SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ACICLOVIR TABLETS BP 800mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 800mg Aciclovir PhEur.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White uncoated tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

1) Treatment of varicella (chickenpox) and herpes zoster (shingles) infections.

4.2 Posology and method of administration

Posology

***Adults: Treatment of herpes zoster infections*:** 800mg 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 (*eg* 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.

Dosage in the paediatric population: Treatment of varicella infection:
Children aged 6 years and over should be given 800mg 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.
When treatment of herpes zoster infections is required in immunocompromised children, intravenous dosing should be considered.

***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).
In the elderly, total aciclovir body clearance declines along with creatinine clearance. Adequate hydration of elderly patients taking high oral doses of aciclovir should be maintained. Special attention should be given to dosage reduction in elderly patients with impaired renal function.

***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 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 10ml/minute), and to 800mg aciclovir three times daily at intervals of approximately six to eight hours for patients with moderate renal impairment (creatinine clearance in the range 10-25ml/minute).
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 renal impairment (creatinine clearance less than 10ml/minute), and to 800mg aciclovir three times daily at intervals of approximately six to eight hours for patients with moderate renal impairment (creatinine clearance in the range 10-25ml/minute).

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

For oral administration.

4.3 Contraindications

- Hypersensitivity to the active substance, 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:

The risk of renal impairment is increased by use with other nephrotoxic drugs.

Aciclovir is eliminated by renal clearance, therefore the dose must be reduced in patients with renal impairment (see section 4.2). 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).

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).

Hydration status: Care should be taken to maintain adequate hydration in patients receiving higher dose oral regimens or i.v., e.g. for the treatment of herpes zoster infection (4g daily), in order to avoid the risk of possible renal toxicity.

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.
- Ciclosporin: There has been a small number of transplant patients with increased serum levels of ciclosporin and signs of nephrotoxicity when aciclovir is given concurrently. Renal function should be monitored closely in patients taking both drugs.
- Cimetidine and probenecid: Cimetidine and probenecid increase the AUC of aciclovir by competing for active secretion by the renal tubules and reduce aciclovir renal clearance. Dosage adjustment is usually not necessary because of the wide therapeutic index of aciclovir.
- Mycophenolate mofetil: 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.
- Zidovudine: Although co-administration of zidovudine and aciclovir is not usually associated with toxicity, there is a single case report of overwhelming fatigue developing in a patient when given the two drugs together. This did not occur when zidovudine and aciclovir were given alone.

4.6 Fertility, pregnancy and lactation

Pregnancy

Experience in humans is limited so the use of aciclovir should be considered only when the potential benefits outweigh the possibility of unknown risks. Herpes simplex encephalitis and varicella pneumonia constitute a significant risk for mother and foetus and primary genital herpes may retard intrauterine growth and increase the risk of premature birth and neonatal herpes infection. (See section 5.3 Preclinical Safety Data). Aciclovir readily crosses the placenta and levels in cord blood are higher than in maternal serum.
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.

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.

4.7 Effects on Ability to Drive and Use Machines

The clinical status of the patient and the adverse event profile of aciclovir should be borne in mind when considering the patients's ability to drive or operate machinery. As aciclovir administration is occasionally associated with drowsiness and somnolence (usually in patients receiving high doses or with impaired renal function), patients should make sure that they are not affected before driving or using machinery.
There have been no studies to investigate the effect of aciclovir on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

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.

An estimate of the frequency of undesirable effects has been included though this is not certain for all adverse effects. The following convention has been used for the classification of undesirable effects in terms of frequency: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10000, <1/1000, very rare (<1/10000).

Blood and the lymphatic system disorders
Very rare: Anaemia, leucopenia and thrombocytopenia.

Immune system disorders
Rare: Anaphylaxis.

Nervous system disorders
Common: Dizziness and headache.
Very rare: Reversible neurological reactions including agitation, tremor, ataxia, dysarthria, psychotic symptoms, encephalopathy, drowsiness, confusional states, hallucinations, somnolence, convulsions, coma and malaise. These effects were usually reported in patients receiving high doses of aciclovir (usually given intravenously), with renal impairment, or with other predisposing factors (see section 4.4). Aciclovir should be used with caution in patients with underlying neurological abnormalities.

Respiratory, thoracic and mediastinal disorders
Rare: Dyspnoea

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea and abdominal pain.

Hepato-biliary disorders
Rare: Reversible rises in bilirubin and liver related enzymes.
Very rare: Hepatitis and jaundice.

Skin and sub-cutaneous tissue disorders
Common: Skin rashes, pruritus (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, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis.

