Ameluz 78 mg/g gel

Summary of Product Characteristics Updated 16-Mar-2021 | Biofrontera Pharma GmbH

1. Name of the medicinal product

Ameluz 78 mg/g gel

2. Qualitative and quantitative composition

One gram (g) gel contains 78 mg of 5-aminolaevulinic acid (as hydrochloride).

Excipients with known effect

One gram gel contains 2.4 mg sodium benzoate (E211), 3 mg soybean phosphatidylcholine, and 10 mg propylene glycol.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Gel.

White to yellowish gel.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of actinic keratosis of mild to moderate severity (Olsen grade 1 to 2; see section 5.1) and of field cancerization in adults.

Treatment of superficial and/or nodular basal cell carcinoma unsuitable for surgical treatment due to possible treatment-related morbidity and/or poor cosmetic outcome in adults.

4.2 Posology and method of administration

Ameluz should only be administered under the supervision of a physician, a nurse or other healthcare professional experienced in the use of photodynamic therapy.

Posology in adults

For treatment of actinic keratoses (AK) of the face or scalp, one session of photodynamic therapy (with daylight or red-light lamp) shall be administered for single or multiple lesions or entire fields with cancerization (areas of skin where multiple AK lesions are surrounded by an area of actinic and sun-induced damage within a limited field). *For treatment of actinic keratoses (AK) in the body region trunk, neck or extremities,* one session of narrow spectrum red-light photodynamic therapy shall be administered. Actinic keratosis lesions or fields shall be evaluated three months after treatment. Treated lesions or fields that have not completely resolved after 3 months shall be retreated.

For treatment of basal cell carcinoma (BCC), two sessions of photodynamic therapy with red-light lamp shall be administered for one or multiple lesions with an interval of about one week between sessions. Basal cell carcinoma lesions shall be evaluated three months after last treatment. Treated lesions that have not completely resolved after 3 months shall be retreated.

Paediatric population

There is no relevant use of Ameluz in the paediatric population. No data are available.

Method of administration

Ameluz is for cutaneous use.

Treatment of AK, field cancerization and BCC using a red-light lamp:

a) Preparation of the lesions: Before administration of Ameluz, all lesions should be carefully wiped with an ethanol or isopropanol-soaked cotton pad to ensure degreasing of the skin. Scales and crusts should be removed accurately and all lesion surfaces roughened gently. Care should be taken to avoid bleeding. Nodular BCC lesions are often covered by an intact epidermal keratin layer which should be removed. Exposed tumour material should be removed gently without any attempt to excise beyond the tumour margins.

b) Application of the gel: Ameluz should be applied to the lesion area or entire cancerized fields of about 20 cm^2, using glove protected fingertips or a spatula. The gel should cover the lesions or entire fields and approximately 5 mm of the surrounding area with a film of about 1 mm thickness. The gel should be allowed to dry for approximately 10 minutes, before a light-tight dressing is placed over the treatment site. Following 3 hours of incubation, the dressing should be removed and the remnant gel wiped off. The gel can be administered to healthy skin around the lesions, whereas application near the eyes, nostrils, mouth, ears or mucosa should be avoided (keep a distance of 1 cm). Direct contact of Ameluz with the eyes or mucous membrane should be avoided. In case of accidental contact, rinsing with water is recommended.

c) Illumination: Immediately after cleaning the lesions, the entire treatment area will be illuminated with a red light source, either with a narrow spectrum around 630 nm and a light dose of approximately 37 J/cm^2 or a broader and continuous

spectrum in the range between 570 and 670 nm with a light dose between 75 and 200 J/cm^2. 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 the illumination time. These factors vary with lamp type. The light dose delivered should be monitored if a suitable detector is available. During illumination the lamp should be fixed at the distance from the skin surface that is indicated in the user manual. A narrow spectrum lamp is recommended to achieve higher clearance rates. Symptomatic treatment of transient adverse site reactions may be considered. A broader and continuous spectrum may be used if narrow-spectrum light sources are not tolerated (see sections 4.8 and 5.1). See also section 6.6.

