Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alacare 8 mg medicated plaster

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each medicated plaster of 4 cm^2 contains 8 mg 5-aminolevulinic acid, 2 mg per cm^2.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Medicated plaster.
Each plaster has a size of 4 cm^2, is square with rounded corners and consists of a skin tone backing foil and a self-adhesive matrix, covered by a release liner which is removed prior to use.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Single use treatment of mild actinic keratoses with a maximum diameter of 1.8 cm on the face and scalp (hairless areas).

4.2 Posology and method of administration

Adults (including the elderly)
For the treatment of AK with one session photodynamic therapy (PDT), apply up to a maximum of six Alacare patches used on six different lesions to the patient on a single treatment session. If the Alacare plaster does not stick to the lesions properly, it can be fixed with an adhesive strip.

After four hours, remove the Alacare plaster(s) and expose the lesion(s) to red light with a narrow band red light source with a spectrum of 630 ± 3 nm and a total light dose of 37 J/cm^2 at the lesion surface. Only CE marked lamps should be used, equipped with necessary filters and/or reflecting mirrors to minimize exposure to heat, blue light and UV radiation. It is important to ensure that the correct light dose is administered. The light dose is determined by factors such as the size of the light field, the distance between lamp and skin surface and illumination time. These factors vary with lamp type, and the lamp should be used according to the user manual. Patient and operator should adhere to safety instructions provided with the light source. During illumination patient and operator should wear protective goggles which correspond to the lamp light spectrum. Untreated skin surrounding the lesion does not need to be protected during illumination.
Lesion responses should be assessed after three months. If the area treated with Alacare is not lesion free at 3 months following single use please use alternative therapies for removal of actinic keratosis lesions.

Paediatric population
There is no experience of treating patients below the age of 18 years.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
No response to previous PDT with 5 aminolevulinic acid-containing preparations.
Porphyria.
Known photodermatoses of varying pathology and frequency, e.g. metabolic disorders such as aminoaciduria, idiopathic or immunological disorders such as polymorphic light reaction, genetic disorders such as xeroderma pigmentosum, and diseases precipitated or aggravated by exposure to sun light such as lupus erythematosus or pemphigus erythematosus.

4.4 Special warnings and precautions for use

Alacare is not recommended for the treatment of pregnant women unless clearly necessary (see 4.6).
Very thick, red, scaly indurated AK lesions should not be treated with Alacare.

There is no experience of treating AK lesions in patients with dark brown or black skin (skin sun sensitivity type V or VI according to Fitzpatrick).
No data regarding efficacy and safety are available for repeated treatment of AK lesions with Alacare.
Any UV-therapy should be discontinued before treatment. As a general precaution, sun exposure of the treated lesion sites and surrounding skin should be avoided for approximately 48 hours following treatment.
Direct eye contact with Alacare should be avoided.
Alacare should only be administered by a nurse or other healthcare professional trained with the use of photodynamic therapies under the supervision of a physician.

The success and assessment of treatment may be impaired if the treated area is affected by the presence of skin diseases (skin inflammation, located infection, psoriasis, eczema, and benign or malignant skin cancers) as well as tattoos. No experience exists with these situations.

Concomitant use of medicinal products with known phototoxic or photoallergic potential such as St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones and tetracyclines may enhance the phototoxic reaction to photodynamic therapy. Concomitant use with other topical medicinal products should be avoided.

4.5 Interaction with other medicinal products and other forms of interactions

As hypericin can increase phototoxic reactions induced by PDT, treatment with hypericin-containing products (St John's Wort, Hypericum perforatum) should be discontinued two weeks before PDT with Alacare.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of 5-aminolevulinic acid in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal and fetal development, parturition and postnatal development (see section 5.3). The potential risk for humans is unknown. Alacare should not be used during pregnancy unless clearly necessary.

Breastfeeding
It is unknown whether 5-aminolevulinic acid is excreted in human breast milk. The excretion of 5-aminolevulinic acid has not been studied in animals. Breast-feeding should be discontinued for 48h after application of Alacare.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

a) Almost all patients (99%) experience adverse reactions localised at the treatment site (local reactions) that are attributable to toxic effects of the photodynamic therapy (phototoxicity). During application of Alacare and prior to illumination of the treatment site, 33% of patients show local reactions, most frequently pruritus, burning and erythema. During illumination, erythema, burning and pain are the local reactions reported most often. The symptoms are usually of mild or moderate severity and require early termination of illumination in 1% of the patients. Cooling of the treated area may alleviate these symptoms. After therapy, pruritus, erythema, scabbing and exfoliation are the most frequent local reactions which are likewise mainly mild to moderate and persist for 1 to 2 weeks or occasionally longer.
A common (< 10%) adverse reaction not involving the treatment site is headache.

b) The incidence of adverse reactions in patients receiving Alacare plus illumination, is shown in the table below.

