Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Skinoren 15% Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1g Skinoren Gel contains 150 mg (15%) azelaic acid.

Excipients with known effect
1 mg Benzoic acid /g Gel
0.12 g Propylene glycol /g Gel

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gel

White to yellowish-white opaque gel

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- For the relief of mild to moderate papular-pustular acne of the facial area.
- For the topical treatment of papulopustular rosacea.

4.2 Posology and method of administration

Skinoren 15 % Gel is intended for cutaneous use only.

Posology
Skinoren Gel should be applied to the affected skin areas twice a day (in the morning and in the evening) and rubbed in gently. Approximately 0.5 g = 2.5 cm (1 inch) of gel is sufficient for the entire facial area.

Pediatric population
Use in adolescents (12-18 years of age) for the treatment of acne vulgaris. Dose adjustment is not required when Skinoren Gel is administered to adolescents aged 12-18 years.
The safety and efficacy of Skinoren Gel for the treatment of acne vulgaris in children below the age of 12 years have not been established.
The safety and efficacy of Skinoren Gel for the treatment of papulopustular rosacea in children below the age of 18 years have not been established.

Geriatric patients
No targeted studies have been performed in patients aged 65 and over.

Patients with hepatic impairment
No targeted studies have been performed in patients with hepatic impairment.

Patients with renal impairment
No targeted studies have been performed in patients with renal impairment.

Method of administration

Before Skinoren Gel is applied, the skin should be thoroughly cleaned with plain water and dried. A mild skin-cleansing agent may be used.

Occlusive dressing or wrappings should not be used, and hands should be washed after applying the gel.

In the event of skin irritation (see section 4.8 Undesirable effects), the amount of gel per application should be reduced or the frequency of use of Skinoren Gel should be reduced to once a day until the irritation ceases. If required, the treatment should be temporarily interrupted for a few days.

It is important to use Skinoren Gel continuously over the entire period of treatment. The duration of use of Skinoren Gel can vary from person to person and also depends on the severity of the skin disorder.

Acne: In general, a distinct improvement becomes apparent after 4 weeks.To obtain optimum results, Skinoren Gel can be used over several months in accordance with the clinical outcome. In case of no improvement after 1 month or exacerbation of acne, Skinoren Gel should be discontinued and other therapeutic options should be considered.

Rosacea: In general, a distinct improvement becomes apparent after 4 weeks of treatment. To obtain optimum results, Skinoren Gel can be used over several months in accordance with the clinical outcome. In case of no improvement after 2 months or exacerbation of rosacea, Skinoren Gel should be discontinued and other therapeutic options should be considered.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

For external use only.

Care should be taken when using Skinoren Gel to avoid contact with the eyes, mouth and other mucous membranes, and patients should be instructed accordingly (see section 5.3 Preclinical safety data). In the event of accidental contact, the eyes, mouth and/or affected mucous membranes should be washed with large amounts of water. If eye irritation persists, patients should consult a physician. The hands should be washed after each application of Skinoren Gel.

Skinoren Gel contains 1 mg benzoic acid in each g. Benzoic acid may cause local irritation.

Skinoren Gel contains 120 mg propylene glycol in each g.

It is advisable to avoid the concomitant use of alcoholic cleansers, tinctures and astringents, abrasives and peeling agents in patients using Skinoren Gel for treatment of rosacea.

Worsening of asthma in patients treated with azelaic acid has been reported rarely during post- marketing surveillance.

4.5 Interaction with other medicinal products and other forms of interactions

No interaction studies have been performed. The composition of Skinoren Gel gives no indication of any undesired interactions of the single components that could adversely affect the safety of the product. No drug-specific interactions were noted during any of the controlled clinical trials.

4.6 Fertility, 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, embryonal-foetal 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 (see section 5.3 Preclinical safety data). Caution should be exercised when prescribing azelaic acid to pregnant women.

Lactation
It is not known if azelaic acid is secreted into 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. 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, caution should be exercised when Skinoren Gel is administered to a nursing woman. Infants must not come into contact with treated skin/breast.

