73 m²)	The dose recommended above (250 or 500 mg/m2 body surface area or 20 mg/kg body weight) should be given every 24 hours.
0 (anuric)–10 mL/min/1.73 m²)	In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (250 or 500 mg/m2 body surface area or 20 mg/kg body weight) should be and administered every 24 hours. In patients receiving haemodialysis the dose recommended above (250 or 500 mg/m2 body surface area or 20 mg/kg body weight) should be halved and administered every 24 hours and after dialysis

4.3 Contraindications

Hypersensitivity to Acyclovir or valaciclovir, or to any of the excipients.

4.4 Special warnings and precautions for use

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 drugs. Care is required if administering i.v. Acyclovir with other nephrotoxic drugs.

Use in patients with renal impairment and in elderly patients:

Acyclovir is eliminated by renal clearance, therefore the dose must be adjusted in patients with renal impairment. Elderly patients are likely to have reduced renal function and therefore the need for dose adjustment 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. Prolonged or repeated courses of Acyclovir in severely immune-compromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued Acyclovir treatment.

In patients receiving Apovir Injection 500 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.

Reconstituted Apovir Injection 500 has a pH of approximately 11 and should not be administered by mouth. Product contains sodium (26mg, approx. 1,13mmol). To be taken into consideration by patients on a controlled sodium diet.

Apovir Injection 500 contains no antimicrobial preservative. Reconstitution and dilution should therefore be carried out under full aseptic conditions immediately before use and any unused solution discarded. The reconstituted or diluted solutions should not be refrigerated.

4.5 Interaction with other medicinal products and other forms of interaction

Acyclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that compete with this mechanism may increase Acyclovir plasma concentrations. Probenecid and cimetidine increase the AUC of Acyclovir by this mechanism and reduce Acyclovir renal clearance. However no dosage adjustment is necessary because of the wide therapeutic index of Acyclovir.

In patients receiving intravenous Zovirax caution is required during concurrent administration with drugs which compete with Acyclovir for elimination, because of the potential for increased plasma concentrations of one or both drugs or their metabolites. Increases in plasma AUCs of Acyclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant agent used in transplant patients, have been shown when the drugs are coadministered.

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

Care is also required (with monitoring for changes in renal function) if administering intravenous Zovirax with drugs which affect other aspects of renal physiology (e.g. cyclosporin, tacrolimus).

An experimental study on five male subjects 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.

4.6 Fertility, pregnancy and lactation

Fertility:

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

In a study of 20 male patients with normal sperm count, oral Acyclovir administered at doses of up to 1g per day for up to six months has been shown to have no clinically significant effect on sperm count, motility or morphology.

Pregnancy:

A post-marketing Acyclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of Zovirax. The registry findings have not shown an increase in the number of birth defects amongst Acyclovir exposed subjects compared to with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause. 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.

Caution should therefore be exercised by balancing the potential benefits of treatment against any possible hazard. Findings from reproduction toxicology studies.

Breast-feeding:

Following oral administration of 200 mg five times a day, Acyclovir has been detected in human breast milk at concentrations ranging from 0.6 to 4.1 times the corresponding plasma concentrations. These concentrations would potentially expose nursing infants to Acyclovir dosages of up to 0.3 mg/kg body weight/day. Caution is therefore advised if Zovirax is to be administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Acyclovir i.v. for infusion is generally used in an in-patient hospital population and information on ability to drive and operate machinery is not usually relevant. There have been no studies to investigate the effect of Acyclovir on driving performance or the ability to operate machinery.

4.8 Undesirable effects

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 ≥ 1/1,000 and < 1/100, rare ≥ 1/10,000 and < 1/1,000, very rare < 1/10,000.

Blood and lymphatic system disorders:

Uncommon: decreases in haematological indices (anaemia,

thrombocytopenia, leukopenia). Immune system disorders:

Very rare: anaphylaxis.

Psychiatric and nervous system disorders:

Very rare: headache, dizziness, agitation, confusion, tremor, ataxia, dysarthria, hallucinations, psychotic symptoms, convulsions, somnolence, encephalopathy, coma.

The above events are generally reversible and usually reported in patients with renal impairment or with other predisposing factors (see 4.4 Special Warnings and Precautions for Use).

Vascular disorders:

Common: phlebitis.

Respiratory, thoracic and mediastinal disorders:

Very rare: dyspnoea.

Gastrointestinal disorders:

Common: nausea, vomiting.

Very rare: diarrhoea,

abdominal pain. Hepato-

biliary disorders:

Common: reversible increases in liver-related enzymes.

Very rare: reversible increases in bilirubin,

jaundice, hepatitis.

Skin and subcutaneous tissue disorders:

Common: pruritus, urticaria, rashes (including

photosensitivity). Very rare: angioedema.

Renal and urinary disorders:

Common: increases in blood urea and creatinine.

