

**IRISH MEDICINES BOARD ACTS 1995 AND 2006**

**MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007**

**(S.I. No.540 of 2007)**

**PA0593/015/001**

Case No: 2041180

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

**Stada Arzneimittel AG**

**Stadastrasse 2-18, D-61118 Bad Vilbel, Germany**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

**Acyclostad 50 mg/g Cream**

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **05/12/2007**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

## Part II

### Summary of Product Characteristics

#### 1 NAME OF THE MEDICINAL PRODUCT

Acyclostad 50mg/g cream

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Acyclostad 50 mg/g cream contains 50 mg of aciclovir per gram of cream.

Excipient: 50mg/g cetyl alcohol and 150mg/g propylene glycol

For a full list of excipients, see 6.1.

#### 3 PHARMACEUTICAL FORM

Cream

White to off-white cream.

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic Indications

Treatment of immunocompetent patients with skin infections caused by herpes simplex virus in particular in initial genital herpes.

##### 4.2 Posology and method of administration

Acyclostad 50 mg/g cream should be applied to infected skin areas 5 times daily at approximately 4 hourly intervals, omitting the night time application.

Acyclostad 50 mg/g cream should be applied to the lesions or impending lesions as early as possible after the start of an infection.

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.

##### 4.3 Contraindications

Hypersensitivity to aciclovir or any of the excipients.

##### 4.4 Special warnings and precautions for use

Acyclostad 50 mg/g cream should not be used on mucous membranes (e.g. mouth, vagina) to avoid local irritation. Accidental eye contact must also be prevented.

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 counseling 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 seriously immunocompromised patients oral aciclovir therapy should be considered. Such patients should be advised to consult their doctor about the treatment of any infection.

This medicinal product contains propylene glycol and cetyl alcohol. It may cause skin irritation and local skin reactions (e.g. contact dermatitis).

## **4.5 Interaction with other medicinal products and other forms of interaction**

No drug interactions have been reported for topical aciclovir.

## **4.6 Pregnancy and lactation**

### *Pregnancy*

Safe use of aciclovir in pregnant women has not been established.

Animal studies have revealed harmful effects of the active ingredient, aciclovir: 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, fetal abnormalities were observed, but only following such high subcutaneous doses that maternal toxicity was produced.

The clinical significance of these findings is uncertain.

### *Lactation*

The active ingredient, aciclovir, has been detected in breast milk following systemic administration. However, pharmacokinetic data show that, after a local treatment with acyclovir, it is not possible to detect aciclovir in the blood plasma.

Caution is required when Acyclostad 50 mg/g cream is to be used by breast-feeding women.

Aciclovir should be used by pregnant women and nursing mothers only on physicians' advice.

## **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 abilities is unlikely.

## **4.8 Undesirable effects**

Adverse reactions have been ranked under headings of frequency using the following convention: Very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1000$ ,  $< 1/100$ ); rare ( $\geq 1/10000$ ,  $< 1/1000$ ); very rare ( $< 1/10000$ ).

### *Immune system disorders*

Very rare: Hypersensitivity reactions of the early reaction type including angioedema.

### *Skin and subcutaneous tissue disorders*

Uncommon: Transient burning or stinging sensation on the application site, mild form of dry skin or flaking, itching.

Rare: Erythema, contact dermatitis after administration. The results of hypersensitivity tests carried out have shown that the reactive substances were mostly components of the cream and not aciclovir itself.

## 4.9 Overdose

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

Oral doses of 800 mg 5 times daily have been administered for 7 days without adverse effects in the treatment of shingles. Single intravenous doses of up to 80 mg/kg have been inadvertently administered without adverse effects.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibiotics and chemotherapeutics for dermatological use

ATC code: D 06 BB 03

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.

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.

### 5.2 Pharmacokinetic properties

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.

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

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. Aciclovir was not found to be carcinogenic in long-term studies in the rat and the mouse. Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in several species. In a non-standard test in rats, no effects on the fetus were observed, except at high doses, that also produced maternal toxicity.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Macrogol stearate, dimethicone, cetyl alcohol, liquid paraffin, white soft paraffin, propyleneglycol, purified water.

### **6.2 Incompatibilities**

The cream must not be mixed with other substances.

### **6.3 Shelf Life**

3 years.

### **6.4 Special precautions for storage**

No special precautions for storage.

### **6.5 Nature and contents of container**

Aluminium tube with polyethylene cap.  
Each tube contains 2, 3, 5, 10, 15 or 20 g.\*  
Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

No special requirements.

## **7 MARKETING AUTHORISATION HOLDER**

STADA Arzneimittel AG  
Stadastr. 2-18  
D-61118 Bad Vilbel

## **8 MARKETING AUTHORISATION NUMBER**

PA 593/15/1

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 27<sup>th</sup> November 1998  
Date of last renewal: 25<sup>th</sup> November 2006

## **10 DATE OF REVISION OF THE TEXT**

June 2007