Note: Efficacy of Ameluz in the treatment of AK in the body regions trunk, neck and extremities has been demonstrated only in the scope of narrow-spectrum PDT. There are no data for these body regions with broader spectrum lamps PDT or with daylight PDT.

Treatment of AK and field cancerization with daylight:

a) *Considerations before treatment:* Daylight treatment should only be used if the conditions are suitable to stay comfortably outdoors for two hours (with temperatures > 10 °C). If the weather is rainy, or is likely to become so, daylight treatment should not be used.

b) *Preparation of the lesions*: Sunscreen should be applied 15 min prior to lesion pretreatment in order to protect sun exposed skin. Only sunscreen with chemical filters and SPF 30 or higher should be used. Sunscreens with physical filters such as titanium dioxide, zinc oxide, etc. should not be used, as these inhibit light absorption and may therefore impact efficacy.

Before administration of Ameluz, all lesions should be carefully wiped with an ethanol or isopropanol-soaked cotton pad to ensure degreasing of the skin. Scales and crusts should be removed carefully and all lesion surfaces roughened gently. Care should be taken to avoid bleeding.

c) *Application of the* gel: A thin layer of Ameluz should be applied to the lesion area or entire cancerized fields using glove protected fingertips or a spatula. The gel should cover the lesions or entire fields and approximately 5 mm of the surrounding area. No occlusive dressing is necessary. The gel can be administered to healthy skin around the lesions, whereas application near the eyes, nostrils, mouth, ears or mucosa should be avoided (keep a distance of 1 cm). Direct contact of Ameluz with the eyes or mucous membrane should be avoided. In case of accidental contact, rinsing with water is recommended. The gel should not be wiped off during the entire daylight PDT.

d) *Illumination using daylight for AK treatment*: If conditions are suitable (see section a. *Considerations before treatment)*, patients shall go outside within 30 minutes after application of the gel and stay for 2 continuous hours in full daylight. Taking shelter in the shade in hot weather is acceptable. Interruption of the time outdoors should be compensated by a longer illumination time. Remaining gel will be removed after completion of light exposure.

Lesions should be re-assessed after three months, at which point any residual lesions or fields may be retreated. It is recommended that the response of BCC lesions may be confirmed by histological examination of biopsy material, if considered necessary. Subsequently, close long-term clinical monitoring of BCC is recommended, with histology if necessary.

4.3 Contraindications

• Hypersensitivity to the active substance, to porphyrins, to soya or peanuts, or to any of the excipients listed in section 6.1.

• 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 erythemtosus.

4.4 Special warnings and precautions for use

Risk of Transient Global Amnesia (TGA)

Photodynamic therapy (PDT) may be a precipitating factor for transient global amnesia in very rare instances. Although the exact mechanism is not known, stress and pain associated with PDT may increase the risk to develop transient amnesia. If amnesia is observed, the PDT must be discontinued immediately (see section 4.8).

Use of immunosupressants

As inflammatory response is important for the effect of PDT, the trials investigating the efficacy and safety of Ameluz excluded patients who were undergoing treatment with immunosuppression therapy. No experience exists for the use of Ameluz in patients taking immunosuppressants.Therefore, the use of immunosuppressants during treatment with Ameluz is not recommended.

Ameluz should not be used on bleeding lesions

Any bleeding must be stopped before application of the gel. No experience exists for the use of Ameluz in patients with inherited or acquired coagulation defects. Special care should be taken to avoid bleeding during lesion preparation in such patients (see section 4.2).

Risk of mucous membrane and eye irritation

Ameluz can cause mucous membrane or eye irritation. The excipient sodium benzoate may be mildly irritant to the skin, eyes and mucous membranes. Propylene glycol may cause irritation.

Special care should be taken to avoid applying Ameluz into eyes or to mucous membranes. In case of accidental contact, the site must be rinsed with water.

Ameluz should not be used on skin areas affected by other diseases or tattoos.

