SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Aciclovir ratiopharm 50 mg/g, crème

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of Aciclovir 50 mg/g cream contains 50 mg of aciclovir.

Excipients with known effect:
Each g contains 250 mg propylene glycol (E1520).
Each g contains 15 mg cetyl alcohol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream.
Soft white odourless cream.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aciclovir cream is indicated for the treatment of immunocompetent patients with localised skin infections caused by the Herpes simplex virus including initial and recurring herpes genitalis and herpes labialis.

4.2 Posology and method of administration

Posology
Aciclovir cream should be applied to infected skin areas 5 times daily at approximately 4 hourly intervals, omitting the night time application.

Method of administration
Aciclovir cream should be applied to the lesions or impending lesions as early as possible after the start of an infection, preferably during the early stages of the infection (prodrome or erythema). However, the treatment may also be started at a later stage (papular or vesicular phase).

Treatment should be continued for 5 days. If, after 5 days, healing is not complete then treatment can be continued for up to an additional 5 days.
If the lesions are still present after 10 days starting from the first day of treatment, patients are advised to consult a physician. (See also section 5.1)

4.3 Contraindications

Hypersensitivity to the active substance, valaciclovir, propylene glycol or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Aciclovir 50 mg/g 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.

Patients with particularly severe and recurrent herpes labialis should be advised to consult a physician.

Patients with genital herpes should abstain from sexual activity for as long as lesions are visible to avoid transmission of infection to their partners.

The severity of recurrent infections varies as a function of the patient's immune status, episode frequency and duration, size of total lesion area and presence or absence of systemic reactions. Patient's management should reflect these factors and, therefore, may consist either of counselling and symptomatic treatment or of causal therapy.
Severe cases of initial genital herpes should be treated with the oral dosage form.
The physical, emotional and psychosocial problems that may result from herpes infections differ from patient to patient. The choice of therapy, therefore, will also depend on each patient's individual situation.

In severely immunocompromised patients (e. g. AIDS patients or bone marrow transplant recipients) oral aciclovir dosing should be considered. Such patients should be encouraged to consult a physician concerning treatment of any infection.

Excipient(s)

Propylene glycol
Propylene glycol may cause skin irritation.

Cetyl alcohol
Cetyl alcohol can cause local skin reactions (e. g. contact dermatitis).

4.5 Interaction with other medicinal products and other forms of interaction

No clinically significant interactions have been identified.

4.6 Fertility, pregnancy and lactation

Pregnancy
The use of aciclovir should be considered only when the potential benefits outweigh the possibility of unknown risks however the systemic exposure to aciclovir from topical application of aciclovir cream is very low.

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.
Animal studies do not indicate reproductive toxicity (see section 5.3).
Breast-feeding
Limited human data show that the drug does pass into breast milk following systemic administration. However, the dosage received by a nursing infant following maternal use of aciclovir cream would be insignificant.

Fertility

There is no information on the effect of aciclovir on human female fertility. Studies in humans showed that oral administration of aciclovir has no significant effect on the count, morphology and motility of spermatozoids. Animal studies do not show effects on fertility at clinically relevant doses (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, an adverse effect on these activities is unlikely.

4.8 Undesirable effects

The following convention has been used for the classification of undesirable effects in terms of frequency:

[Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to< 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), Not known (cannot be estimated from the available data)]

Due to the nature of the adverse events observed, it is not possible to determine unequivocally which events were related to the administration of the drug and which were related to the disease. Spontaneous reporting data has been used as a basis for allocating frequency for those events observed post-marketing.

Immune system disorders
Very rare:
- Immediate hypersensitivity reactions including angioedema and urticaria.

Skin and subcutaneous tissue disorders
Uncommon:
- Transient burning or stinging at the application site;
- 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.

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 national reporting system listed in Appendix V.

4.9 Overdose

No untoward effects would be expected if the entire contents of a 10 g cream tube containing 500 mg of aciclovir were ingested orally.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibiotics and chemotherapeutics for dermatological use, ATC code: D06BB03

Aciclovir is a purine (guanine) nucleoside analogue. Aciclovir is an antiviral agent which is highly active in vitro against herpes simplex virus (HSV) types I and II, varicella zoster virus (VZV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV).

Mechanism of action
If a cold sore is left untreated, the viral titre is highest when lesions are at their most severe (around 12 to 48 hours after the first signs of emergence of a cold sore). The cold sore decreases in severity once the blisters have burst and it begins to heal by forming a scab, 48 to 96 hours after emergence of the cold sore. Viral shedding decreases sharply in this stage. A treatment period of four days therefore includes the period with the highest viral titre, before the natural healing process begins.