Renal and urinary disorders
Rare: Increases in blood urea and creatinine; renal impairment, usually during intravenous therapy, which is usually reversible and responds to hydration and/or dosage reduction but may progress to acute renal failure in patients with predisposing factors.
Very rare: Acute renal failure, renal pain
Renal pain may be associated with renal failure.

General disorders
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 20 g aciclovir on a single occasion, usually without toxic effects. Accidental, repeated overdoses of oral aciclovir over several days have been associated with gastrointestinal effects (*eg* nausea and vomiting) and neurological effects (*eg* headache and confusion).

Overdosage of i.v. 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.

Treatment
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 - ATC code: J05A B

Aciclovir is an antiviral agent which is highly active *in vitro* against herpes simplex virus (HSV) types I and II and varicella zoster virus. Toxicity to mammalian host cells is low.

Aciclovir is phosphorylated after entry into herpes infected cells to the active compound aciclovir triphosphate. The first step in this process is dependant on the presence of the HSV-coded thymidine kinase. Aciclovir triphosphate acts as an

inhibitor of, and substrate for, the herpes-specified DNA polymerase, preventing further viral DNA synthesis without affecting the normal cellular processes.

Herpes simplex virus develops resistance to aciclovir by selection of mutants deficient in thymidine kinase which are usually of diminished virulence with reduced infectivity and latency. Resistance is rare in immunocompetent patients on short courses of oral therapy but it is more prevalent in immunocompromised patients who have often received prolonged courses of treatment. Herpes zoster resistance develops by a similar mechanism and has been reported in immunocompromised patients undergoing prolonged therapy with aciclovir.

5.2 Pharmacokinetic properties

Absorption
Aciclovir is slowly and incompletely absorbed from the gastrointestinal tract. The peak plasma concentration occurs about 2 hours following ingestion.

Distribution
There is a wide distribution to various tissues, including the CSF where concentrations achieved are about 50% of those achieved in plasma. Protein binding is reported to range from 9-33%. Aciclovir crosses the placenta and is excreted in breast milk in concentrations approximately 3 times higher than those in maternal serum.

Metabolism and Elimination
Renal excretion is the major route of elimination by both glomerular filtration and tubular secretion. The terminal or beta-phase half-life is reported to be about 2-3 hours for adults without renal impairment. As aciclovir persists in the plasma of patients with renal insufficiency, in chronic renal failure this value is increased and may be up to 19.5 hours in anuric patients. As renal function decreases, a greater percentage of the drug is eliminated by metabolic conversion to carboxymethoxymethyl guanine. During haemodialysis the half-life is reduced to 5.7 hours, with 60% of a dose of aciclovir being removed in 6 hours. Faecal excretion may account for about 2% of a dose.

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 Cssmax was found to be 61.2 microMol (13.8 micrograms/ml) and Cssmin to be 10.1 microMol (2.3 micrograms/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).

5.3 Pre-clinical Safety Data

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.
Two generation studies in mice do not reveal any effect of aciclovir on fertility.

The results of a wide range of mutagenicity test *in vitro* and *in vivo* indicate that aciclovir does not pose a genetic risk to man. Aciclovir was not found to be carcinogenic in long term studies in the rat and the mouse. 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. Aciclovir has been shown to have no definite effect upon sperm count, morphology or motility in man.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Also contains**:** colloidal anhydrous silica, magnesium stearate, polyvidone, sodium starch glycollate, E460.

6.2. Incompatibilities

None known.

6.3. Shelf-Life

Shelf-life
Three years from the date of manufacture.

Shelf-life after dilution/reconstitution
Not applicable.

Shelf-life after first opening
Not applicable.

6.4. Special Precautions for Storage

Store below 25°C in a dry place.

6.5. Nature and Content of Container

The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene containers with polyfoam wad or polyethylene

ullage filler and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass containers with screw caps and polyfoam wad or cotton wool.

The product may also be supplied in blister packs in cartons:
a) Carton**:** Printed carton manufactured from white folding box board.
b) Blister pack**:** (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil with 5-7g/M^2 PVC and PVdC compatible heat seal lacquer on the reverse side.

The product may be contained in blister packs which enhances security of the pack increasing resistance to deliberate contamination, pilfering, etc.

Pack sizes: 25s , 28s ,30s ,35s ,56s ,60s ,100s.

Product may also be supplied in bulk packs, for reassembly purposes only, in polybags contained in tins, skillets or polybuckets filled with suitable cushioning material. Bulk packs are included for temporary storage of the finished product before final packaging into the proposed marketing containers.

Maximum size of bulk packs: 50,000.

6.6 Special precautions for disposal and other handling

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS, UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 00142/0403

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 February 1997

10 DATE OF REVISION OF THE TEXT

28/08/2018