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 malignant skin cancers) as well as tattoos. No experience exists with these situations.

Ameluz transiently increases phototoxicity

Any UV-therapy should be discontinued before treatment. As a general precaution, sun exposure on the treated lesion sites and surrounding skin should be avoided for approximately 48 hours following treatment. 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.

Risk of allergic reaction

Ameluz contains soybean phosphatidylcholine and should not be applied to patients known to be allergic to peanut or soya (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

Ameluz does not increase 5-aminolaevulinic acid or protoporphyrin IX plasma levels following topical application.

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of 5-aminolaevulinic acid in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Ameluz during pregnancy.

Breast-feeding

It is unknown whether 5-aminolaevulinic acid/metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued for 12 hours after treatment with Ameluz.

Fertility

There are no data available on the effect of 5-aminolaevulinic acid on fertility.

4.7 Effects on ability to drive and use machines

Ameluz has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

In clinical trials with Ameluz, local skin reactions at the application site were observed in most of the subjects treated for actinic keratosis and basal cell carcinoma. This is to be expected as the therapeutic principle of photodynamic therapy is based on phototoxic effects of protoporphyrin IX which is synthesized from the active ingredient 5-aminolaevulinic acid.

The most common signs and symptoms are application site irritation, erythema, pain, and oedema. The intensity of these effects is dependent on the type of illumination used for photodynamic therapy. The increased effects correlate with the higher clearance rate of narrow spectrum lamps (see section 5.1). Intensity of adverse reactions, particularly pain, was lower when Ameluz was used in combination with daylight PDT.

Most adverse reactions occur during illumination or shortly afterwards. The symptoms are usually of mild or moderate intensity (investigator's assessment on a 4-point scale), and last for 1 to 4 days in most cases; in some cases, however, they may persist for 1 to 2 weeks or even longer. In rare cases, the adverse reactions required interruption or discontinuation of the illumination.

Tabulated list of adverse reactions

The incidence of adverse reactions in 624 subjects exposed to photodynamic therapy with Ameluz in pivotal clinical trials is listed below. All these adverse reactions were non serious. The table additionally includes serious adverse reactions reported post-marketing. Frequencies are defined as 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), and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Summary of related adverse drug reactions (ADRs) reported in patients treated with photodynamic therapy with 5-aminolaevulinic acid

System organ class	Frequency	Adverse reaction
Infections and infestations	Uncommon	At application site: Pustules
		Not at application site: Rash pustular
Psychiatric disorders	Uncommon	Nervousness
Nervous system disorders	Common	Headache
	Uncommon	Transient global amnesia (incl. confusion and disorientation)*, Dysaesthesia
Eye disorders	Uncommon	Eyelid oedema, vision blurred, visual impairment
Skin and subcutaneous disorders	Uncommon	Blister, dry skin, petechiae, skin tightness
Musculoskeletal and connective tissue disorders	Uncommon	Back pain
General disorders and administration site conditions	Very common	At application site: Erythema, pain (incl. burning pain), irritation, pruritus, oedema, scab, exfoliation, induration, paraesthesia
	Common	At application site: Vesicles, discharge, erosion, reaction, discomfort, hyperalgesia, haemorrhage, warmth
	Uncommon	At application site: Discoloration, ulcer, swelling, inflammation, eczema infected, hypersensitivity*[1]
		Not at application site: Chills, feeling hot, pyrexia, pain, fatigue, ulcer, swelling
Injury, poisoning and procedural complications	Uncommon	Wound secretion
Vascular disorders	Uncommon	Hot flush

* Data from post-marketing period.

[1] This reaction also occurs before illumination.

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 the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdose following topical administration is unlikely and has not been reported in clinical studies. If Ameluz is accidentally ingested, systemic toxicity is unlikely. Protection from sun light exposure for 48 hours and observation are nevertheless recommended.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, sensitizers used in photodynamic/radiation therapy, ATC code: L01XD04

Mechanism of action

Following topical application of 5-aminolaevulinic acid (ALA), the substance is metabolized to protoporphyrin IX, a photoactive compound which accumulates intracellularly in the treated actinic keratosis and basal cell carcinoma lesions. Protoporphyrin IX is activated by illumination with red light of a suitable wavelength and energy. In the presence of

oxygen, reactive oxygen species are formed. The latter causes damage of cellular components and eventually destroys the target cells.