Aciclovir itself is a pharmacodynamically inactive compound. After penetrating cells infected with herpes simplex virus (HSV), aciclovir is converted to antivirally-active aciclovir triphosphate. This conversion is catalysed by viral HSV thymidine kinase, an enzyme essential for viral replication. HSV thus synthesises its own antiviral agent. The affinity of aciclovir for viral DNA polymerase is 10-20 times greater than its affinity for cellular DNA polymerase. Aciclovir thus selectively inhibits viral enzyme activity. Viral DNA polymerase incorporates aciclovir into viral DNA.
As aciclovir is devoid of a 3'-hydroxyl group, no more nucleotides can be added by the formation of 3'-5' bonds, causing chain termination and hence effective reduction of viral replication. Both herpes simplex virus types 1 and 2 are highly sensitive to aciclovir.

Clinical efficacy and safety
Aciclovir cold sore cream was compared with the placebo cream in two large, double blind, randomised clinical studies involving 1,385 subjects. In these studies, time from start of treatment to healing was 4.6 days using aciclovir cream and 5.0 days using the placebo ($p< 0.001$). Duration of pain was 3.0 days in the aciclovir cream group and 3.4 days in the placebo group ($p=0.002$). Overall, approximately 60% of subjects started treatment at an early stage of infection (prodrome or erythema) and 40% at a late stage (papule or blister). In the group that started treatment in the early stage, the time to healing in the aciclovir cream group was 4.3 days and the duration of pain 3.0 days (placebo group 4.8 days and 3.4 days respectively); in the group that started treatment in the late stage, the time to healing in the aciclovir cream group was 4.6 days and the duration of pain 2.9 days (placebo group 5.3 days and 3.4 days respectively).

In severely immunocompromised patients, prolonged or repeated aciclovir therapy may result in the selection of viral strains with reduced sensitivity. These patients, therefore, will no longer respond to aciclovir.

Resistance is normally the result of a TK-deficient phenotype, however changes in the viral TK or viral DNA polymerase have also been reported. *In vitro* exposure of herpes simplex viruses to aciclovir may also give rise to emergence of less susceptible viruses. The relationship between susceptibility of the HSV found *in vitro* and the clinical response to aciclovir is not clear.

5.2 Pharmacokinetic properties

Absorption
Aciclovir penetrates the skin. Intradermal levels are higher than the minimum inhibitory concentration in tissue at steady state. It has not been possible to detect aciclovir in the blood following topical application to the skin. The data reported below are therefore based on oral or intravenous administration.

Biotransformation and elimination

The main metabolite is 9-carboxy(methoxy)methylguanine. It accounts for about 10-15 % of the renally excreted drug. Most of an aciclovir dose reaching the plasma is eliminated as unchanged drug via the kidneys (by both glomerular filtration and tubular excretion).

The plasma half-life of aciclovir in patients with normal kidney function is about 3 hours. Plasma protein binding is relatively low (9-33 %). Interactions due to displacement from plasma protein binding sites are, therefore, unlikely.

5.3 Preclinical safety data

Mutagenicity
A large number of in vitro tests shows that, at very high concentrations, chromosomal damage may occur. During in vivo studies, no chromosomal damage has been observed.

Carcinogenicity
Aciclovir was not found to be carcinogenic in long-term studies in the rat and the mouse.

Embryotoxicity
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 significance of these findings is uncertain.

Fertility
Largely reversible effects on spermatogenesis were reported in rats and dogs only at high doses far in excess of human therapeutic levels. However, no effects on fertility were reported in two-generation studies of mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol (E1520)
White soft paraffin (E905)
Liquid paraffin (E905)
Cetyl alcohol
Dimeticon
Stearoyl macrogolglycerides (Arlatone 983)
Purified water

6.2 Incompatibilities

The cream must not be mixed with other substances.

6.3 Shelf life

36 months.
Shelf life after first opening of the tube: 28 days.

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

Aluminium tubes of 2, 3, 10, and 15 g, with HDPE screw caps.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

ratiopharm GmbH
Graf-Arco-Strasse 3
89079 Ulm
Duitsland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 22285

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van de eerste verlening van de vergunning: 17 mei 2002
Datum van laatste verlenging: 17 mei 2007

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 4.2, 4.4, 4.6, 4.8, 5.1, 5.2 en 5.3: 3 april 2025