Summary of Product Characteristics for Pharmaceutical Products

1. **Name of the medicinal product:**
   Virhir tablets 400mg
2. **Qualitative and quantitative composition**
   Each uncoated tablet contains Acyclovir USP 400mg.
   For the full list of excipients, see section 6.1
3. **Pharmaceutical form**
   White, oval shaped, biconvex, having break line on one side uncoated tablets.
4. **Clinical particulars**

4.1 Therapeutic indications

Virhir Tablets are indicated for the treatment of herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital herpes (excluding neonatal HSV and severe HSV infections in immunocompromised children).
Virhir Tablets are indicated for the suppression (prevention of recurrences) of recurrent herpes simplex infections in immunocompetent patients.
Virhir Tablets are indicated for the prophylaxis of herpes simplex infections in immunocompromised patients.
Virhir Tablets are indicated for the treatment of varicella (chickenpox) and herpes zoster (shingles) infections.

4.2 Posology and method of administration

Posology

Dosage in adults

Treatment of herpes simplex infections: 200 mg Virhir should be taken five times daily at approximately four hourly intervals omitting the night time dose. Treatment should continue for 5 days, but in severe initial infections this may have to be extended.
In severely immunocompromised patients (e.g. after marrow transplant) or in patients with impaired absorption from the gut the dose can be doubled to 400 mg Virhir, or alternatively, intravenous dosing could be considered.
Dosing should begin as early as possible after the start of an infection; for recurrent episodes this should preferably be during the prodromal period or when lesions first appear.
Suppression of herpes simplex infections in immunocompetent patients: 200 mg Virhir should be taken four times daily at approximately six-hourly intervals.
Many patients may be conveniently managed on a regimen of 400 mg Virhir twice daily at approximately twelve hourly intervals.
Dosage titration down to 200 mg Virhir taken thrice daily at approximately eight-hourly intervals or even twice daily at approximately twelve-hourly intervals may prove effective.
Some patients may experience break-through infection on total daily doses of 800 mg Virhir.

Therapy should be interrupted periodically at intervals of six to twelve months, in order to observe possible changes in the natural history of the disease.
Prophylaxis of herpes simplex infections in immunocompromised patients: 200 mg Virhir should be taken four times daily at approximately six-hourly intervals.
In severely immunocompromised patients (e.g. after marrow transplant) or in patients with impaired absorption from the gut, the dose can be doubled to 400 mg Virhir, or alternatively, intravenous dosing could be considered.
The duration of prophylactic administration is determined by the duration of the period at risk.
Treatment of varicella and herpes zoster infections: 800 mg Virhir should be taken five times daily at approximately four-hourly intervals, omitting the night time dose. Treatment should continue for seven days.
In severely immunocompromised patients (e.g. after marrow transplant) or in patients with impaired absorption from the gut, consideration should be given to intravenous dosing.
Dosing should begin as early as possible after the start of an infection: Treatment of herpes zoster yields better results if initiated as soon as possible after the onset of the rash. Treatment of chickenpox in immunocompetent patients should begin within 24 hours after onset of the rash.

Paediatric population

Treatment of herpes simplex infections, and prophylaxis of herpes simplex infections in the immunocompromised: Children aged two years and over should be given adult dosages and children below the age of two years should be given half the adult dose.
For treatment on neonatal herpes virus infections, intravenous Virhir is recommended.
Treatment of varicella infection:

6 years and over:	800 mg Virhir four times daily
2 - 5 years:	400 mg Virhir four times daily
Under 2 years:	200 mg Virhir four times daily

Treatment should continue for five days.
Dosing may be more accurately calculated as 20 mg/kg bodyweight (not to exceed 800 mg) Virhir four times daily.
No specific data are available on the suppression of herpes simplex infections or the treatment of herpes zoster infections in immunocompetent children.

Dosage in the elderly:

The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly (see Dosage in renal impairment below).
Adequate hydration of elderly patients taking high oral doses of Virhir should be maintained.

Dosage in renal impairment:

Caution is advised when administering Virhir to patients with impaired renal function. Adequate hydration should be maintained.
In the management of herpes simplex infections in patients with impaired renal function, the recommended oral doses will not lead to accumulation of Virhir above levels that have been established safe by intravenous infusion. However, for patients with severe renal impairment (creatinine clearance less than 10 ml/minute) an adjustment of dosage to 200 mg Virhir twice daily at approximately twelve-hourly intervals is recommended.
In the treatment of herpes zoster infections, it is recommended to adjust the dosage to 800 mg Virhir twice daily at approximately twelve hourly intervals for patients with severe renal impairment (creatinine clearance less than 10 ml/minute) and to 800 mg Virhir three times daily at intervals of approximately eight hours for patients with moderate renal impairment (creatinine clearance in the range 10 – 25 ml/minute).

