Zovirax® Tablets

Aciclovir

1. Trade Name of the Medicinal Product

Zovirax 200, 400 and 800 mg tablets

2. Qualitative and Quantitative Composition

Aciclovir 200 mg, 400 mg and 800 mg.

For a complete list of excipients see section 6.1

3. Pharmaceutical Form

Tablets

4. Clinical particulars

4.1 Therapeutic Indications

Tablets 200 mg: Treatment of severe herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital herpes (except neonatal HSV and severe HSV infection in children with reduced immune response). Suppressive treatment of genital herpes in patients with frequently recurring infection. Prophylaxis against herpes simplex infections in immunocompromised patients in vulnerable periods.

Tablets 400 mg: Suppressive treatment of genital herpes in patients with frequently recurring infection. Prophylaxis against herpes simplex infections in immunocompromised patients in vulnerable periods.

Tablets 800 mg: Treatment of acute cases of herpes zoster infections where a severe progression of disease can be expected.

4.2 Posology and Method of Administration

Herpes simplex infections:

Adults and children > 2 years: 1 tablet of 200 mg every 4 hours during the awaken part of the day, i.e. 5 times daily. Dosing should begin as early as possible after the start of infection. In the treatment of recurrent infections, treatment should be started as early as in the prodromal period or when lesions first appear. The treatment should last for 5-10 days depending on the severity of the disease.

Suppressive treatment of genital herpes simplex:

Adults: 800 mg daily divided on 2 or 4 dosages. Lower dosages may sometimes be sufficient. Continuous treatment should not be longer than 3-6 months. The treatment should be initiated and supervised by a doctor with experience from diagnosing and treatment of genital herpes simplex.

Some immunecompetent patients may experience break-through infections on total daily doses of 800 mg aciclovir.

No specific data are available on the suppression of herpes simplex infections in immunecompetent children.

Prophylaxis of herpes simplex infections in immunocompromised patients:

Adults and children > 2 years: 1 tablet of 200 mg should be taken four times daily at approximately six-hourly intervals. In severely immunocompromised patients or in patients with impaired absorption from the gut, the dose can be doubled to 400 mg. Time of prophylactic treatment depends on the time the patient is exposed to risk.

Herpes zoster infections:

Adults: 1 tablet of 800 mg should be taken every 4 hours during the awaken part of the day, i.e. 5 times daily. Treatment should continue for seven days. Dosing should begin as early as possible after the start of an infection.

Elderly

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

Renal impairment

Caution is advised when administering aciclovir to patients with impaired renal function. Adequate hydration should be maintained.

In treatment of herpes simplex in patients with severe renal impairment (creatinine clearance less than 10 mL/min) adjust dose to 200 mg acyclovir 2 times daily with 12 hours interval.

In the treatment of herpes zoster infections, it is recommended to adjust the dosage to 800 mg twice daily, at approximately twelve-hourly intervals, for patients with severe renal impairment (creatinine clearance less than 10 mL/min) and to 800 mg three times daily, at intervals of approximately eight hours, for patients with moderate renal impairment (creatinine clearance in the range 10 to 25 mL/min).

In the prophylactic treatment 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 IV infusion. However, for patients with severe renal impairment (creatinine clearance less than 10 mL/min) an adjustment of dosage to 200 mg twice daily at approximately twelve-hourly intervals is recommended.

4.3 Contraindications

Zovirax tablets are contra-indicated in patients known to be hypersensitive to aciclovir, valaciclovir or the other excipients listed in section 6.1.

4.4 Special Warnings and Precautions for Use

Aciclovir is eliminated by renal clearance. Sufficient hydration should be maintained to avoid renal damage that can lead to renal impairment in patients on high dose of oral acyclovir. The risk of renal impairment increases with concomitant use of other nephrotoxic drugs.

Renal impairment involves a risk of accumulation of acyclovir and thus increased risk of reversible neurological and psychiatric side effects. These side effects are generally reversible on discontinuation of treatment (see section 4.8). Both elderly patients and patients with renal impairment should be closely monitored for evidence of these effects and dose reduction should be considered (see section 4.2). Adequate hydration of these patients should be maintained.

