**Summary of Product Characteristics for Pharmaceutical Products**

1. **Name of the medicinal product:**
   **APOVIR INJECTION 250** (Aciclovir Sodium for Infusion BP 250 mg/vial)

2. **Qualitative and quantitative composition**

**Each Vial Contains**

Aciclovir sodium
Eq to Aciclovir BP.....250 mg
Water for Injection q.s

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 250** is indicated for the treatment of Herpes simplex infections in immunocompromised patients and severe initial genital herpes in the non-immunocompromised.
**APOVIR INJECTION 250** is indicated for the prophylaxis of Herpes simplex infections in immunocompromised patients.
**APOVIR INJECTION 250** is indicated for the treatment of Varicella zoster infections.
**APOVIR INJECTION 250** is indicated for the treatment of herpes encephalitis.
**APOVIR INJECTION 250** 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**

A course of treatment with **APOVIR INJECTION 250** 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 250** is determined by the duration of the period at risk.

The required dose of aciclovir for infusion should be administered by slow intravenous infusion over a one-hour period.
After reconstitution aciclovir for infusion may be administered by a controlled-rate infusion pump. Alternatively, the reconstituted solution may be further diluted to give an aciclovir concentration of not greater than 5 mg/ml (0.5% w/v) for administration by infusion. For instructions on reconstitution and dilution of the product before administration.

Dosage in adults:
Patients with Herpes simplex (except herpes encephalitis) or Varicella zoster infections should be given **APOVIR INJECTION 250** in doses of 5 mg/kg body weight every 8 hours provided renal function is not impaired.
Immunocompromised patients with Varicella zoster infections or patients with herpes encephalitis should be given **APOVIR INJECTION 250** in doses of 10 mg/kg body weight every 8 hours provided renal function is not impaired.
In obese patients dosed with intravenous aciclovir based on their actual body weight, higher plasma concentrations may be obtained. 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 250** 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 250** in doses of 250 mg per square meter of body surface area every 8 hours if renal function is not impaired.
The dosage of **APOVIR INJECTION 250** 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.

Dosage in the elderly:
The possibility of renal impairment in the elderly must be considered. In the elderly, total aciclovir body clearance declines in parallel with creatinine clearance. Special attention should be given to dosage reduction in elderly patients with impaired creatinine clearance.
Adequate hydration should be maintained.
Dosage in renal impairment:
Caution is advised when administering **APOVIR INJECTION 250** 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.

### 4.3 Contraindications
Hypersensitivity to aciclovir 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 aciclovir.
Intravenous doses should be given by infusion over one hour to avoid precipitation of aciclovir 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. aciclovir with other nephrotoxic drugs.
Use in patients with renal impairment and in elderly patients: Aciclovir 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 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.
In patients receiving **APOVIR INJECTION 250** 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 250** has a pH of approximately 11 and should not be administered by mouth.
This medicinal product contains less than 1 mmol (23 mg) sodium, i.e. essentially “sodium-free”.

**APOVIR INJECTION 250** contains no antimicrobial preservative. Reconstitution and dilution should therefore be carried out under full aseptic conditions immediately before use and any unused solution discarded.

## 4.5 Interaction with other medicinal products and other forms of interaction

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion.
Any drugs administered concurrently that compete with this mechanism may increase aciclovir plasma concentrations.
Probenecid and cimetidine increase the AUC of aciclovir by this mechanism and reduce aciclovir renal clearance.
However, no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.
In patients receiving intravenous **APOVIR INJECTION 250** caution is required during concurrent administration with drugs which compete with aciclovir for elimination, because of the potential for
increased plasma levels of one or both drugs or their metabolites.
Increases in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant agent used in transplant patients, have been shown when the drugs are

Co-administered.
If lithium is administered concurrently with high dose aciclovir 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
**APOVIR INJECTION 250** 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 aciclovir
increases AUC of totally administered theophylline with approximately 50%. It is recommended to
measure plasma concentrations during concomitant therapy with aciclovir.

### 4.6 Pregnancy and Lactation

Fertility:
There is no information on the effect of aciclovir on human female fertility.
In a study of 20 male patients with normal sperm count, oral aciclovir 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 aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of **APOVIR INJECTION 250**.
The registry findings have not shown an increase in the number of birth defects amongst aciclovir 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 aciclovir 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 are

included in Section 5.3.