Clinical efficacy and safety

Treatment of actinic keratosis (AK) and field cancerization:

Efficacy and safety of Ameluz for the treatment of actinic keratosis (AK) has been evaluated in 746 patients enrolled in clinical trials. In clinical phase III, a total of 486 patients were treated with Ameluz. All patients had at least 4 mild to moderate actinic keratosis lesions. The application site preparation and duration of incubation followed the description under section 4.2. If not completely cleared 12 weeks after initial treatment, lesions or cancerized fields were treated a second time with an identical regimen.

A) Photodynamic therapy with red-light for AK of face and scalp

In study ALA-AK-CT002, a randomised, observer blinded clinical trial with 571 AK patients and a follow-up duration of 6 and 12 months, photodynamic therapy with Ameluz was tested for non-inferiority to a commercially registered cream containing 16% methyl-aminolevulinate (MAL, methyl-[5-amino-4-oxopentanoate]) and superiority over placebo. The red light source was either a narrow light spectrum lamp (Aktilite CL 128 or Omnilux PDT) or a lamp with a broader and continuous light spectrum (Waldmann PDT 1200 L, or Hydrosun Photodyn 505 or 750). The primary endpoint was complete patient clearance 12 weeks after the last photodynamic therapy. Ameluz (78.2%) was significantly more effective than MAL (64.2%, [97.5%- confidence interval: 5.9; ∞]) and placebo (17.1%, [95%-confidence interval: 51.2; 71.0]). Total lesion clearance rates were higher for Ameluz (90.4%) compared to MAL (83.2%) and placebo (37.1%). Clearance rates and tolerability were dependent on the illumination source. The following table presents the efficacy and the adverse reactions transient pain and erythema occurring at the application site during photodynamic therapy with different light sources:

Table 2a: Efficacy and adverse reactions (transient pain and erythema) occurring at the application site during photodynamic therapy with different light sources for the treatment of AK in clinical trial ALA-AK-CT002

Light source	Medicinal product	Total patient clearance (%)	Application site erythema (%)			Application site pain (%)		
			mild	moderate	severe	mild	moderate	severe
Narrow spectrum	Ameluz	85	13	43	35	12	33	46
	MAL	68	18	43	29	12	33	48
Broad spectrum	Ameluz	72	32	29	6	17	25	5
	MAL	61	31	33	3	20	23	8

Clinical efficacy was re-assessed at follow-up visits 6 and 12 months after the last photodynamic therapy. Recurrence rates after 12 months were slightly better for Ameluz (41.6%, [95%-confidence interval: 34.4; 49.1]) as compared to MAL (44.8%, [95%-confidence interval: 36.8; 53.0]) and dependent on the light spectrum used for illumination, in favour of narrow spectrum lamps. Prior to the decision to undergo photodynamic therapy it should be taken into consideration that the probability of a subject to be completely cleared 12 months after the last treatment was 53.1% or 47.2% for treatment with Ameluz and 40.8% or 36.3% for MAL treatment with narrow spectrum lamps or all lamp types, respectively. The probability of patients in the Ameluz group to require only 1 treatment and remain completely cleared 12 months after the photodynamic therapy was 32.3%, that of patients in the MAL group 22.4% on average with all lamps.

Cosmetic outcome assessed 12 weeks after the last photodynamic therapy (with baseline sum score 0 excluded) was judged as: very good or good in 43.1% of subjects in the Ameluz group, 45.2% in the MAL group and 36.4% in the placebo group; and unsatisfactory or impaired in 7.9%, 8.1% and 18.2% of subjects, respectively.