Prolonged or repeated treatment with acyclovir in patients with severely impaired immune systems can result in selection of virus strains with reduced sensitivity for acyclovir which may not respond optimally to treatment (see section 5.1).

Tablets of 200 mg acyclovir contains lactose. Patients with rare hereditary problems with galactose intolerance, a special form of hereditary lactase deficiency (Lapp lactase deficiency) or glucose-galactose malabsorption should not use the 200 mg strength of this medicine.

4.5 Interactions with other Medicaments and other forms of Interaction

Theofylline

Experimental studies show that aciclovir coadministrated with theofylline, increases the AUC of theofylline by 50 % when given orally. It is recommended to monitor the concentration of theofylline in plasma when coadministrated with aciclovir.

Cimetidine

Cimetidine reduces the renal clearance of aciclovir and increases the AUC with ca. 20%.

Probenecid

Probenecid reduces the renal clearance of aciclovir and increases the AUC with 40%.

Lithium

There is one reported case of lithium coadministrated with intravenous aciclovir given in high doses, and the high dose of aciclovir probably caused very high serum concentrations of lithium. If this is the case, it is a very severe interaction and a close monitoring of the serum lithium concentrations is recommended.

Aciclovir is eliminated primarily unchanged in the urine among others by tubular secretion. Any drugs administered concurrently that compete with this mechanism may increase aciclovir plasma concentrations. Increases in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolate mofetil (immunosuppressant agent used in transplant patients) have been shown when the drugs are coadministrated.

Dose adjustments are not necessary because acyclovir has a wide therapeutic window.

4.6 Fertility, pregnancy and lactation

Pregnancy: A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of Zovirax. This documentation has shown no increase in birth defects among children of mothers who had received acyclovir, compared with the rest of the population. There is no special or general feature of deformities that may suggest a common cause. Systemic administration of aciclovir in conventional studies did not produce embryotoxic or teratogenic effects in rats, rabbits or mice.

In studies performed with unconventional methods in rats, foetal abnormalities were observed, but only following such high doses that maternal toxicity was produced (see section 5.3). The clinical relevance of these findings is uncertain. Use during pregnancy should be avoided unless the benefit outweighs the potential risk.

Breast feeding: Aciclovir passes on to human breast milk from 0.6 – 4.1 times the plasma concentration. It is calculated that a treatment of 200 mg 5 times daily will expose the breast feeding baby with a daily dose of ca. 0.3 mg/kg/day. The medicinal product should not be used during breast feeding.

Fertility: There is no information available regarding the impact of aciclovir on human female fertility. In a study including 20 male patients with normal sperm production, oral doses of aciclovir up to 1 g per day in six months had no clinical significant effect on the number of sperms, sperm motility or morphology. Studies in mice has shown no effect on fertility after oral dosage, however it has been reported testicular atrophy in rats and aspermatogenesis in dogs at high doses (se section 5.3).

4.7 Effects on Ability to Drive and Use Machines

Clinical status of the patient and the adverse event profile of aciclovir should be borne in mind when considering the patient´s ability to drive or operate machinery. 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.

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4.8 Undesirable Effects

The most common adverse event is rash, which occur in about 3% of the patients treated.

The adverse events are listed after organ class and frequency. The following convention has been used for the classification of undesirable effects in terms of frequency: common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000) included isolated reports. Common and uncommon adverse events are generally established from clinical trials. Very rare adverse events are generally established from spontaneous reports post marketing

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

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 disorder:
Common: Pruritus, rashes (including photosensitivity)
Uncommon: Urticaria, accelerated diffuse hair loss (accelerated diffuse hair loss is associated with various diseases and drugs and therefore a connection to acyclovir treatment is uncertain).
Rare: Angioedema

Renal and urinary disorders:
Rare: Increases in serum urea and serum creatinine
Very rare: Acute renal failure, pain in the kidneys

Pain in the kidneys can be associated with renal failure.