Method of administration:

Virhir tablets are for oral administration and may be dispersed in a minimum of 50 ml of water or swallowed whole with a little water. Ensure that patients on high doses of Virhir are adequately hydrated.

4.3 Contraindications

Hypersensitivity to Virhir or valacyclovir, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Use in patients with renal impairment and in elderly patients:
Virhir is eliminated by renal clearance, therefore the dose must be adjusted in patients with renal impairment (see 4.2 Posology and Method of Administration).
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 (see 4.8 Undesirable Effects).
Prolonged or repeated courses of Virhir in severely immune-compromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued Virhir treatment (see section 5.1).
Hydration status:
Care should be taken to maintain adequate hydration in patients receiving high oral doses of Virhir.
The risk of renal impairment is increased by use with other nephrotoxic drugs.
The data currently available from clinical studies is not sufficient to conclude that treatment with Virhir reduces the incidence of chickenpox-associated complications in immunocompetent patients.
Virhir 400 mg Tablets contain sodium
Virhir 400 mg Tablets contain less than 1 mmol (23 mg) of sodium per

tablet, that is to say it is essentially 'sodium-free.'

4.5 Interaction with other medicinal products and other forms of interaction

Virhir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that compete with this mechanism may increase Virhir plasma concentrations. **Probenecid and cimetidine** increase the AUC of Virhir by this mechanism and reduce Virhir renal clearance. Similarly, increases in plasma AUCs of Virhir and of the inactive metabolite of **mycophenolate mofetil**, an immunosuppresant agent used in transplant patients have been shown when the drugs are coadministered. However, no dosage adjustment is necessary because of the wide therapeutic index of Virhir.

An experimental study on five male subjects indicates that concomitant therapy with Virhir increases AUC of totally administered **theophylline** with approximately 50%. It is recommended to measure plasma concentrations during concomitant therapy with Virhir.

4.6 Pregnancy and Lactation

Pregnancy:

The use of Virhir should be considered only when the potential benefits outweigh the possibility of unknown risks.

A post-marketing Virhir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of Virhir. The registry findings have not shown an increase in the number of birth defects amongst Virhir exposed subjects compared with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause. Systemic administration of Virhir 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 however 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 Virhir five times a day, Virhir 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 Virhir dosages of up to 0.3 mg/kg/day. Caution is therefore advised if Virhir is to be administered to a nursing woman.

Fertility:

There is no information on the effect of Virhir on human female fertility. In a study of 20 male patients with normal sperm count, oral Virhir 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.

See clinical studies in section 5.3.

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of Virhir on driving performance or the ability to operate machinery. A detrimental effect on such activities cannot be predicted from the pharmacology of the active substance, but the adverse event profile should be borne in mind.

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 ≥ 1/1000 and < 1/100,
Rare ≥ 1/10,000 and < 1/1000,
Very rare < 1/10,000.

Blood and the lymphatic system disorders:

Very rare: Anaemia, leukopenia, thrombocytopenia.

Immune system disorders:

Rare: Anaphylaxis.

Psychiatric and nervous system disorders:

Common: Headache, dizziness.

Very rare: 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).

Respiratory, thoracic and mediastinal disorders:

Rare: Dyspnoea.

Gastrointestinal disorders:

Common: Nausea, vomiting, diarrhoea, abdominal pains.

Hepato-biliary disorders:

Rare: Reversible rises in bilirubin and liver related enzymes.

Very rare: Hepatitis, jaundice.

Skin and subcutaneous tissue disorders:

Common: Pruritus, rashes (including photosensitivity).

Uncommon: Urticaria. Accelerated diffuse hair loss. Accelerated diffuse hair loss has been associated with a wide variety of disease processes and medicines, the relationship of the event to Virhir therapy is uncertain.

Rare: Angioedema.

Renal and urinary disorders:

Rare: Increases in blood urea and creatinine.

Very rare: Acute renal failure, renal pain.

Renal pain may be associated with renal failure and crystalluria.