In study ALA-AK-CT003, Ameluz was also compared with placebo treatment in a randomised, double-blind clinical trial enrolling 122 AK patients. The red light source provided either a narrow spectrum around 630 nm at a light dose of 37 J/cm^2 (Aktilite CL 128) or a broader and continuous spectrum in the range between 570 and 670 nm at a light dose of 170 J/cm^2 (Photodyn 750). The primary endpoint was complete patient clearance after 12 weeks following the last photodynamic therapy. Photodynamic therapy with Ameluz (66.3%) was significantly more effective than with placebo (12.5%, $p < 0.0001$). Total lesion clearance was higher for Ameluz (81.1%) compared to placebo (20.9%). Clearance rates and tolerability were dependent on the illumination source in favour of the narrow spectrum light source. Clinical efficacy was maintained during the follow-up periods of 6 and 12 months after the last photodynamic therapy. Prior to the decision to undergo photodynamic therapy it should be taken into consideration that the probability of a subject to be completely cleared 12 months after the last treatment was 67.5% or 46.8% for treatment with Ameluz with narrow spectrum lamps or all lamp types, respectively. The probability to require only one treatment with Ameluz and remain completely cleared 12 months later was 34.5% on average with all lamps.

Table 2b: Efficacy and adverse reactions (transient pain and erythema) occurring at the application site during photodynamic therapy with different light sources for the treatment of AK in clinical trial ALA-AK-CT003

Light source	Medicinal	Total patient	Application site erythema (%)	Application site pain (%)

	product	clearance (%)						
			mild	moderate	severe	mild	moderate	severe
Narrow spectrum	Ameluz	87	26	67	7	30	35	16
Broad spectrum	Ameluz	53	47	19	0	35	14	0

In both AK studies ALA-AK-CT002 and -CT003 the clearance rates were higher after illumination with narrow light spectrum devices but the incidence and intensity of administration site disorders (e.g. transient pain, erythema) increased in patients illuminated with these devices (see tables above and section 4.8).

The cosmetic outcome was assessed as very good or good in 47.6% of the subjects in the Ameluz group compared to 25.0% of subjects in the placebo group. An unsatisfactory or impaired cosmetic outcome was judged for 3.8% of the subjects in the Ameluz group and in 22.5% of the subjects in the placebo group.

Field cancerization is characterised by an area of skin where multiple AK lesions are present and there is likely to be an underlying and surrounding area of actinic damage (a concept known as field cancerization or field change); the extent of this area may not be evident visually or by physical examination. In a third randomised, double-blind clinical trial, ALA-AK-CT007, enrolling 87 patients, Ameluz and placebo were compared on entire treatment fields (field cancerization) containing 4 to 8 AK lesions in a field area of maximum 20 cm^2. The red light source provided a narrow spectrum around 635 nm at a light dose of 37 J/cm^2 (BF-RhodoLED). Ameluz was superior to placebo with respect to patient complete clearance rates (90.9% vs. 21.9% for Ameluz and placebo, respectively; $p < 0.0001$) and lesion complete clearance rates (94.3% vs. 32.9%, respectively; $p < 0.0001$), as controlled 12 weeks after the last PDT. 96.9 % of patients with AK on the face or forehead were cleared from all lesions, 81.8 % of patients with AK on the scalp were totally cleared. Lesions of mild severity were cleared by 99.1 % vs. 49.2 %, those of moderate severity by 91.7 % vs. 24.1 % for treatment with Ameluz and placebo, respectively. After only 1 PDT complete patient clearance resulted in 61.8 % vs. 9.4 %, and complete lesion clearance in 84.2 % vs. 22.0 % for Ameluz and placebo treatment, respectively.

Clinical efficacy was maintained during the follow-up periods of 6 and 12 months after the last PDT. After Ameluz treatment, 6.2% of the lesions were recurrent after 6 and additionally 2.9% after 12 months, respectively (placebo: 1.9% after 6 and additionally 0% after 12 months, respectively). Patient recurrence rates were 24.5 % and 14.3 % after 6 months, and additionally 12.2 % and 0 % after 12 months for Ameluz and placebo, respectively.