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

Very rare: renal impairment, acute renal failure and renal pain.

Adequate hydration should be maintained. Renal impairment usually responds rapidly to rehydration of the patient and/or dosage reduction or withdrawal of the drug. Progression to acute renal failure however, can occur in exceptional cases.

Renal pain may be associated with renal failure

and crystalluria.

General disorders and administration site conditions:

Very rare: fatigue, fever, local inflammatory reactions

Severe local inflammatory reactions sometimes leading to breakdown of the skin have occurred when Apovir Injection 500 has been inadvertently infused into extracellular tissues.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after Authorisation 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 to the National Regulatory Authority via Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org/

4.9 Overdose

Overdosage of intravenous Acyclovir 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 overdosage.

Patients should be observed closely for signs of toxicity. Haemodialysis significantly enhances the removal of Acyclovir from the blood and may, therefore, be considered an option in the management of overdose of this drug.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: J05AB01.

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

Absorption

Acyclovir is only partially absorbed from the gut. The average oral bioavailability varies between 10 and 20%. 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 administered as oral suspension or capsule. 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} concentrations following doses of 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. As plasma protein binding is relatively low (9 to 33%), drug interactions involving binding site displacement are not anticipated. Cerebrospinal fluid concentrations are approximately 50% of corresponding plasma concentrations at steady-state.

Metabolism

Acyclovir is predominantly excreted unchanged by the kidney. The only significant urinary metabolite is 9-[(carboxymethoxy) methylguanine, and accounts for 10-15% of the dose excreted in the urine.

Elimination

In adults mean systemic exposure ($AUC_{0-\infty}$) to Acyclovir ranges between 1.9 and 2.2 microgram*h/mL after a 200 mg dose. At this dose, the mean terminal plasma half-life after oral administration has been shown to vary between 2.8 and 4.1 hours.

In adults, the terminal plasma half-life of Acyclovir after administration of Apovir Injection 500 is about 2.9 hours. Renal clearance of Acyclovir (CL_r= 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.

In adults, mean steady state peak plasma concentrations ($C^{ss}max$) following a one-hour infusion of 2.5 mg/kg, 5 mg/kg and 10 mg/kg were 22.7 micromolar (5.1 microgram/ml),
43.6 micromolar (9.8 microgram/ml) and 92 micromolar (20.7 microgram/ml) respectively. The corresponding trough concentrations

(C^{ss}min) 7 hours later were 2.2 micromolar (0.5 microgram/ml), 3.1 micromolar (0.7 microgram/ml) and 10.2 micromolar (2.3 microgram/ml) respectively. In children over 1 year of age similar mean peak (C^{ss}max) and trough (C^{ss}min) concentrations 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 for 10 mg/kg.

In neonates (0 to 3 months of age) treated with doses of 10 mg/kg administered by infusion over a one-hour period every 8 hours the C^{ss}max was found to be 61.2 micromolar (13.8 microgram/ml) and the C^{ss}min to be 10.1 micromolar (2.3 microgram/ml). A separate group of neonates treated with 15 mg/kg every 8 hours showed approximate dose proportional increases, with a Cmax of 83.5 micromolar (18.8 microgram/ml) and Cmin of 14.1 micromolar (3.2 microgram/ml). The terminal plasma half-life in these patients was 3.8 hours.

5.2 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:

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

No excipients

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30^0 C. Protect from light and moisture.

6.5 Nature and contents of container

10 ml clear Tubular vial, stoppered with a 20 mm gray bromo butyl rubber stopper and sealed with 20 mm snap off seal with blue plastic cover.

6.6 Special precautions for disposal

Instructions for reconstitution

Withdraw 11 mL of the supplied 0.3 M sodium phosphate buffer with a needle and syringe and inject into the vial containing Artesunate injection powder for injection (the final concentration of artesunate is 10 mg/mL when reconstituted). Swirl gently (do not shake) for up to 5 to 6 minutes until the powder is fully dissolved and no visible particles remain.

Instructions for use and disposal

Visually inspect the solution within the vial to ensure that no visible particles remain and there is no discoloration of the solution. Do not administer if the solution is discolored or contains particulate matter.

Inject the reconstituted solution IV as a slow bolus over 1-2 minutes. Do not administer via continuous
IV infusion.

Discard the vial and any unused portion of the medicinal product after use.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURER

Marketing Authorisation Holder:

NATIONAL PHARMACY LIMITED

P.O.BOX 17843 –
00500, NAIROBI,
KENYA.

Manufacturer:

KAMLA LIFESCIENCES LTD.

G-54/1, Tarapur, M.I.D.C.,
Boisar, District -Palghar-401506

8.0 MARKETING AUTHORIZATION NUMBER

H2025/CTD11060/24160

9.0 DATE OF FIRST AUTHORIZATION /RENEWAL OF THE AUTHORIZATION

2025 September 17

10.0 DATE OF REVISION OF TEXT

2025 September 17