Breast-feeding:
Following oral administration of 200 mg five times a day, aciclovir has been detected in human 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 body weight/day. Caution is therefore advised if **APOVIR INJECTION 250** is to be administered to a nursing woman.

## 4.7 Effects on ability to drive and use machines

Aciclovir 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 aciclovir 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 levels are believed to be related to the peak plasma levels 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. 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 aciclovir has been inadvertently infused into extravascular tissue.

**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.

### 4.9 Overdose

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 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.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

Aciclovir 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 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, HSV-2, VZV and EBV is highly selective. The enzyme thymidine kinase (TK) of normal, uninfected 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.

### 5.2 Pharmacokinetic properties

**Absorption**

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 levels ($C^{SS}$ 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) 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 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 Cmax 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. In the elderly, total body clearance falls with increasing age and is associated with decreases in creatinine clearance although there is little change in the terminal plasma half-life. In patients with chronic renal failure 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. In a clinical study in which morbidly obese female patients (n=7) were dosed with intravenous aciclovir based on their actual body weight, plasma concentrations were found to be approximately twice that of normal weight patients (n=5), consistent with the difference in body weight between the two groups.

**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 aciclovir after administration of aciclovir is about 2.9 hours. Most of the drug is excreted unchanged by the kidney. 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. 9carboxymethoxy-methylguanine is the only significant metabolite of aciclovir and accounts for 10 to 15% of the dose excreted in the urine.
When aciclovir 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.Preclinical safety data
Mutagenicity:
The results of a wide range of mutagenicity tests in vitro and in vivo indicate that aciclovir is unlikely to pose a genetic risk to man.
Carcinogenicity:
Aciclovir was not found to be carcinogenic in long term studies in the rat and the mouse.
Teratogenicity:
Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rats, rabbits 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 aciclovir greatly in excess of those employed therapeutically. Two generation studies in mice did not reveal any effect of aciclovir on fertility. Data to evaluate a potential effect on the environment is currently limited .

## 6. Pharmaceutical Particulars

### 6.1 List of Excipients

Sodium hydroxide (used to adjust pH)

### 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
For reconstituted solutions, chemical and physical in-use stability has been demonstrated for 12 hours at 25°C or in a

refrigerator (2°C – 8°C).
From a microbiological point of view, once opened, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

### 6.4 Special Precautions for storage

Store in the original package. For storage conditions after reconstitution and/or dilution of the medicinal product, see section 6.3.

### 6.5 Nature and Content of container

7.5 ml clear vial, stoppered with a 20 mm bromo butyl rubber stopper and sealed with 20mm Aluminum flip-off seal.

### 6.6 Special precautions for disposal and other handling

For single use only.
Prepare immediately prior to use. Reconstitution:
**APOVIR INJECTION 250** should be reconstituted using Water for Injections to provide a solution containing 250 mg aciclovir per ml. Volume following reconstitution: 10.1-10.2 ml
From the calculated dose, determine the appropriate number and strength of vials to be used. To reconstitute each vial add the recommended volume of infusion fluid and shake gently until the contents of the vial have dissolved completely.
The solution reconstituted with Water for Injections is stable for a period of 12 hours at temperature below 25°C or in a refrigerator (2°C – 8°C).

Administration:
The required dose of **APOVIR INJECTION 250** should be administered by slow intravenous infusion over a one-hour period.
After reconstitution **APOVIR INJECTION 250** may be administered by a controlled-rate infusion pump.
Alternatively, the reconstituted solution may be further diluted to give an aciclovir concentration of not greater than 5 mg/ml (0.5% w/v) for administration by infusion.
Add the required volume of reconstituted solution 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 reconstituted solution (100 mg aciclovir) 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 aciclovir concentration substantially below 0.5% w/v. Thus one 100 ml infusion bag may be used for any dose between 250 mg and 500 mg aciclovir (10 and 20 ml of reconstituted solution) but a second bag must be used for doses between 500 mg and 1000 mg.
Since no antimicrobial preservative is included, reconstitution and 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.
Discard any unused solution. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. Marketing Authorization Number 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. Market Authorization Number**
24160

**9. Date of first authorization/renewal of the authorization**
2025 July 17

**10. Date of revision of the text**
2030 July 17