Fertility
There are no data on the effect of Skinoren gel on human fertility. Results from animal studies showed no effect on fertility in male or female rats (see section 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines

Skinoren Gel has no influence on the ability to drive and use machines.

4.8 Undesirable effects

From clinical studies and post-marketing surveillance, most frequently observed side effects included application site pruritus, application site burning and application site pain.

Frequencies of side-effects observed in clinical studies and post-marketing surveillance and given in the table below are defined according to the MedDRA frequency convention:

Very common (≥1/10),
Common (≥1/100, <1/10),
Uncommon (≥1/1,000; <1/100),
Rare (≥1/10,000, <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[1]
Immune system disorders				hypersensitivity (which may occur with one or more of the following adverse reactions: angioedema, eye swelling, swelling face, dyspnoea)**,** worsening of asthma (see section 4.4)
Skin and subcutaneous tissue disorders			contact dermatitis, acne*	skin irritation, urticaria
General disorders and administration site conditions	application site burning, application site pain, application site pruritus	applicationsite rash, application site paraesthesia, application site dryness, application site oedema*	application site erythema, application site exfoliation**, application site warmth**, application site discolouration**, application site discomfort*, appplication site urticaria*	

* for indication Rosacea
**for indication Acne

[1] These adverse reactions have been reported during post-approval use of Skinoren gel.

Generally, local skin irritation regresses in the course of the treatment.

Pediatric population
Treatment of acne vulgaris in adolescents 12-18 years of age:
In 4 clinical phase II and II/III studies involving adolescents 12-17 years of age (120/383; 31 %), t he overall incidence of adverse events for Skinoren Gel was similar for the groups aged 12-17 years (40 %), aged ≥ 18 years (37 %) and for the entire patient population (38 %). This similarity also applied to the group aged 12-20 years (40 %).

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 HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

Due to the very low local and systemic toxicity of azelaic acid intoxication is unlikely.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other anti-acne preparations for topical use, ATC code: D10A X03

Acne:
An antimicrobial action and a direct influence on follicular hyperkeratosis are assumed to be the basis for the therapeutic efficacy of azelaic acid in acne. *In vitro* and *in vivo*, azelaic acid inhibits the proliferation of keratinocytes and normalizes the disturbed terminal epidermal differentiation processes in acne. Clinically, a significant reduction of the colonization density of *Propionibacterium acnes* and a significant reduction in the fraction of free fatty acids in the skin surface lipids are observed. In two double blind randomized clinical studies Skinoren Gel was significantly superior to its vehicle in the median reduction of the sum of papules and pustules, and was 6 % less effective than benzoyl peroxide 5 % (p = 0.056). In these studies effectiveness of Skinoren Gel on comedones has been evaluated as a secondary parameter. Skinoren Gel was more effective than its vehicle in the median relative reduction of comedones, and was less effective in comparison to benzoyl peroxide 5 %.

Rosacea:
While the pathophysiology of rosacea is not completely understood, there is increasing consensus that inflammation involving the elevation of several pro-inflammatory effector molecules such as kallikrein-5 and cathelicidin as well as reactive oxygen species (ROS), is a central process of this disease. Azelaic acid has been demonstrated to modulate the inflammatory response in normal human keratinocytes by: a) activating the peroxisome proliferator-activated receptor γ (PPARγ); b) inhibiting the trans-activation of nuclear factor-kB (NF-kB); c) inhibiting the production of pro-inflammatory cytokines and d) inhibiting the release of ROS from neutrophils, as well as direct scavenging effects on existing ROS. In addition, azelaic acid has been shown to directly inhibit kallikrein-5 and cathelicidin expression in three models: *in vitro* (human keratinocytes), in murine skin and in the facial skin of patients with rosacea. These anti-inflammatory properties of azelaic acid may play a role in the treatment of rosacea. While the clinical significance of these findings regarding kallikrein-5 and cathelicidin and their impact on the pathophysiology of rosacea has not yet been fully demonstrated in a large clinical study, initial studies in human facial skin appear to confirm the *in vitro* and murine findings. In the two vehicle controlled 12 week clinical studies in papulopustular rosacea, Skinoren Gel was statistically significantly superior to its vehicle with regard to the reduction in inflammatory lesions, Investigator's Global Assessment, overall rating of improvement and with regard to improvement of erythema. In the clinical study with the active comparator metronidazole 0.75 % gel in papulopustular rosacea, Skinoren Gel showed significant superiority with regard to lesion count reduction(72.7 %versus 55.8 %), overall rating of improvement and with regard to improvement of erythema (56 % versus 42 %). The rate of cutaneous adverse events, which in most cases were mild to moderate, was 25.8 % with Skinoren Gel and 7.1 % with metronidazole 0.75 % gel. There was no noticeable effect on the teleangiectasias in the three clinical studies.

