National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. Name of the medicinal product:

BAFNACARE -400 (Aciclovir Tablets BP 400 mg)

2. Qualitative and quantitative composition

Each uncoated tablet contains: Aciclovir BP 400 mg

S. No	Name of the Ingredient	Specification	Qty per tablet (mg)	Function
	Dry Mixing:			
1.	Aciclovir	BP	400.000	Active
2.	Maize starch	BP	86.500	Diluent
3.	Colloidal anhydrous silica	BP	1.500	Disintegrant
	Binder:			
4.	Povidone (K-30)	BP	18.000	Diluent
5.	Isopropyl Alcohol	BP	114.286	Solvent
	Pre- Lubrication:			
6.	Microcrystalline Cellulose (PH 102)	BP	60.000	Diluent
7.	Colloidal Anhydrous Silica	BP	1.000	Disintegrant
8.	Sodium Starch Glycolate (Type –A)	BP	21.000	Disintegrant
9.	Purified Talc	BP	6.000	Diluent
	Lubrication:			
10.	Magnesium stearate	BP	6.000	Lubricant
	Total Uncoated tablet weight		**600.000**	

3. Pharmaceutical form

Uncoated Tablet

White to off white, Capsule shaped, biconvex, uncoated tablets debossed "ACV" on one side and "400" on other side.

4. Clinical Particular

4.1 Therapeutic Indications:

1) 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).
2) Suppression (prevention of recurrences) of recurrent herpes simplex infections in immunocompetent patients.
3) Prophylaxis of herpes simplex infections in immunocompromised patients.

4) Treatment of varicella (chickenpox) and herpes zoster (shingles) infections.
Route of administration: Oral.

4.2 Posology and Method of Administration

Posology

Dosage in adults

Treatment of herpes simplex infections: 200mg aciclovir should be taken five times daily at approximately four hourly intervals omitting the night time dose. Treatment should continue for five days, but in severe initial infections this may have to be extended.

In severely immunocompromised patients (eg after marrow transplant) or in patients with impaired absorption from the gut the dose can be doubled to 400mg 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:
200mg aciclovir should be taken four times daily at approximately six-hourly intervals.

Many patients may be conveniently managed on a regime of 400mg aciclovir twice daily at approximately twelve-hourly intervals.

Dosage titration down to 200mg aciclovir taken three times daily at approximately eight-hourly intervals or even twice daily at approximately twelve-hourly intervals, may prove effective.

Some patients may experience break-through infections on total daily doses of 800mg 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:
200mg aciclovir should be taken four times daily at approximately six hourly intervals.

In severely immunocompromised patients (eg after marrow transplant) or in patients with impaired absorption from the gut, the dose can be doubled to 400mg 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.

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 the adult doses 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: 400mg aciclovir four times daily.
Under 2 years: 200mg aciclovir four times daily.
Treatment should continue for 5 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. 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
For oral administration.

Patients who experience difficulty in swallowing the tablets may disperse them in a minimum of 50ml water which should be stirred before drinking. 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.

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.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, 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 immunosuppressant 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.

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.

Breast-feeding

Following oral administration of 200mg aciclovir five times a day, aciclovir has been detected in breast milk at concentrations ranging from 0.6-4.1 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 mother.

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. Some side effects such as drowsiness and somnolence may impair a patients ability to concentrate and react. Patients should make sure that they are not affected before driving or operating 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, not known (cannot be estimated from the available data).

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

Respiratory, thoracic and mediastinal disorders

Rare: Dyspnoea

Gastrointestinal disorders

Common: Nausea, vomiting, diarrhoea, abdominal pains

Hepatobiliary 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: Fever, fatigue

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, 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 immune-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 (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 (Css_{max}) 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 Css_{max} 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 aciclovir 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

Aciclovir 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 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.

<u>Special patient populations</u>

<u>Elderly</u>

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 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

6.1 List of Excipients

Maize starch

Colloidal anhydrous silica

Povidone

Isopropyl Alcohol

Microcrystalline Cellulose

Sodium Starch Glycolate

Purified Talc

Magnesium stearate

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Store below 30°C in the Original Package in order to protect from moisture

6.5 Nature and Contents of Container

Alu/Clear PVC Blister Packing: 4 x 14 Tablets

6.6 Special precautions for disposal and other handling

No Special requirements

7. Marketing Authorization Holder

Bafna Pharmaceuticals Ltd.,
No.147, Madhavaram Redhills High Road, Grantlyon village,
Vadakarai Post,
Chennai – 600 052. India
Tel: 0091 – 44 – 26320366

8. Marketing Authorization number(s)

----

9. Date of first authorization/renewal of the authorization

----

10. Date of revision of the text

16/12/2023