

# SKINOREN<sup>®</sup>

## *20% Azelaic Acid Cream*

---

### **Presentation**

---

1 g of white to slightly yellowish opaque cream contains 0.2 g (20 %) micronised azelaic acid.

---

### **Uses**

---

#### ***Actions***

The antimicrobial property of azelaic acid and a direct influence on follicular hyperkeratosis are assumed to be the basis for the therapeutic efficacy of SKINOREN<sup>®</sup> in acne.

A significant reduction of the colonization density of *Propionibacterium acnes* and a significant reduction of the fraction of free fatty acids in the skin surface lipids are observed under treatment with SKINOREN<sup>®</sup>.

Azelaic acid inhibits the proliferation of cultivated keratinocytes (suppression of DNA synthesis) and accelerates the comedolysis of tetradecane-induced comedones in the rabbit ear model. Electronmicroscopic and immunohistochemical analyses of skin biopsies taken after treatment with SKINOREN<sup>®</sup> reveal ultrastructural changes, in particular of the keratohyaline granules and of filaggrin, an important factor in keratinisation. These findings suggest that, under clinical conditions, SKINOREN<sup>®</sup> affects the keratinocytes and the pattern of keratinisation.

#### ***Pharmacokinetics***

Azelaic acid penetrates into all layers of human skin after dermal application of the cream. Penetration is faster into damaged skin than into intact skin. A total of 3.6 % of the dose applied was absorbed percutaneously after a single topical application of 1 g azelaic acid (5 g cream).

Calculated on this basis, the application of 5g cream twice daily results in a systemic substance load of 1- 1.5mg/kg body weight. Azelaic acid is bound to plasma proteins to the extent of 43%.

A portion of the azelaic acid absorbed through the skin is excreted in unchanged form with the urine. The remaining portion is broken down by  $\beta$ -oxidation into

dicarboxylic acids with shorter chains (C 7, C 5 carboxylic acids) which have likewise been demonstrated in the urine.

### ***Indications***

Topical treatment of acne vulgaris.

---

## **Dosage and Administration**

---

Before SKINOREN® is applied, the skin should be thoroughly cleaned with clear water or, if applicable, a mild skin-cleansing agent.

SKINOREN® should be applied to the affected areas of skin twice a day (morning and evening) and rubbed gently into the skin. SKINOREN® should not be applied sparingly; however, excessive amounts of cream must be avoided (approximately 1 inch of cream is sufficient for the entire facial area).

In the event of excessive irritation of the skin, the amount of cream per application should be reduced or the frequency of use of SKINOREN® should be reduced to once a day until the irritation ceases. Treatment might have to be temporarily interrupted for a few days.

It is important to continue to use SKINOREN® regularly over the entire period of treatment.

The duration of use of SKINOREN® can vary from person to person and also depends on the severity of the skin disorder.

In acne, a distinct improvement becomes apparent after about 4 weeks. To obtain the best results, however, SKINOREN® should be used regularly over several months.

---

## **Contraindications**

---

Hypersensitivity to propylene glycol.

---

## **Warnings and Precautions**

---

For external use only.

Local tolerance studies with the formulation in the rabbit eye showed a moderate to high-grade irritative effect; which is ascribed to the active substance. On

accidental contamination, the eye should immediately be rinsed with copious amounts of water.

### **Preclinical safety data**

Animal-experimental studies of the systemic and local tolerance failed to show any systemic or local organotoxic effects after administration of both the active substance itself and the cream formulation in amounts up to the maximum that can be applied. Intoxication is therefore unlikely even after oral ingestion of large amounts of the formulation. In vitro and in vivo studies with the active substance produced no evidence for genotoxic effects on germinal and somatic cells. No signs that the active substance has sensitising properties were found in the maximisation test in the guinea pig .

### ***Pregnancy and Lactation***

#### **Use in Pregnancy**

Reproduction-toxicity studies (fertility, embryotoxicity, teratogenicity) in animals have not produced any evidence for a risk on use during pregnancy.

#### **Use in Lactation**

The amount of azelaic acid theoretically transferred per day to the baby with the breast milk is negligible and should not imply any risk, particularly when its extremely low toxicity is considered.

---

## **Adverse Effects**

---

Local skin irritation (mostly burning or itching sensations, occasionally reddening and scaling) may occur - usually at the start of treatment. In the majority of cases the irritation symptoms are mild and generally regress in the course of treatment.

---

## **Interactions**

---

None so far known.

---

## **Overdosage**

---

Animal-experimental studies of the systemic and local tolerance failed to show any systemic or local organotoxic effects after administration of both the active

substance itself and the cream formulation in amounts up to the maximum that can be applied. Intoxication is therefore unlikely.

---

## Pharmaceutical Precautions

---

**Shelf life:** 5 years.

**Special precautions for storage:** Do not store above 30 °C.

---

## Medicine Classification

---

Pharmacy Medicine

---

## Package Quantities

---

Tubes containing 30 g

Standard tube with membrane closure and screw cap (tube material aluminium, internal coating done with epoxide, end seal band made of polyamide-based compound, external coating made of polyester, screw cap made of high-density polyethylene).

---

## Further Information

---

### List of excipients

Arlatone 983 S (polyoxyethylene fatty acid ester)  
Cutina CBS (mixture of mono-diglyceridene, fatty alcohols, triglycerides and wax esters)  
cetearyloctanoate  
propylene glycol  
glycerol 85%  
benzoic acid  
purified water

### Instructions for use/handling

Store all drugs properly and keep them out of reach of children.

---

## **Name and Address**

---

### **Sponsor**

CSL (New Zealand) Limited  
666 Great South Road  
Penrose, Auckland 6, NEW ZEALAND  
Telephone: 09 579 8105

---

## **Date of Preparation**

---

18 October 2006