The field treatment applied in this study allowed the assessment of skin quality changes at baseline and 6 and 12 months after the last PDT by severity. The percentage of patients with skin impairment before PDT and 12 months after PDT is listed in the table below. All skin quality parameters in the treated area continuously improved up to the 12-month follow-up time point.

Table 3a: Skin quality parameters in the treated area during 12- month follow-up (ALA-AK-CT007)

Type of skin impairment	Severity	AMELUZ		Placebo	
		Before PDT (%)	12 months after PDT (%)	Before PDT (%)	12 months after PDT (%)
Roughness/ dryness/ scaliness	None	15	72	11	58
	Mild	50	26	56	35
	Moderate/ severe	35	2	33	8
Hyper-pigmentation	None	41	76	30	62
	Mild	52	24	59	35
	Moderate/ severe	7	0	11	4
Hypo-pigmentation	None	54	89	52	69
	Mild	43	11	44	27
	Moderate/ severe	4	0	4	4
Mottled or irregular pigmentation	None	52	82	48	73
	Mild	44	17	41	15
	Moderate/ severe	4	2	11	12

Scarring	None	74	93	74	89
	Mild	22	7	22	12
	Moderate/ severe	4	0	4	0
Atrophy	None	69	96	70	92
	Mild	30	4	30	8
	Moderate/ severe	2	0	0	0

B) Photodynamic therapy with red-light for AK in the region trunk, neck and extremities

In clinical trial ALA-AK-CT010, the efficacy of Ameluz in the treatment of AK on other body regions (extremities, trunk and neck) was compared with placebo treatment in a randomized, double-blind, intra-individual Phase III clinical trial comparing 50 patients with 4-10 AKs on opposite sites of the extremities and/or the trunk/neck. The red light source provided a narrow spectrum around 635 nm at a light dose of 37 J/cm^2 (BF-RhodoLED). The primary endpoint was total lesion clearance 12 weeks after the last photodynamic therapy. Ameluz was superior to placebo with respect to mean lesion complete clearance rates (86.0% vs. 32.9%, respectively) and patient complete clearance rates (67.3% vs. 12.2% for Ameluz and placebo, respectively), as controlled 12 weeks after the last PDT, whereas the rate of lesions assessed as fully cleared by the investigator and simultaneously cleared according to histopathology of a biopsy was lower in both groups: 70.2% in the Ameluz and 19.1 % in the placebo group.

C) Photodynamic therapy with daylight for AK of the face or scalp

The efficacy of Ameluz in combination with daylight PDT was tested in a randomised, observer-blind, intra-individual phase III clinical trial (ALA-AK-CT009) enrolling 52 patients with 3-9 AKs on each side of the face and/ or scalp. Ameluz was tested for non-inferiority to a cream containing 16% methyl-aminolevulinate (MAL, methyl-[5-amino-4-oxopentanoate]) commercially registered for daylight PDT. Each side of the face/scalp was treated with one of the two products. Daylight PDT was performed outdoors for 2 continuous hours in full daylight. On sunny days, shelter in the shade could be taken should the patient feel uncomfortable in direct sunlight. Rainy periods or time required indoors prolonged the outdoor exposure accordingly. Daylight may not be sufficient for Ameluz daylight treatment during winter months in certain parts of Europe. Ameluz daylight photodynamic therapy is feasible all year long in southern Europe, from February to October in middle Europe, and from March to October in northern Europe.

The complete lesion clearance rate for Ameluz in combination with a single daylight PDT was 79.8%, compared to 76.5% for comparator MAL. The study demonstrated the non-inferiority of Ameluz compared to MAL cream [lower 97.5% -confidence limit 0.0]. Adverse events and tolerability were comparable for both treatments. Clinical efficacy was re-assessed at follow-up visits 6 and 12 months after the last photodynamic therapy (daylight PDT). Mean lesion recurrence rates after 12 months were numerically lower for Ameluz (19.5%) as compared to MAL (31.2%).

