Preparation Strength Packsize: Skinoren® C
Segrate no: 86468638

IIT004-00 - Page 1 + 2 - 148 x 210 mm – DRA_90040

Skinoren®

Anti-acne agent

063332-XX

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Manufactured by:
LEO Pharma Manufacturing Italy S.r.l
Important information, please read carefully!

Composition

Skinoren contains a white, opaque cream. 1 g Skinoren cream contains 200 mg (20 %) azelaic acid.
For the full list of excipients, see section *List of excipients*.

Pharmacodynamic Properties

Pharmacotherapeutic group: other anti-acne preparations for topical use, ATC code: D10AX03
The antimicrobial action and a direct influence on follicular hyperkeratosis are assumed to be the basis for the therapeutic efficacy of Skinoren in acne. Clinically, 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 is observed. In vitro and in vivo, azelaic acid inhibits the proliferation of keratinocytes and normalizes the disturbed terminal epidermal differentiation processes in acne. In the rabbit ear model, azelaic acid accelerates the comedolysis of tetradecane-induced comedones. Experimental results demonstrate that azelaic acid exerts a dose- and time-dependent inhibitory effect on the growth and viability of abnormal melanocytes. The molecular mechanisms by which this is accomplished are not entirely clarified. Currently available data suggest that the main effects of azelaic acid in the treatment of melasma are brought about by an inhibition of the DNA synthesis and/or an inhibition of the cellular respiration of the abnormal melanocytes.

Pharmacokinetics Properties

Azelaic acid penetrates into all layers of human skin after topical application of the cream. Penetration is faster into damaged skin than into intact skin. A total of 3.6 % of the dose applied is absorbed percutaneously after a single topical application of 1 g azelaic acid (5 g cream). 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 ß-oxidation into dicarboxylic acids with shorter chain length (C_7, C_5) which have likewise been found in the urine.

Indications

Treatment of acne vulgaris.

Dosage and administration

Cutaneous use
Skinoren cream should be applied to the affected areas of skin twice a day (morning and evening) and rubbed in gently. The amount of Skinoren cream to be applied will depend on the size of the affected area. As a guide, a daily dose of approximately 2.5cm/1inch of cream is sufficient for the entire facial area. Before Skinoren cream is applied, the skin should be thoroughly cleaned with clear water, or if applicable, a mild skin-cleansing agent. It is important to continue to use Skinoren cream regularly over the entire period of treatment. The duration of use of Skinoren cream can vary from patient to patient and also depends on the severity of the acne. In patients with acne, in general, a distinct improvement becomes apparent after about 4 weeks. To obtain the best results, however, Skinoren should be used regularly over several months. However, Skinoren should not be used continuously for more than 12 months at any time. In the event of excessive irritation of the skin (see "Side effects"), the amount of cream per application should be reduced or the frequency of use of Skinoren cream should be reduced to once a day until the irritation ceases, or the treatment should be temporarily interrupted for a few days.

Pediatric population
Dose adjustment is not required when Skinoren cream is administered to adolescents aged 12-18 years of age. The safety and efficacy of Skinoren cream in children below the age of 12 years have not been established.

Side effects

In clinical studies, most frequently observed side effects included application site burning, application site pruritus, and application site erythema.
Frequencies of side effects observed in clinical studies and given in the table below are defined according to the MedDRA frequency convention:
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).

System organ class	very common	common	uncommon	rare
Skin and subcutaneous tissue disorders			seborrhea, acne, skin depigmentation	cheilitis

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2. PROOF FROM RBE	Mock-up Approval Stamp (MAS)		
Date 14/06/19	**Graphic Design**	**Editorial Proof**	**Second Approver**
New proof requested ☐	**According to:** SOP_000647, SOP_000962, SOP_003993 and SOP_008676 ☐	**According to:** SOP_000647, SOP_000962 and SOP_008676 _ ☐	Product name ☐
Sign.:			Dosage form ☐
			Strength/Stripes ☐
Date:	1st Sign.: Date:	Sign.: Date:	Pack size ☐
			Prompts ☐
	2nd Sign.: Date:		Material No./Reg. No. ☐
			Barcode ☐
			Sign.: Date:

System organ class	very common	common	uncommon	rare
General disorders and administration site conditions	application site burning, application site pruritus, application site erythema	application site exfoliation, application site pain, application site dryness, application site discolouration, application site irritation	application site paraesthesia, application site dermatitis, application site discomfort, application site oedema	application site vesicles, application site eczema, application site warmth, application site ulcer
Immune system disorders				drug hypersensitivity

Generally, local skin irritation regresses in the course of treatment.
The following additional adverse reactions have been reported during post-approval use of Skinoren cream (frequency unknown):

- Angioedema, Dermatitis contact, Eye swelling, Swelling face (which may occur with Hypersensitivity)
- Rash
- Urticaria
- Worsening of Asthma

In clinical studies involving adolescents 12-18 years of age (454/1336;34%), the local tolerability of Skinoren cream was similar in pediatric and adult patients.

Contraindications

Hypersensitivity to the active substance or to any of the excipients of the cream, in particular propylene glycol.

Overdose

Skinoren cream is intended for external use only. Findings from animal experiments show that vomiting may occur after ingestion of large amounts. No organotoxic changes are likely though no human data on overdosage are available.
Results from acute toxicity studies do not indicate that any risk of acute intoxication is to be expected following a single dermal application of an overdose (application over a large area under conditions favourable to absorption) or inadvertent oral ingestion.

Special warnings and special precautions for use

For external use only. Care must be taken when using Skinoren cream to avoid contact with the eyes, mouth and other mucous membranes, and patients should be instructed accordingly.In the event of accidental contact, the eyes, mouth and/or affected mucous membranes should be washed with large amount of water. If eye irritation persists, patients should consult a physician.
The hands should be washed after each application of the Skinoren cream.
Benzoic acid is mildly irritant to the skin, eyes and mucous membranes. Propylene glycol may cause skin irritation.

Pregnancy and lactation

Pregnancy
There are no adequate and well-controlled studies of topically administered azelaic acid in pregnant women.
Animal studies do indicate the potential for effects with respect to pregnancy, embryo-fetal development, parturition or postnatal development. However, the dose levels without observed adverse effects in animals ranged across studies from 3-32 times the maximum recommended human dose based on body surface area. It is advisable to avoid Skinoren cream during pregnancy unless the benefit outweighs the risk.

Lactation
It is not known if azelaic acid is secreted in human milk *in vivo.* However an *in vitro* equilibrium dialysis experiment demonstrated that passage of drug into maternal milk may occur. But the distribution of azelaic acid into maternal milk is not expected to cause a significant change from baseline azelaic acid levels in the milk since azelaic acid is not concentrated in milk and less than 4% of topically applied azelaic acid is systemically absorbed not increasing endogenous azelaic acid exposure above physiological levels. However, Skinoren cream should not be used by lactating woman unless the benefit outweighs the risk.

Storage Conditions

Store below 30°C. Store all drugs carefully and keep them out of reach of children.

Dosage form and packaging

Tubes with 30 g cream

Excipients

Benzoic acid, Cetearyl octanoate, Glycerol 85%, Glyceryl stearate + cetearyl alcohol + cetyl palmitate + cocoglycerides (CUTINA CBS), Propylene glycol, Purified water, Stearoyl macrogolglycerides

Shelf Life

Please refer to labels. After first opening of the container, the in-use stability is 6 months.

Name and address of Manufacturer

LEO Pharma Manufacturing Italy S.r.l.
Via E. Schering 21 - 20090 Segrate MI Italy

Date of revision of the text

19 March 2018

Singapore **86468638**

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