5.2 Pharmacokinetic properties

Azelaic acid penetrates into all layers of the skin after topical application of the gel. 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 (administered as 5 g Skinoren 20 % Cream). Clinical investigations in acne patients indicated similar absorption rates of azelaic acid from Skinoren Gel and Skinoren Cream.

A portion of the azelaic acid absorbed through the skin is excreted in unchanged form in the urine. The remaining portion is broken down by β-oxidation into dicarboxylic acids with shorter chain length (C_7, C_5), which have likewise been found in the urine.

Steady-state plasma levels of azelaic acid in rosacea patients after 8 weeks twice daily treatment with Skinoren Gel were within the range also observed in volunteers and acne patients on normal diets. This indicates that the extent of percutaneous absorption of azelaic acid following twice daily application of Skinoren Gel does not alter the systemic burden of azelaic acid derived from dietary and endogenous sources in a clinically meaningful way.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and toxicity to reproduction.

Embryofetal developmental studies with oral administration of azelaic acid to rats, rabbits, and cynomolgus monkeys during the period of organogenesis revealed embryotoxicity at doses where some maternal toxicity was noted. No teratogenic effects were observed. The embryofetal NOAEL was 32 time the MRHD based on BSA in rats, 6.5 times the MRHD based on BSA in rabbits and 19 time the MRHD based on BSA in monkeys(see section 4.6 Fertility, pregnancy and lactation).
In a peri- and post-natal developmental study in rats where azelaic acid was administered orally from gestational day 15 to through day 21 postpartum slight disturbances in the post-natal development of fetuses were noted at oral doses that generated some maternal toxicity. The NOAEL was 3 times the MRHD based on BSA. No effects on sexual maturation of the fetuses were noted in this study

In vitro and *in vivo* studies with azelaic acid produced no evidence of mutagenic effects on germ and somatic cells. Conventional long-term carcinogenicity studies with oral administration of azelaic acid have not been performed. In a 26-week dermal carcinogenicity study using male and female transgenic (Tg.AC) mice, Skinoren Gel and the gel vehicle did increase the number of papillomas in male animals after twice daily application at the treatment site. This effect was not observed after single administration in male and female mice. This effect may be associated with the vehicle application. The clinical relevance of the findings in animals to humans is not clear, especially in the light of the doubtful validity of the Tg.AC test system.

If azelaic acid came into contact with the eyes of monkeys and rabbits, signs of moderate to severe irritation became evident. Therefore, contact with the eyes should be avoided.

Azelaic acid administered once intravenously had no effects on the nervous system (Irwin test), cardiovascular function, intermediary metabolism, smooth muscles and liver and kidney function.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzoic acid (E 210)
Carbomers
Disodium edetate
Lecithin
Polysorbate 80
Propylene glycol
Purified water
Sodium hydroxide
Triglycerides medium chain

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium tube with internal epoxide coating and polyethylene screw cap.

Tubes of 5, 30, 50, 2 x 50 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

LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

8 MARKETING AUTHORISATION NUMBER

PA1025/009/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 June 2003

Date of last renewal: 03 July 2007

10 DATE OF REVISION OF THE TEXT