Adverse reactions involving the treatment site (local reactions)		
General disorders and application site conditions	Very common ≥ 1/10	Erythema, exfoliation, irritation, pain, pruritus, scab
	Common ≥ 1/100, < 1/10	Bleeding, desquamation, discharge, discomfort, erosion, hyper/hypopigmentation, oedema, reaction, swelling, vesicles
	Uncommon ≥ 1/1000, < 1/100	Burn, discolouration, excoriation, inflammation, ulcer

Infections and infestations	Common ≥ 1/100, < 1/10	Pustules
	Uncommon ≥ 1/1000, < 1/100	Infection
Adverse reactions not involving the treatment site		
Nervous system disorders	Common ≥ 1/100, < 1/10	Headache
Infections and Infestations	Uncommon ≥ 1/1000, < 1/100	Pyoderma
Psychiatric disorders	Uncommon ≥ 1/1000, < 1/100	Emotional distress
Respiratory, thoracic and mediastinal disorders	Uncommon ≥ 1/1000, < 1/100	Epistaxis
Skin and subcutaneous tissue disorders	Uncommon ≥ 1/1000, < 1/100	Skin discolouration
Investigations	Uncommon ≥ 1/1000, < 1/100	Alanine aminotransferase increased

Reporting of suspected adverse reactions

Reporting of 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, Earlsfort Terrace, IRL-Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517. Website: www.hpra.ie, E-mail: medsafety@hpra.ie.

4.9 Overdose

No case of overdose has been reported. Nevertheless, reactions at the treatment site may be more pronounced if the Alacare plasters are applied for much more than 4 hours or if a much higher light dose than the recommended 37 J/cm^2 is chosen.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
*Sensitisers*used in Photodynamic/Radiation therapy, ATC Code: L01XD04

Mechanism of action

After topical application of 5-aminolevulinic acid, protoporphyrin IX (PPIX) accumulates intracellularly in the treated AK lesions. The intracellular PPIX is a photoactive, fluorescing compound and, upon light activation in the presence of oxygen, singlet oxygen is formed which causes damage to cellular compartments of the light-exposed target cells, in particular the mitochondria.

Clinical efficacy and safety

With regard to clinical safety and efficacy, Alacare was compared with placebo treatment, in a randomised observer blinded clinical trial which enrolled 107 patients with a follow-up duration of 6, 9 and 12 months. All patients had a minimum of 3 mild to moderate AK lesions on the head and/or face. Alacare was applied to AK lesions for 4 hours without preparation of the lesion, after which they were illuminated with red light at l 630 ± 3 nm (37 J/cm^2).

12 weeks after treatment, complete clinical clearance on lesion and on patient basis of a once-only photodynamic therapy with Alacare was statistically significantly more effective than photodynamic therapy with placebo. This was sustained during follow-up, in which patients were seen every 3 months (after 6, 9 and 12 months). In an open randomised trial, which enrolled 349 patients, Alacare PDT in the same regime as described above, was compared with cryosurgery and placebo-PDT. In this trial, Alacare-PDT proved non-inferior to cryosurgery. After 12 weeks in the Full Analysis Set 87% of lesions treated with Alacare-PDT were cleared, compared to 77% after cryosurgery (Odds Ratio 1.86; 95% CI [1.18, 2.93]) and 32% after placebo-PDT. Differences were sustained during the complete follow-up period (after 6, 9 and 12 months).Recurrence rates of cleared lesions 12 months after therapy were 12% for Alacare-PDT and 18% for cryosurgery (Odds Ratio 0.627; 95% CI [0.461, 0.854]).

5.2 Pharmacokinetic properties

Pharmacokinetic data from a clinical trial in patients with mild to moderate actinic keratoses on the head and/or face, who had 8 Alacare plasters applied for 4h, showed a baseline corrected Cmax of 16.4 µg/L and an AUC_{0-24} of 101.4 µg*h/L of systemic exogenous 5-aminolevulinic acid. Tmax was at 4 hours. The excretion of 5-ALA in urine during the first 12 hours after application was low. The maximum excretion was 2.06 % of the total dose, the median was 1.39 % PPIX was not detected in any of the plasma samples.

In another clinical trial in 12 AK patients with mild to moderate AK lesions on the head and/or face, it could be shown that Alacare-induced PPIX specific fluorescence is higher in AK lesions than in normal skin and increases with duration of the Alacare exposure. However, extending application interval beyond 4h did not result in higher PPIX fluorescence.

5.3 Preclinical safety data

Preclinical studies on general toxicity and genotoxicity studies in the presence or absence of photoactivation, do not indicate potential risks for man. Conventional carcinogenicity studies have not been performed with 5- aminolevulinic acid. Studies reported in the literature do not indicate a carcinogenic potential. Studies on the reproductive function have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Plasters: Acrylic pressure sensitive adhesive
(Poly[(2-ethylhexyl)acrylate-co-methylacrylate-co-acrylic acid-co-glycidylmethacrylate])

Backing film: Pigmented polyethylene Aluminium vapor coated polyester

Release liner (polyethylene terephthalate film) which is removed prior to application.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
Use within 3 months after first opening.

6.4 Special precautions for storage

After opening store plaster in the sachet in order to protect from light.

6.5 Nature and contents of container

4 medicated plasters sealed in protective sachets consisting of 4 layers: paper (outer layer), polyethylene LDPE, aluminium, ethylene copolymer (inner layer).

Pack sizes of 4 or 8 medicated plasters (1 or 2 protective sachet[s]).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

After removal, the used patch should be folded in half, adhesive side inwards so that the adhesive is not exposed, and then discarded safely.

7 MARKETING AUTHORISATION HOLDER

Photonamic GmbH & Co. KG
Eggerstedter Weg 12
25412 Pinneberg
Germany

8 MARKETING AUTHORISATION NUMBER

PA2071/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th August 2009
Date of last renewal: 8th June 2014

10 DATE OF REVISION OF THE TEXT

February 2019