General disorders and administration site conditions:

Common: Fatigue, fever.

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 via Pharmacy and Poisons Board- Pharmacovigilance Electronic Reporting System (PvERS); *https://pv.pharmacyboardkenya.org* .

4.9 Overdose

Symptoms and signs:

Virhir is only partly absorbed in the gastrointestinal tract. Patients have ingested overdoses of up to 20g Virhir on a single occasion, usually without toxic effects. Accidental, repeated overdoses of oral Virhir over several days have been associated with gastrointestinal effects (such as nausea and vomiting) and neurological effects (headache and confusion).

Overdosage of intravenous Virhir 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 intravenous overdosage.

Management:

Patients should be observed closely for signs of toxicity. Haemodialysis significantly enhances the removal of Virhir from the blood and may, therefore, be considered a management option in the event of symptomatic overdose.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

ATC code: J05AB01

Virhir is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against human herpes viruses, including herpes simplex virus (HSV) types I and II and varicella zoster virus (VZV).

The inhibitory activity of Virhir for HSV I, HSV II and VZV is highly selective. The enzyme thymidine kinase (TK) of normal, uninfected cells does not use Virhir effectively as a substrate, hence toxicity of mammalian host cells is low; however, TK encoded by HSV and VZV converts Virhir to Virhir monophosphate, a nucleoside analogue which is further converted to the diphosphate and finally to the triphosphate by cellular enzymes. Virhir triphosphate interferes with the viral DNA polymerase and inhibits viral DNA replication with resultant chain termination following its incorporation into the viral DNA.

Prolonged or repeated courses of Virhir in severely immune-compromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued Virhir treatment. Most of the clinical isolates with reduced sensitivity have been relatively deficient in viral TK, however, strains with altered viral TK or viral DNA polymerase have also been reported. In vitro exposure

of HSV isolates to Virhir can also lead to the emergence of less sensitive strains. The relationship between the in vitro-determined sensitivity of HSV isolates and clinical response to Virhir therapy is not clear.

5.2 Pharmacokinetic properties

Absorption

Virhir is only partially absorbed from the gut. The average oral bioavailability varies between 10 and 20%. Under fasting conditions, mean peak concentrations (Cmax) 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 (Cssmax) 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 Cssmax concentration 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 Virhir 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 concentration are approximately 50% of corresponding plasma concentration at steady-state.

Metabolism

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

Elimination

In adults mean systemic exposure (AUC0-∞) to Virhir 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.

Renal clearance of Virhir (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 Virhir are dependent on renal function. Therefore, dosage adjustment is recommended for renally impaired patients.

There are no pharmacokinetic data for the oral formulation in neonates. The only available pharmacokinetic data are for the IV formulation in this age group.

Special patient populations

Elderly

In the elderly patients with normal renal function total clearance falls with increasing age due to decreases in creatinine clearance. However, the possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly.

Renal impairment

In patients with chronic renal failure the mean terminal half-life was found to be 19.5 hours. The mean Virhir half-life during haemodialysis was 5.7 hours. Plasma Virhir concentration dropped approximately 60% during dialysis.

5.3 Preclinical safety data

Mutagenicity:

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

Carcinogenicity:

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

Teratogenicity:

Systemic administration of Virhir 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 Virhir greatly in excess of those employed therapeutically. Two generation studies in mice did not reveal any effect of Virhir on fertility.

6. Pharmaceutical Particulars

6.1 List of Excipients

Excipients	Specification	Standard Quantity (mg)/ tablet
Microcrystalline Cellulose	USP	93.000mg
Corn Starch (Dry mixing)	USP	141.500mg
Corn Starch (Binding)	USP	30.000mg
Sodium starch Glycolate	USP	20.000mg
PVP K30 (Povidone)	USP	7.500mg
Purified Water	USP	q.s
Purified Talc	USP	10.000mg
Magnesium Stearate	USP	8.000mg

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

36 months

6.4 Special Precautions for storage

No special storage conditions are required.

6.5 Nature and Content of container

10 tablets pack in one Alu-PVC Blister.
Such 1 Blister pack in carton along with insert.

6.6 Special precautions for disposal and other handling

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

7. Marketing Authorization Holder

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Website: www.Hirallabs.Com

8. Marketing Authorization Number

CTD8776

9. Date of first authorization/renewal of the authorization

17/04/2023

10. Date of revision of the text

10th May, 2025