Table 3b: Total Lesion Clearance (Percentage of Completely Cleared Individual Lesions) in clinical trial ALA-AK-CT009

	N	BF-200 ALA Mean + SD (%)	N	MAL Mean + SD (%)	Lower 97.5% Confidence Limit	P value
PPS – non-inferiority	49	79.8 +/- 23.6	49	76.5 +- 26.5	0.0	<0.0001
FAS – superiority	51	78.7 +/- 25.8	51	75.0 +/- 28.1	0.0	0.1643

Treatment of basal cell carcinoma (BCC):

Efficacy and safety of Ameluz for the treatment of basal cell carcinoma (BCC) with a thickness of <2mm has been evaluated in 281 patients enrolled in a phase III clinical trial (ALA-BCC-CT008). In this study a total of 138 patients were treated with Ameluz. All patients had 1 to 3 BCC lesions on the face/forehead, bald scalp, extremities and/or neck/trunk. In this study, photodynamic therapy with Ameluz was tested for non-inferiority to a cream containing 16% methyl-aminolevulinate (MAL, methyl-[5-amino-4-oxopentanoate]). The red light source provided a narrow spectrum around 635 nm at a light dose of 37 J/cm^2 (BF-RhodoLED). The primary endpoint was complete patient clearance 12 weeks after the last photodynamic therapy.

The complete patient clearance rate for Ameluz was 93.4%, compared to 91.8% for the comparator MAL. The study demonstrated the non-inferiority of Ameluz compared to MAL cream [97.5% -confidence interval -6.5]. Of the BCC lesions, 94.6% were cleared with Ameluz, 92.9% with MAL. For nodular BCC, 89.3% of the lesions were cleared with Ameluz, 78.6% with MAL. Adverse events and tolerability were comparable for both treatments.

Clinical efficacy was re-assessed at follow-up visits 6 and 12 months after the last photodynamic therapy. Lesion recurrence rates after 6 and 12 months were 2.9% and 6.7%, respectively, for Ameluz, and 4.3% and 8.2% for MAL.

Table 4: Efficacy of PDT for the treatment of BCC for all patients and selected subgroups in clinical trial ALA-BCC-CT008

	Ameluz Patient number n (%)	Ameluz Full patient clearance n (%)	Ameluz Full lesion clearance n (%)	MAL Patient number n (%)	MAL Full patient clearance n (%)	MAL Full lesion clearance n (%)
Total	121	113 (93.4)	140 (94.6)	110	101 (91.8)	118 (92.9)
Subgroups:						
Patients with more than 1 BCC	23 (19.0)	23/23 (100.0)	n.a.	16 (14.5)	14/16 (87.5)	n.a.
Superficial (only)	95 (78.5)	90/95 (94.7)	114/119 (95.8)	83 (75.5)	80/83 (96.4)	95/98 (96.9)
Nodular (only)	21 (17.4)	18/21 (85.7)	25/28 (89.3)	21 (19.1)	16/21 (76.2)	22/28 (78.6)
Others (including mixed s/nBCCs)	5 (4.1)	5/5 (100.0)	1/1 (100.0)	6 (5.5)	5/6 (83.3)	1/1 (100.0)
Thickness >1mm	n.a.	n.a.	8/11 (72.7)	n.a.	n.a.	8/12 (66.7)
BCC on the head (only)	13 (10.7)	10/13 (76.9)	14/17 (82.4)	14 (12.7)	10/14 (71.4)	12/17 (70.6)
BCC on the trunk (only)	77 (63.6)	75/77 (97.4)	95/97 (97.9)	73 (66.4)	70/73 (95.9)	84/87 (96.6)

Patient distribution in the subgroups was similar for both products and represents the distribution in the general population, where more than 70% of BCCs are located in the head/trunk region. BCCs located in this region mainly belong to the superficial subtype. In conclusion, even though subgroup sizes are too small to draw significant conclusions on individual groups, the distribution of the two products to the relevant subgroups is very similar. Thus, it seems not plausible that this could negatively impact the non-inferiority claim of the primary study endpoint or the general trends observed across all subgroups.

