Pharmaceutical Laboratories S.A.

SUMMARY OF PRODUCT CHARACTERISTICS

(S P C)

UNIPLEX® Cream 5% w/w

1. **PRODUCT NAME**

   UNIPLEX® Cream 5% w/w.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION (in active substance)**

   One gram of cream contains 50mg of aciclovir.

3. **PHARMACEUTICAL FORM**

   Cream for external use 5% w/w.

4. **CLINICAL DATA**

4.1. Therapeutical indications

UNIPLEX® cream is indicated:

- For the treatment of Herpes Simplex virus infections of the skin including initial and recurrent genital herpes and herpes labialis in immunocompetent patients with an intact immune system.

4.2. **Dosage and administration:**

- UNIPLEX® cream should be applied to the affected areas of the skin five times daily at approximately four hourly intervals, omitting the night time application.
- UNIPLEX® cream should be applied to the lesions or impending lesions as soon as possible, preferably during the early stages of infection.
- Treatment should be continued for 5 days. If healing has not occurred, then treatment may be continued for up to an additional 5 days.

4.3. **Contraindications**

UNIPLEX® cream is contraindicated in patients known to be hypersensitive to aciclovir, valaciclovir, propylene glycol or any of the excipients of the cream.

4.4. **Warnings and Precautions during Administration**

- The cream is not recommended for application to mucous membranes such as in the mouth, eye or vagina, as it may be irritant. Particular care should be taken to avoid accidental introduction into the eye.
- In severely immunocompromised patients oral aciclovir dosing should be considered. Such patients should be encouraged to consult a physician concerning the treatment of any infection.
- Regarding the potential risk of transmitting the virus to a sexual partner, it is important to advise patients with genital herpes to abstain from sexual activity when sores or other symptoms of herpes are present.
- The severity of recurrent infections varies depending on the patient's immune status, the frequency and duration of

episodes, the extent of the affected area of skin, and whether or not there are systemic reactions. These factors must be taken into account during treatment. Treatment may consist of counseling and symptomatic support or treatment of the cause of the disease. The physical, emotional and psycho-social problems caused by herpes infections vary depending on the patient. Therefore, the choice of treatment depends on the condition of each patient.

4.5. Drug interactions

The interactions of aciclovir with other topical medications are not known.

4.6. Pregnancy and lactation

Use during pregnancy:

There are insufficient data available on the use of aciclovir cream during pregnancy in humans to assess possible adverse effects. In animal tests, the drug has been shown to be harmful. 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.

Records of drug use in pregnant women after the release of aciclovir provided data on the exposure of pregnant women to all forms of aciclovir. These data do not show an increase in the number of defective births among patients who received aciclovir compared to the general population, and any defective births are not

characterized by any uniqueness or specific form indicating a common cause.

Because these data are currently insufficient, it should only be administered during pregnancy if the expected benefit of treatment for the mother outweighs the potential risks to the fetus.

Use during Lactation:

Limited data show that aciclovir can be detected in breast milk after systemic administration. However, from pharmacokinetic data it appears that it was not possible to determine aciclovir levels after topical aciclovir treatment.

Should not be administered during lactation unless the expected benefit to the mother outweighs the potential risk to the infant.

4.7. Effect on the ability to drive or use machinery

There is no information on the effect of aciclovir cream on the ability to drive and use machines. However, an adverse effect on these activities is not likely.

4.8. Adverse reactions

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.

Skin and subcutaneous tissue disorders:

Uncommon

• Transient burning or stinging following application of ACICLOVIR Cream.

• Mild drying or flaking of the skin.

• Itching.

Rare

• Erythema.

• Contact dermatitis following application. Where sensitivity tests have been conducted, the reactive substances have most often been shown to be components of the cream rather than aciclovir.

Immune system disorders:

Very rare

• Immediate hypersensitivity reactions including angioedema and urticaria.

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 directly to the National Organization for Medicines, Mesogeion 284, GR-15562 Holargos, Athens, Tel: + 30 21 32040380/337, Fax: + 30 21 06549585, Website: http://www.eof.gr

4.9. Overdose

Overdose after topical application of aciclovir is unlikely to occur due to limited transdermal absorption. No adverse reactions were reported after oral ingestion of a 10 g tube of Aciclovir cream (containing 500 mg of aciclovir).

Oral doses of one 800 mg tablet five times a day for seven days are indicated for the treatment of herpes zoster.

Single intravenous doses up to 80 mg/kg of body weight were negligently administered without side effects.

Aciclovir is dialysable by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamics

ATC code: D06BB03

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 dependent 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 normal cellular processes.

Virology

In vitro exposure of herpes simplex viruses to aciclovir may lead to reduced viral susceptibility. These viruses are usually deficient in thymidine kinase. This enzyme is responsible for the activation of aciclovir. However, animal studies have shown that these strains are less viral.

Similar virus strains have been observed from time to time during controlled and open studies in a few, widely and severely immunocompromised patients such as bone marrow transplant recipients or in patients with congenital, severe combined immunodeficiency.

The appearance of infections from these viruses did not worsen the clinical condition, while in some cases the virus disappeared again spontaneously.

In the treatment of such severely immunocompromised patients, the possible occurrence of suppressed, susceptible viruses should be considered. However, long clinical experience should provide more

evidence for the association between in vitro virus susceptibility and clinical response to aciclovir therapy.

5.2. Pharmacokinetic properties

Aciclovir penetrates into the skin. The intracutaneous concentration levels are higher than the minimal inhibitory concentration in tissue at steady state.

After topical application of aciclovir, no aciclovir plasma concentrations could be determined.

As the aciclovir plasma concentrations following topical application are below the limit of detection, no pharmacokinetic studies are available on topical aciclovir. Therefore, the following data is based on the data after oral or intravenous administration

The most important metabolite is 9-carboxymethoxymethylguanine and accounts for 10 to 15% of the amount excreted in the urine. Plasma aciclovir is mainly excreted unchanged by the kidneys (by glomerular filtration as well as by tubular filtration).

In patients with normal renal function, the plasma half-life is approximately 3 hours. Protein binding is relatively low (9-33%). Therefore, no interactions related to the displacement from the binding sites are expected.

5.3. Pre-clinical data relative to safety

A large number of in vitro tests show that, at very high concentrations, chromosomal damage can occur. During in vivo studies, no chromosomal damage was observed.

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. Two generation studies in mice did not reveal any effect of orally administered aciclovir on fertility.

There is no information on the effect of aciclovir cream on female fertility. In patients with normal sperm count, chronic oral aciclovir administration has not been shown to have any effect on the number, morphology or motility of human sperm.

6. PHARMACEUTICAL DATA

6.1. List of excipients

Poloxamer 407, Cetostearyl alcohol, Paraffin soft, Sodium lauryl sulphate, Paraffin liquid, Propylene glycol, Water purified.

6.2. Incompatibilities

UNIPLEX® cream is not intended to be mixed with other medicinal products.

6.3. Shelf life

3 (three) years provided that medicinal product is kept in its original packaging according to the storage conditions.

6.4. Special precautions for storage

It is stored in its original packaging at temperature ≤ 25°C.

6.5. **Nature and contents of container**

Carton box that contains a 10 g aluminium tube of cream for external use and a Patient Information Leaflet.

6.6. **Special precautions for disposal and other handling**

No special requirements.

6.7. **Marketing Authorization Holder**

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7. **MARKETING AUTHORIZATION NUMBER**

8570/06.02.2007.

9. **ISSUE DATE OF THE FIRST MARKETING AUTHORIZATION**

05.12.1990

10. **DATE OF LAST REVISION**

16.10.2008