ÆSCULAPIUS
FARMACEUTICI

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

EFRIVIRAL 400 mg/5 ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EFRIVIRAL 400 mg/5 ml oral suspension

5 ml of suspension contain:

- Aciclovir 400,0 mg

For the complete list of excipients, see 6.1

3. PHARMACEUTICAL FORM

Suspension for oral use

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

EFRIVIRAL is indicated:

- for the treatment of Herpes simplex infections of the skin and mucous membranes, including primary and recurrent Herpes genitalis;
- for the suppression of Herpes simplex recurrences in immunocompetent patients;
- for the prophylaxis of Herpes simplex infections in immunocompromised patients;
- for the treatment of Varicella and Herpes zoster.

4.2. Posology and method of administration

A measuring spoon is attached to the packaging of EFRIVIRAL - Suspension.

Adults

Treatment of Herpes simplex infections

2.5 ml of suspension 5 times a day at intervals of about 4 hours, omitting the night dose. The treatment should be continued for 5 days but prolongation may be necessary in cases of serious primary infections.

In severely immunocompromised patients (eg after a bone marrow transplant) or in patients with decreased intestinal absorption, the dosage may be doubled to 5 ml of the suspension or, alternatively, the possibility of administering Acyclovir by intravenous route.

The therapy should be started as soon as possible and, in case of recurrent infections, preferably during the prodromal phase or when the first lesions appear.

Suppressive therapy of recurrence of Herpes simplex infections in immunocompetent patients

2.5 ml of suspension 4 times a day at 6 hour intervals. Many patients can be successfully treated by administering 5 ml of the suspension 2 times a day at 12-hour intervals.

Dosages of 2.5 ml of suspension 3 times a day at 8 hour intervals or 2 times a day at 12 hour intervals may also be effective. In some patients, recurrence of the infection may occur with a total daily dose of 10 ml of EFRIVIRAL.

Therapy should be interrupted periodically at intervals of 6 or 12 months, in order to observe any changes in the natural history of the disease.

Prophylaxis of Herpes simplex infections in immunocompromised patients

2.5 ml of suspension 4 times a day at 6 hour intervals. In severely immunocompromised patients (eg after a bone marrow transplant) or in patients with decreased intestinal absorption, the dosage may be doubled to 5 ml of the suspension or, alternatively, the possibility of intravenous acyclovir administration may be assessed.
The duration of the prophylaxis must be considered in relation to that of the risk period.

Treatment of Herpes zoster and Varicella

10 ml of suspension 5 times a day at intervals of about 4 hours, omitting the night dose. Treatment must be continued for 7 days.
In severely immunocompromised patients (eg after a bone marrow transplant) or in patients with decreased intestinal absorption, the possibility of intravenous acyclovir administration may be assessed.
The therapy should be started immediately after the onset of the infection, indeed the treatment obtains better results if established when the first lesions appear.

Children

For the treatment of Herpes simplex infections and for their prophylaxis in immunocompromised children older than 2 years the dosage is similar to that of adults.
Under two years the dosage is reduced by half.
For the treatment of Varicella, in children over 6 years age the dosage is 10 ml of suspension 4 times a day; in those aged 2 to 6 years the dosage is 5 ml of suspension 4 times a day; in those younger than 2 years of age the recommended dosage is 2.5 ml suspension 4 times a day. The administration of 20 mg / kg of body weight (not exceeding 800 mg) 4 times a day, allows a more precise dose adjustment. Treatment must be continued for 5 days.
No specific data are available regarding the suppression of Herpes simplex infections or the treatment of Herpes zoster in immunocompetent children.
For the treatment of Herpes Zoster in immunocompromised children the administration of intravenous Acyclovir should be considered.

Elderly patients

In the elderly, total clearance decreases with decreasing creatinine clearance associated with age.
Adequate hydration should be maintained in patients who take high doses of oral EFRIVIRAL.
Particular attention should be given to assessing the possibility of dose reduction in elderly patients with impaired renal function.