In a clinical trial designed to investigate the sensitization potential of ALA with 216 healthy subjects, 13 subjects (6%) developed allergic contact dermatitis after continuous exposure for 21 days with doses of ALA that were higher than doses normally used in the treatment of AK. Allergic contact dermatitis has not been observed under regular treatment conditions.

Actinic keratosis lesion severity was graded according to the scale described by Olsen et al., 1991 (J Am Acad Dermatol 1991; 24: 738-743):

Grade		**Clinical description of severity grading**
0	none	no AK lesion present, neither visible nor palpable
1	mild	flat, pink maculae without signs of hyperkeratosis and erythema, slight palpability, with AK felt better than seen
2	moderate	pink to reddish papules and erythematous plaques with hyperkeratotic surface, moderately thick AK that are easily seen and felt
3	severe	very thick and / or obvious AK

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Ameluz in all subsets of the paediatric population in actinic keratosis. A class waiver exists for basal cell carcinoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

In vitro dermal absorption into human skin was studied using Ameluz containing radiolabelled 5-aminolaevulinic acid (ALA). After 24 hours, the mean cumulative absorption (including accumulation in the dermis) through human skin was 0.2% of the administered dose. Corresponding studies in human skin with actinic keratosis lesions and/or roughened surface were not performed.

Distribution

In a phase II clinical trial, 5-aminolaevulinic acid and protoporphyrin IX serum levels and ALA urine levels were measured before, 3 and 24 hours after administration of Ameluz for photodynamic treatment. None of the post-dose levels were increased in comparison to the naturally occuring pre-dose levels, showing absence of a relevant systemic absorption after topical administration.

A maximal use PK study was conducted in 12 patients bearing at least 10 mild to moderate AKs on the face or forehead. An entire tube of placebo and Ameluz followed by PDT was applied in a fixed sequence design with a washout period of 7 days to evaluate baseline and Ameluz dependent plasma concentrations of ALA and PpIX. In most patients an up to 2.5-fold increase of basic ALA plasma concentrations was observed during the first 3 hours after Ameluz application, which is still within the normal range of previously reported and published endogenous ALA concentrations. The plasma concentrations of metabolite PpIX were generally low in all patients and in none of the patients, an obvious increase of PpIX plasma concentrations was observed after Ameluz application.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on dermal toxicity studies or studies reported in the literature of repeated dose toxicity, genotoxicity and reproductive toxicity.

Carcinogenicity studies have not been performed with ALA.

6. Pharmaceutical particulars

6.1 List of excipients

Xanthan gum

Soybean phosphatidylcholine

Polysorbate 80

Triglycerides, medium-chain

Isopropyl alcohol

Disodium phosphate dihydrate

Sodium dihydrogen phosphate dihydrate

Propylene glycol

Sodium benzoate (E211)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened tube: 24 months

After first opening: 12 weeks

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Keep the tube tightly closed after first opening.

6.5 Nature and contents of container

One outer carton containing one aluminium tube with epoxyphenol inner lacquer and a latex seal and a screw cap of high density polyethylene. Each tube contains 2 g of gel.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Each lamp should be used according to the user manual. Only CE marked lamps should be used, equipped with the necessary filters and/or reflecting mirrors to minimize exposure to heat, blue light and ultra violet (UV) radiation. The technical specifications of the device need to be checked before using a specific light source, and the requirements must be met for the intended light spectrum. Both the patient and the medical personnel conducting the photodynamic therapy should adhere to any safety instructions provided with the light source used. During illumination, patient and medical personnel should wear suitable protective goggles. There is no need to protect healthy untreated skin surrounding the treated actinic keratosis lesions.

7. Marketing authorisation holder

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8. Marketing authorisation number(s)

EU/1/11/740/001

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 14 December 2011

Date of latest renewal: 21 November 2016

10. Date of revision of the text

02/2021

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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