1. Name of the medicinal product

Aciclovir Dispersible Tablets BP 200 mg

2. Qualitative and quantitative composition

Each 200 mg tablet contains 200 mg Aciclovir.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet
A White colored, round shaped, flat face beveled edges, uncoated dispersible tablets, breakline on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of herpes simplex infections of the skin and mucous membranes including initial and recurrent genital herpes (excluding neonatal HSV and severe HSV infections in immunocompromised children). Suppression of recurrent herpes simplex infections. Prevention of herpes simplex infections in immunocompromised patients. Treatment of herpes zoster infections. Treatment of varicella (chickenpox) infections.

4.2 Posology and method of administration

Posology
Dosage in adults

Treatment of herpes simplex infections:
200 mg 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 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 should be taken four times daily at approximately six-hourly intervals. Many patients may be conveniently managed on a regimen of 400 mg twice daily at approximately twelve-hourly intervals.
Dosage titration down to 200 mg taken thrice daily at approximately eighthourly 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 800mg.
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 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, 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:
800mg 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.

Dosage in children
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 aciclovir is recommended.

Treatment of varicella infection 6 years and over: 800mg
four times daily.
2 – 5 years: 400 mg four times daily.
Under 2 years: 200 mg four times daily.

Treatment should continue for five days.
Dosing may be more accurately calculated as 20mg/kg bodyweight (not to exceed 800mg) 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 aciclovir should be maintained.

Dosage in renal impairment:
Caution is advised when administering aciclovir 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 aciclovir 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 aciclovir twice daily at approximately twelve-hourly intervals is recommended.
In the treatment of herpes zoster infections it is recommended to adjust the dosage to 800mg aciclovir twice daily at approximately twelve - hourly intervals for patients with severe renal impairment (creatinine clearance less than 10 ml/minute), and to 800mg aciclovir 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
Route of administration: Oral

Aciclovir Dispersible Tablets may be dispersed in a minimum of 50ml of water or swallowed whole with a little water. Ensure that patients on high doses of aciclovir are adequately hydrated.

4.3 Contraindications

Hypersensitivity to aciclovir, or valaciclovir or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Severe cutaneous adverse reactions:

Cases of severe cutaneous adverse reactions (SCARs), including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) and erythema multiforme (EM) have been reported in patients treated with aciclovir.

As SCARS can be life-threatening or fatal, if signs and symptoms suggestive of SCARS appear, treatment with aciclovir must be discontinued immediately, and alternative treatment should be given. Patients who have developed SCARS with the use of aciclovir or valaciclovir must not receive aciclovir (*see Contraindications and Adverse Reactions*).

Use in patients with renal impairment and in elderly patients:

Aciclovir is eliminated by renal clearance, therefore the dose must be reduced in patients with renal impairment (see section 4.2 Posology and Method of Administration).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). Hydration status: Adequate hydration should be maintained, especially in the elderly and, in patients with impaired renal function, in patients given i.v or those receiving high oral doses of aciclovir.

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 aciclovir reduces the incidence of chickenpox-associated complications in immunocompetent patients.

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 (see section 5.1).

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

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.
Similarly increases in plasma AUCs of aciclovir 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 aciclovir.

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 Fertility, 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.
See clinical studies in section 5.2

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

A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of aciclovir. The registry findings have not shown an increase in the number of birth defects described amongst aciclovir exposed subjects compared with the general population, and any birth defects have not shown any 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 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 aciclovir five times a day, Aciclovir 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 aciclovir dosages of up to 0.3mg/kg/day. Caution is therefore advised if aciclovir is to be administered to a nursing woman.

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of aciclovir 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. The clinical status of the patient and the adverse event profile should be borne in mind when considering the patients's ability to drive or 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 ≥ 1/1000 and <1/100, rare ≥1/10,000 and <1/1000, very rare <1/10,000.

Blood and 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 section 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 aciclovir therapy is uncertain.

Rare: Angioedema
Very rare: Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme (EM)
(*see Special warnings and precautions for use*)

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 Authorization 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 the national pharmacovigilance reporting system.

4.9 Overdose

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

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 intravenous overdosage.

Management: patients should be observed closely for signs of toxicity. Haemodialysis

significantly enhances the removal of acyclovir 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 J05A B01.

Aciclovir 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 aciclovir for HSV I and HSV II and VZV 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 and VZV 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.

Prolonged or repeated courses of aciclovir in severely immuno-compromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued aciclovir 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 aciclovir 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 aciclovir therapy is not clear.

5.2 Pharmacokinetic properties

Absorption

Aciclovir 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 200mg Aciclovir administered every four-hours. A less than proportional increase is observed for C_{ssmax} concentration following doses of 400 mg and 800 mg administered fourhourly, 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 aciclovir is distributed within total body water. Apparent values after oral administration (Vd/F) ranged from 2.3 to 17.8 L/kg. Cerebrospinal fluid concentration are approximately 50% of corresponding plasma concentration at steady-state. As plasma protein binding is relatively low (9 to 33%) , drug interactions involving binding site displacement are not anticipated.

Metabolism

Aciclovir is predominantly excreted unchanged by the kidney. 9carboxymethoxymethyl-guanine is the only significant urinary metabolite of aciclovir, and accounts for 10-15% of the dose excreted in the urine.

Elimination

In adults mean systemic exposure (AUC0-∞) to aciclovir ranges between 1.9 and 2.2 microgram*h/mL after a 200 mg dose. At this dose, the mean terminal plasma halflife after oral administration has been shown to vary between 2.8 and 4.1 hours.

Renal clearance of aciclovir (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 aciclovir 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 body clearance falls with increasing age associated with 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 aciclovir half-life during haemodialysis was 5.7 hours. Plasma aciclovir 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 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.

6. Pharmaceutical Particulars

6.1List of excipients

Maize Starch
Pre-Gelatin Starch
Microcrystalline Cellulose (PH 101)
Hydroxypropyl methyl cellulose (H.P.M.C. E 5) Dibasic calcium phosphate
Polyvinyl Pyrrollidine K 30 (PVP K 30)
Isopropyl Alcohol @
Neotame
Orange Flavour
Colloidal Silicon Dioxide

Sodium Starch Glycolate
Polacrillin Potassium T-314 (Kyron T - 314) Citric Acid
Sodium Bicarbonate
Purified talcum
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

No special storage conditions are required.

6.5 Nature and contents of container

10 Tablets packed Alu -Alu Blister , such 2 Blisters packed in printed Carton along with package insert.

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing Authorization Holder

Nesher Pharma Ltd.

8**. Marketing Authorization Number**

H2025/CTD12775/26408

9. Date of First Authorization

16/12/2025

10. Date of Revision of text

16/12/2025

SUMMARY OF PRODUCT CHARACTERISTICS