General disorders and administration site conditions;
Common: Fatigue, fever

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 (such as nausea and vomiting) and neurological effects (headache and confusion). Overdosage of intravenous aciclovir has resulted in elevations of serum creatinine, serum urea and subsequent renal failure. Neurological effects including confusion, hallucinations, agitation, seizures and coma have been described in association with intravenous overdosage. 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: Antivirals, nucleoside analogue. *ATC-code*: J05A B01

Mechanism of action: Aciclovir is in herpes infected cells phosphorylated to the active metabolite aciclovir triphosphate in the presence of herpes simplex coded thymidine kinase. Aciclovir triphosphate interferes with the viral DNA-polymerase and DNA replication. Incorporation of aciclovir triphosphate in the viral DNA results in chain termination

Pharmacodynamic effects: Aciclovir has an inhibitory activity *in vitro* and *in vivo* towards herpes simplex virus (HSV) type 1 and 2, varicella zoster virus (VZV), Epstein Barr virus (EBV), and cytomegalo virus (CMV). Aciclovirs activity against HSV1, HSV2, VZV, EBV and CMV is very selective. Toxicity towards mammal cells is low as influence on normal cellular processes in non-infected cells is insignificant.

Results from clinical trials show that early treatment of herpes zoster with aciclovir has a positive affect on pain and can reduce the incidence of postherpetic neuralgia.

5.2 Pharmacokinetic Properties

Absorption: Incomplete absorption from the gastro-intestinal tractus. Up to 20% is absorbed rapidly. Maximum absorption is achieved after 60 – 90 minutes. The amount of absorbed drug does not increase proportionally with increasing dose.

The plasma half-life of aciclovir after administration of intravenous aciclovir is 2.9 hours. Most of the drug is excreted unchanged via the kidneys. Renal clearance of aciclovir is substantially greater than creatinine clearance, indicating tubular secretion in addition to glomerular filtration.

9-carboxymethoxy-methylguanine is the only significant metabolite of aciclovir and accounts for approximately 10 to 15 % of the administered dose.

Cerebrospinal fluid levels are approximately 50% of corresponding plasma levels. Plasma protein binding is relatively low (9 to 33 %) and drug interactions involving displacement is not anticipated.

Special populations: 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. In elderly the clearance is reduced, which is associated with reduces creatinine clearance even though the half-life is hardly altered.

In neonates (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 micromolar (13.8 micrograms/mL) and the Cssmin to be 10.1 micromolar (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 micrograms/mL) and Cmin of 14.1 micromolar (3.2 micrograms/mL).

5.3 Preclinical Safety Data

Preclinical data indicate no particular risk for humans based on conventional studies of genotoxicity and carcinogenicity.

No malformations were seen in conventional reproduction studies. In a special study, head and tail malformations were seen after subcutaneous administration of high doses on day 11 and 21 of pregnancy in rats. Similar malformations are seen in *in vitro* systems where 9.5 day old rat foetus was cultivated for 48 hours in high doses of aciclovir. This indicates that aciclovir directly can influence the development of the foetus.

There have been reports of testicular atrophy in rats and aspermatogenesis in dogs with doses on 80-320 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets 200 mg: Microcrystalline cellulose, lactose monohydrate, povidone, sodium starch glycolate, magnesium stearate.

Tablets 400 mg: Microcrystalline cellulose, povidone, sodium starch glycolate, magnesium stearate.

Tablets 800 mg: Microcrystalline cellulose, povidone, sodium starch glycolate, magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The expiry date is indicated on the packaging.

6.4 Special Precautions for Storage

Store below 25°C. Keep dry.

6.5 Containers (type and content)

200 mg: Blister packs with 25 tablets
400 mg: Blister packs with 25 tablets
800 mg: Blister packs with 35 tablets

6.6 Instruction for Use/Handling

Not applicable

7. MARKETING AUTHORISATION HOLDER

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8. Manufactured by:

Glaxo Wellcome. S.A*, Aranda de Duero, Spain

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Date of text revision: 14.07.2014

THIS IS A MEDICAMENT

Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you. Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of the reach of children.

Council of Arab Health Ministers, Union of Arab Pharmacists.

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