Brand Name : AGOVIR-400 Tablets **Generic Name :** Aciclovir Tablets BP 400 mg	2021
Module 1 Administrative Information and Product Information **1.5** Product Information	**Confidential**

1.5 PRODUCT INFORMATION

1.5.1 Prescribing information (Summary of products characteristics)

SUMMARY PRODUCT CHARACTERISTICS

1. Name of drug product:

AGOVIR-400 Tablets (Aciclovir Tablets BP 400 mg)

2. Qualitative and Quantitative Composition:

Each uncoated tablet contains: Aciclovir BP 400 mg

3. Pharmaceutical form:

White Coloured, Round, uncoated tablets.

4. Clinical particulars:

4.1 Therapeutic indications

Aciclovir 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).

Aciclovir Tablets are indicated for the suppression (prevention of recurrences) of recurrent herpes simplex infections in immunocompetent patients.

Aciclovir Tablets are indicated for the prophylaxis of herpes simplex infections in immunocompromised patients.

Aciclovir 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

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Treatment of herpes simplex infections: 200 mg Aciclovir 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 Aciclovir, 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 Aciclovir should be taken four times daily at approximately six-hourly intervals.

Many patients may be conveniently managed on a regimen of 400 mg Aciclovir twice daily at approximately twelve hourly intervals.

Dosage titration down to 200 mg Aciclovir 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 Aciclovir.

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 Aciclovir 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 Aciclovir, 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 Aciclovir 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

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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:	800 mg Aciclovir four times daily
2 - 5 years:	400 mg Aciclovir four times daily
Under 2 years:	200 mg Aciclovir 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) Aciclovir 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 800 mg Aciclovir twice daily at approximately twelve hourly intervals for patients with severe renal impairment (creatinine clearance less than 10 ml/minute), and to 800 mg 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:

Aciclovir 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 aciclovir are adequately hydrated.

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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

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.

Hydration status: Care should be taken to maintain adequate hydration in patients 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.

Sodium

<Invented name> contains 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

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 mycophenolatemofetil, an immunosuppresant agent used in transplant patients have been shown when the drugs are co administered. 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.

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4.6 Fertility, pregnancy and lactation

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 amongst aciclovir 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 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.

Breastfeeding

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 0.3 mg/kg/day. Caution is therefore advised if aciclovir is to be administered to a nursing woman.

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.

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, 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.

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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

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.

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 the Yellow Card Scheme at:

www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 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

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

ATC code: J05AB01

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, 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 of 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*-

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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. Mean steady state peak plasma concentrations ($C^{ss}max$) following doses of 200 mg administered four- hourly were 3.1 microMol (0.7 micrograms/ml) and equivalent trough plasma levels (Cssmin) were 1.8 microMol (0.4 micrograms/ml). Corresponding Cmax levels following doses of 400 mg and 800 mg administered four- hourly were 5.3 microMol (1.2 micrograms/ml) and 8 microMol (1.8 micrograms/ml) respectively and equivalent Cssmin levels were 2.7 microMol (0.6 micrograms/ml) and 4 microMol (0.9 micrograms/ml).

Elimination

In adults the terminal plasma half-life of aciclovir after administration of intravenous 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. 9-carboxymethoxymethylguanine is the only significant metabolite of aciclovir, and accounts for approximately 10 - 15% of the administered dose recovered from 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 is extended by 18% and 40% respectively.

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 microMol (5.1 micrograms/ml), 43.6 microMol (9.8 micrograms/ml) and 92 microMol (20.7 micrograms/ml), respectively. The corresponding trough levels (Cssmin) 7 hours later were 2.2 microMol (0.5 micrograms/ml), 3.1 microMol (0.7 micrograms/ml), and 10.2 microMol (2.3 micrograms/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 and young infants (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 microMol (13.8 micrograms/ml) and $C^{ss}min$ to be 10.1 microMol (2.3 micrograms/ml). The terminal plasma half-life in these patients was 3.8 hours. 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).

In the elderly, total body clearance falls with increasing age 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.

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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 is not anticipated.

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:

6.1 List of Excipients:

Lactose	BP
Microcrystalline cellulose	BP
Sodium starch Glycolate	BP
Colloidal silicon dioxide	BP
Maize starch	BP
Sodium methyl paraben	BP
Sodium propyl paraben	BP
Polyvinyl pyrrolidone K-30 (Povidone)	BP
Purified talc	BP
Cross Carmellose sodium	BP
Magnesium stearate	BP

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Polyplasdone XL-10	BP

6.2 Incompatibilities:
None Reported

6.3 Shelf-Life:
36 months from the date of manufacture.

6.4 Special Precautions for Storage:
Store in a cool, dry and dark place. Protect from light.

6.5 Nature and Contents of Container:
100 tablets packed in one Jar, such jar packed in export worthy shipper along with its pack insert.

6.6 Special precautions for disposal:
None reported.

7. Registrant:

AGOG PHARMA LTD.
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Co-Op. Estate Ltd., Gauraipada,
Vasai (E), Dist. Thane, India.

8. Manufacturer:

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9. Date of revision of the text :

1.5.2 Container labelling