Kidney failure

In the treatment of Herpes simplex infections, in patients with reduced renal function the recommended oral posology should not cause Aciclovir to accumulate above the levels considered acceptable for intravenous administration. However, in patients with severe renal impairment (creatinine clearance less than 10 ml / min), it is recommended to adjust the dose to 2.5 ml suspension, administered 2 times a day at intervals of approximately 12 hours.
In the treatment of Varicella and Herpes zoster it is recommended to change the dosage to 10 ml of suspension administered 2 times a day at intervals of approximately 12 hours, in patients with severe renal insufficiency (creatinine clearance below 10 ml / min) and 10 ml suspension 3 times a day, administered at intervals of approximately 8 hours in patients with moderate renal impairment (creatinine clearance between 10 and 25 ml / min).

4.3. Contraindications

The oral formulations of EFRIVIRAL are contraindicated in patients with known hypersensitivity to Acyclovir.

4.4. Special warnings and precautions for use

Shake the suspension before use.

4.5. Interaction with other medicinal products and other forms of interaction

Probenecid increases the mean half-life and area under the Acyclovir plasma concentration curve. Other drugs that interfere with renal function may change the pharmacokinetics of Acyclovir. However, in clinical practice, no other interactions with Acyclovir have been observed.

4.6. Pregnancy and lactation

As the clinical data on the administration during pregnancy are limited, during this period the drug should be administered only in cases of absolute necessity under the direct medical supervision.

Systemic administration of Acyclovir to rabbit, mouse or rat did not produce embryotoxic or teratogenic effects.

In an experimental trial not included in the classic teratogenesis tests, abnormalities of the fetus were observed after subcutaneous doses of Acyclovir so high as to produce toxic effects on the mother. The clinical relevance of these results is uncertain. Following the oral administration of 200 mg of EFRIVIRAL, 4 times / day, Acyclovir was observed in breast milk at concentrations of 0.6-4.1 times the corresponding plasma levels. These levels would potentially expose the infants to acyclovir doses up to 0.3 mg / kg / day. Therefore, the use of EFRIVIRAL during lactation should be avoided.

Fertility

Reversible toxic effects on spermatogenesis have been reported in rats and dogs only at doses significantly higher than the therapeutic ones. Two-generation studies in the mouse did not show effects of Acyclovir, administered orally, on fertility. There are no data on fertility in women.

EFRIVIRAL has not been shown to affect the number, morphology and motility of sperm in humans.

4.7. Effects on ability to drive and use machines

EFRIVIRAL does not affect the ability to drive and use machines.

4.8. Undesirable effects

In some patients, after administration of oral EFRIVIRAL skin rashes appeared, and promptly disappeared with discontinuation of therapy.

Symptoms such as nausea, vomiting, diarrhea and abdominal pain are reported on the gastro-enteric apparatus.

Occasionally, reversible neurological reactions have been observed, in particular dizziness, confusional state, hallucinations and drowsiness, generally in patients with renal insufficiency or other predisposing factors.

Occasionally, a more rapid and widespread hair loss has been observed. Since the latter has been associated with a wide range of diseases and with the intake of various drugs, the relationship with Aciclovir is uncertain.
Rarely, a moderate and transient increase in blood values of bilirubin and liver enzymes was observed after oral administration of EFRIVIRAL. Moderate increases in urea and creatinine have also been reported, slight decreases in haematological indices, headache and asthenia.

4.9. Overdose

Acyclovir is only partially absorbed at intestinal level. It is therefore unlikely that there will be serious toxic effects even in the event that 5 g of Acyclovir are ingested in one time. No data are available on the consequences of ingesting larger doses.
Single intravenous doses up to 80 mg / kg were accidentally administered without side effects.
Treatment
Patients who have ingested Acyclovir doses above 5 g should be closely monitored.
Acyclovir is dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: EFRIVIRAL is an antiviral with activity against Herpes Simplex Virus and Varicella-Zoster Virus. ATC code: J05AB01
Aciclovir is a synthetic purine nucleoside analog with inhibitory activity, in vitro and in vivo, against human herpetic viruses, including Herpes Simplex Virus (HSV) type 1 and 2 and the Virus Varicella Zoster (VZV). In cell cultures, Acyclovir showed the highest antiviral activity against HSV-1, followed by HSV-2. The inhibitory activity of Acyclovir against HSV-1 and HSV-2 is highly selective.
The enzyme Thymidine kinase of normal, uninfected cells does not effectively use Acyclovir as a substrate; therefore the toxicity for the host cells is poor; on the contrary, the thymidine viral kinase converts Aciclovir into acyclovir monophosphate, a nucleoside analogue, which is further converted to di-phosphate and tri-phosphate by cellular enzymes. Aciclovir tri-phosphate interferes with viral DNA polymerase and inhibits viral DNA replication; its incorporation into the viral DNA causes the interruption of the catenary lengthening process of the latter. Prolonged or repeated cycles of Acyclovir in severely immunocompromised patients may be associated with the selection of viral strains with reduced sensitivity, which may not respond to continuous treatment with Acyclovir. Most of the isolated viral strains, with reduced sensitivity, showed a relative deficit of viral Thymidine kinase; however, strains with thymidine kinase or altered viral DNA polymerase were also observed. Even the in vitro exposure to aciclovir of isolated HSV strains can be associated with the appearance of less sensitive strains. The relationship between the in vitro determined sensitivity of isolated HSV strains and the clinical response to Aciclovir therapy is not clarified.

