PACKAGE INSERT TEMPLATE FOR AZELAIC ACID CREAM/LOTION

Brand or Product Name
[Product name] Cream 20% w/w
[Product name] Lotion 20% w/v

Name and Strength of Active Substance(s)

Azelaic acid …..20 % w/w

Product Description
[Visual description of the appearance of the product (eg colour, viscosity etc)
eg White, smooth glossy cream with a characteristic odour

Pharmacodynamics
Azelaic acid is a naturally-occurring, saturated, straight-chain dicarboxylic acid (1,7-heptanedicarboxylic acid) .

The mechanism of action is not fully known but it is thought that azelaic acid causes antibacterial effects by inhibiting the synthesis of cellular protein in aerobic and anaerobic microorganisms, especially Propionibacterium acnes and Staphylococcus epidermidis. Within aerobic microorganisms, azelaic acid reversibly inhibits a variety of oxidoreductive enzymes including tyrosinase, mitochondrial enzymes of the respiratory chain, thioredoxin reductase, 5-alpha-reductase, and DNA polymerases. In anaerobic microorganisms, glycolysis is disrupted.

Also, azelaic acid improves acne vulgaris by decreasing microcomedo formation and normalizing the keratin process. Azelaic acid may be effective against both inflamed and noninflamed lesions. Specifically, azelaic acid reduces the thickness of the stratum corneum, shrinks keratohyalin granules by reducing the amount and distribution of filaggrin (a component of keratohyalin) in epidermal layers, and lowers the number of keratohyalin granules. This is suggestive of the ability to decrease microcomedo formation.

Pharmacokinetics

Absorption
Topical: Bioavailability is 4%

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After dermal administration of the cream, azelaic acid penetrates into all layers of human skin. The penetration is more rapid into damaged skin than into intact skin.

After application of a single topical dose, about 3% to 5% of the dose penetrates into the stratum corneum and about 10% into the epidermis and dermis. Percutaneous absorption is affected by the vehicle in which the medication is incorporated

Metabolism
Partially metabolized by mitochondrial beta-oxidation into short-chained dicarboxylic acids (C_7, C_5 carboxylic acids) which have been found in the urine.

Elimination
Primarily undergoes renal excretion as unchanged drug in the urine
Topical elimination half-life is 12 hours

Indication
Acne Vulgaris

Recommended Dosage
Azelaic acid should be applied to the affected area of skin twice a day (morning and evening) and rubbed gently into the skin. Before it 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 azelaic acid cream/lotion regularly over the entire period of treatment.
The duration of use 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, azelaic acid cream/lotion should be used regularly over several months. However, azelaic acid cream/lotion should not be used continuously for more than 12 months at any time.
The amount to be applied will depend on the size of the affected area. As a guide, a daily dose of approximately 2.5cm/ 1 inch of cream is sufficient for the entire facial area. Excessive amounts of cream must be avoided.
In the event of excessive irritation of the skin, the amount of cream per application should be reduced or the frequency of use should be reduced to once a day until the irritation ceases, or the treatment should be temporarily interrupted for a few days.

Mode of Administration
Topical

Contraindications
Hypersensitivity to the active substance or to any of the excipients in the cream/lotion

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Warnings and Precautions

- Lentigo maligna (may progress to invasive malignant melanoma)
- May cause hypopigmentation (particularly in patients with dark complexions)

*For external use only.

*Contact with the eyes, mouth and other mucous membranes should be avoided.
In case of accidental contact with the eyes, rinse the eyes thoroughly with running water.
If eye irritation persists, patients should consult a physician.

*Hands should be washed after each application of the cream/lotion.

Effects on the ability to drive and use machines

Azelaic acid cream/lotion has no influence on the ability to drive and use machines.

Interactions with Other Medicaments
No interactions known

Statement on Usage During Pregnancy and Lactation
Pregnancy
There are no adequate and well-controlled studies of azelaic acid in pregnant women. The effects, if any, on the developing fetus are unknown. In animal studies, embryotoxicity and maternal toxicity were observed in monkeys, rabbits, and rats administered azelaic acid doses between 19 and 162 times the maximum recommended human dose. As animal reproduction studies do not always predict human response, and because of the lack of human safety information, azelaic acid should be used in pregnant women only if the potential benefit outweighs the potential risk to the fetus

Lactation
Azelaic acid may be excreted in breast milk, but the level of azelaic acid is not expected to be significant because less than 4% of a topically applied dose is systemically absorbed.
However, Azelaic acid cream/lotion cream should not be used by lactating woman unless the benefit outweighs the risk.

Adverse Effects / Undesirable Effects

Skin and subcutaneous tissue disorders: Topical application of azelaic acid may produce a transient skin irritation such as burning, stinging, pruritus, dryness, and scaling. It is usually mild and disappears on continued treatment, but in a few patients the irritation may persist, requiring

reduced frequency of application or temporary suspension of treatment. There have been rare reports of hypopigmentation, rash, and photosensitivity. Rash has been reported rarely in post-marketing surveillance.

Administration site conditions: application site burning, pruritus, erythema, exfoliation, pain, dryness, discolouration, irritation, paraesthesia, dermatitis, discomfort, oedema, vesicles, eczema, warmth, ulcer

Immune system disorders: hypersensitivity

Worsening of asthma in patients treated with azelaic acid has been reported rarely during postmarketing surveillance

Overdose and Treatment

No human data on over dose is available. No known cases of azelaic acid overdosage resulting from topical administration of azelaic acid cream/lotion have been reported. 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.

Components of formulation may be irritating to mucous membranes and emetogenic. Nausea, vomiting, and diarrhea are most likely manifestations. Eye, skin, and mucous membrane irritation may occur.

Storage Conditions
[eg Store below….°C]

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]

Updated November 2012