SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

CICLOVIRAL 50 mg/g Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of cream contains 50 mg of aciclovir (5% of aciclovir, w/w).

Excipients:
Each gram of cream contains 67,5 mg of cetostearyl alcohol
Each gram of cream contains 400 mg of propylene glycol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

CICLOVIRAL cream is indicated in the treatment of labial herpes resulting from infection by the *Herpes simplex* virus type 1.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Method of administration: cutaneous use.

Adults and children aged 12 years or older:

CICLOVIRAL cream should be applied five times daily, at approximately 4-hour intervals, omitting the nighttime period. CICLOVIRAL cream should be applied to lesions or imminent lesions, as early as possible after the infection has started. In recurrent episodes, it is particularly important to start treatment in the early stages (prodrome or erythema), or when lesions appear.

Studies in patients with labial herpes have demonstrated that treatment is still effective when started after the lesions have appeared (papular and vesicular stages).

Treatment should be continued for 4 days. If healing has not occurred after 4 days, treatment may be continued for up to 10 days. If lesions are still present after 10 days, users should be advised to consult a doctor.

Children aged 2 to 12 years:

The CICLOVIRAL cream doses used in adults are recommended, under medical surveillance, for the following reasons: the stratum corneum is comparable in children and adults; no safety concerns are raised regarding the potential limit of systemic absorption of aciclovir from CICLOVIRAL cream; and there is no evidence to suggest the existence of any differences between age groups regarding the natural history of recurrent episodes of labial herpes.

Users should wash their hands before and after applying the cream. Users should also avoid touching or rubbing the lesions, or even touching the lesions with a towel, to avoid aggravating or transferring the infection.

4.3. CONTRAINDICATIONS

Hypersensitivity to aciclovir or to any of the excipients.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

CICLOVIRAL cream should not be applied to mucous membranes, namely in the mouth, eyes or vagina, since it may irritate these areas.

Patients should take precautions in order to avoid transmitting the virus, particularly when active lesions are present.

CICLOVIRAL cream contains propylene glycol. It may cause skin irritation.

CICLOVIRAL cream contains cetostearyl alcohol. It may cause local skin reactions (e.g., contact dermatitis).

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No interactions with other medicinal products have been observed, with the exception of probenecid, which increases the half-life of aciclovir and the area under the plasma concentration curve, in case of systemic administration of aciclovir.

4.6. PREGNANCY AND LACTATION

Pregnancy

No studies have been conducted concerning the use of CICLOVIRAL cream during pregnancy; however, records of use of aciclovir formulations during pregnancy have not revealed any increase in the number of malformations, compared to the general population. Additionally, the observed malformations showed no unique characteristics or consistent patterns suggestive of a common cause.

Studies in animals have not revealed any teratogenic effects for CICLOVIRAL cream.

Malformations were observed in a non-standard test performed in rats. However, these findings were not observed in three other tests performed in rats, mice and rabbits (see section 5.3).

Although systemic exposure to aciclovir following cutaneous use of CICLOVIRAL cream is very low, CICLOVIRAL use by pregnant women should only be considered when the potential benefits outweigh possible unknown risks.

Lactation

No studies have been conducted concerning the use of CICLOVIRAL cream during lactation; however, limited data in humans reveal that aciclovir is excreted in human milk following systemic administration. Although the dose received by a nursing infant following maternal use of CICLOVIRAL cream would be negligible, CICLOVIRAL use during lactation should only be considered when the potential benefits outweigh possible unknown risks.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Not relevant.

4.8. UNDESIRABLE EFFECTS

A transient burning sensation may occur sporadically, following the application of CICLOVIRAL cream. Some cases of mild drying and flaking of the skin have been reported following cutaneous application of aciclovir. Erythema, pruritus and contact dermatitis may occur in rare cases.

4.9. OVERDOSE

No adverse events would be expected if the entire contents of a CICLOVIRAL cream tube, containing 500 mg of aciclovir, were ingested orally. Oral doses of 800 mg of aciclovir were administered five times daily (4 grams daily), for 7 days, with no adverse events.

Accidental intravenous administration of doses up to 80 mg/kg has not caused adverse events.

Aciclovir is removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: 13.1.4 - Medicines used to treat skin conditions. Anti-infective agents for topical application to the skin. Antiviral agents.
ATC code: D06BB03

Aciclovir is an antiviral agent with high *in vitro* activity against the Herpes simplex (HSV) type I and II and Varicella-zoster viruses. Toxicity to mammalian host cells is low.

After penetrating the cells infected by the Herpes simplex virus, aciclovir is phosphorylated to the active compound aciclovir triphosphate. The first step in this process is dependent on the presence of thymidine kinase, an enzyme encoded by the virus. Aciclovir triphosphate acts simultaneously as a substrate and an inhibitor of the viral DNA polymerase, preventing further synthesis of viral DNA without affecting normal cellular processes.

Aciclovir toxicity for non-infected mammalian host cells is low, since aciclovir cannot be used by mammalian thymidine kinase as a substrate.

Clinical studies with aciclovir cream have demonstrated statistically significant efficacy in healing of lesions and pain relief, compared to placebo.

The healing time was 22% shorter in patients treated with aciclovir cream, compared to patients treated with placebo (average duration decreased by up to 0.5 days). Time to pain disappearance was reduced by approximately 20% (average duration decreased by up to 0.4 days). Approximately 60% of patients started treatment at an early stage (prodrome or erythema), with the remaining 40% starting treatment at a later stage (papular or vesicular stage).

5.2. PHARMACOKINETIC PROPERTIES

Aciclovir absorption through the skin appears to be minimal following cutaneous use in intact skin. The results of a study in several patients with localised infections by the Varicella-zoster virus have demonstrated that absorption through the skin is minimal when aciclovir cream is applied to the affected areas.

Aciclovir distribution following cutaneous use has not yet been determined. *In vitro*, aciclovir appears to be preferentially distributed to cells infected with the virus.

Aciclovir metabolism following absorption through the skin has not yet been completely established.

In a study involving a cutaneous application of aciclovir in patients with localised infections caused by the Varicella-zoster virus, 9.4% or less of the total daily dose of aciclovir was excreted unchanged in the urine.

5.3. PRECLINICAL SAFETY DATA

Experience in animals has not evidenced an increased risk of mutagenic, carcinogenic or teratogenic effects, or any effects on fertility.

LD_{50} by oral route in mice is higher than 10,000 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

CICLOVIRAL cream contains the following excipients: cetostearyl alcohol, liquid paraffin, propylene glycol, sodium laurilsulfate, poloxamer 407, white vaseline and purified water.

6.2. INCOMPATIBILITIES

Not applicable.

6.3. SHELF LIFE

3 years.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30ºC.

6.5. NATURE AND CONTENTS OF CONTAINER

CICLOVIRAL cream is packed in aluminium tubes with an internal epoxy phenolic coating and a polypropylene cap.

Each tube contains 10 g of cream.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

There are no special requirements.

7. MARKETING AUTHORISATION HOLDER

MEDINFAR CONSUMER HEALTH - PRODUTOS FARMACÊUTICOS, LDA.
Rua Henrique Paiva Couceiro, 27
Venda Nova, 2700-451 Amadora

Portugal

8. MARKETING AUTHORISATION NUMBER(S)

Registration No.: 9745505 – 10 g of 50 mg/g cream, aluminium tube

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8 May 1990
Date of latest renewal: 8 May 2005

10. DATE OF REVISION OF THE TEXT

12/2011