5.2. Pharmacokinetic properties

Acyclovir is only partially absorbed at the intestinal level. The peak of the plasma concentrations at "steady state" (Cssmax), after doses of 200 mg every 4 hours is 3.1 µMol (0.7 µg / ml) and the minimum concentration (Cssmin) is 1.8 µMol (0.4 µg / ml). After doses of 400 mg and 800 mg every 4 hours the Cssmax is, respectively, 5.3 µMol (1.2 µg / ml) and 8 µMol (1.8 µg / ml) and the Cssmin is, respectively, of 2.7 µMol (0.6 µg / ml) and 4 µMol (0.9 µg / ml). From the studies with Acyclovir given intravenously, the half-life of the drug is

about 2.9 hours. Most of the drug is excreted unchanged by the renal route. The renal clearance of Acyclovir is considerably greater than that of creatinine, which indicates that tubal secretion contributes to the glomerular filtration as well as to the renal elimination of the drug. The only major metabolite is 9-carboxymethoxymethyl-guanine corresponding to about 10-15% of the urinary excreted dose. In the elderly, total clearance decreases with increasing age together with creatinine clearance, however there are slight changes in the terminal plasma half-life. In patients with chronic renal failure, the mean half-life is 19.5 hours whereas during hemodialysis the average half-life of Acyclovir is 5.7 hours and the levels are reduced by about 60% on average. The levels of the drug in the liquor correspond to about 50% of the plasma ones. Plasma protein binding is relatively low (9 to 33%) and no drug interactions due to shifts from the binding site are expected.

5.3. Preclinical safety data

The results of a large number of in vitro and in vivo mutagenesis tests indicate that Aciclovir does not involve genetic risks for humans.
In long-term studies in rats and mice, Acyclovir was not carcinogenic.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

EFRIVIRAL 400 mg/5 ml oral suspension:
Sorbitol 70% (not crystallized), glycerol, dispersible cellulose, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, orange aroma, purified wate

- **Additional notes**

EFRIVIRAL 400 mg/5 ml oral suspension

- The medicinal product contains 31.5 g of sorbitol. When taken according to the recommended dosage, each dose provides up to 3.15 g of sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.
- May cause even delayed allergic reactions

6.2. Incompatibilities

Incompatibilities with other medicines are unknown.

6.3. Shelf life

400 mg/5ml oral suspension: 3 years.

6.4. Special precautions for storage

400 mg/5ml oral suspension: store at a temperature not higher than 30° C

6.5. Nature and contents of container

EFRIVIRAL 400 mg/5 ml oral suspension, 100 ml glass bottle with measuring spoon.

6.6. Special precautions for disposal and other handling

Opening and closing the bottle: to open, press and simultaneously turn. To close, tighten thoroughly.

7. MARKETING AUTHORISATION HOLDER

AESCULAPIUS FARMACEUTICI S.r.l. - Via Cefalonia, 70 - 25124 BRESCIA

8. MARKETING AUTHORISATION NUMBER(S

EFRIVIRAL 400 mg/5 ml oral suspension: MA n°: 027534116

9. DATE OF FIRST AUTHORISATION /RENEWAL OF THE AUTHORISATION

Renewal date: June 2010

10. DATE OF REVISION OF THE TEXT

March 2017