HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AMELUZ safely and effectively. See full prescribing information for AMELUZ.

AMELUZ® (aminolevulinic acid hydrochloride) topical gel
Initial U.S. Approval: 1999

----------RECENT MAJOR CHANGES----------

Indications and Usage (1) 09/2026

----------INDICATIONS AND USAGE----------

AMELUZ, a porphyrin precursor, in combination with photodynamic therapy using BF-RhodoLED or RhodoLED XL lamp, is indicated for:

- lesion-directed and field-directed treatment of actinic keratoses (AK) of mild-to-moderate severity on the face and scalp in adults (1).
- the treatment of superficial basal cell carcinoma (sBCC) in adults (1).

----------DOSAGE AND ADMINISTRATION----------

- Administer AMELUZ only by a health care provider (2.1).
- AMELUZ is for topical use only (2.1).
- Use AMELUZ in combination with red light photodynamic therapy (PDT). See BF-RhodoLED or RhodoLED XL user manual for detailed lamp safety and operating instructions (2.1).
- Photodynamic therapy with AMELUZ involves preparation of lesions, application of the product, occlusion and illumination with BF-RhodoLED or RhodoLED XL lamp (2.3).
- Apply an approximately 1 mm thick layer of AMELUZ to skin lesion(s). Cover individual lesions (sBCC or AK) or the entire AK field with AMELUZ. Include approximately 5 to 10 mm of the surrounding skin. Do not exceed an application area of 60 cm^2. Do not use more than 6 grams of AMELUZ (3 tubes) at one time (2.2).
- Retreat lesions that have not completely resolved approximately 3 months after the initial treatment (2.1).

----------DOSAGE FORMS AND STRENGTHS----------

Topical gel: 10% (3).

----------CONTRAINDICATIONS----------

AMELUZ is contraindicated in patients with:

- Known hypersensitivity to porphyrins (4).
- Known hypersensitivity to any component of AMELUZ, which includes soybean phosphatidylcholine (4).
- Porphyria (4).
- Photodermatoses (4).

----------WARNINGS AND PRECAUTIONS----------

- *Hypersensitivity:* Hypersensitivity reactions have been reported with the use of AMELUZ prior to photodynamic therapy (PDT). If a hypersensitivity reaction occurs, wash off AMELUZ and institute appropriate therapy (5.1).
- *Transient Amnestic Episodes:* Transient amnestic episodes have been reported with use of AMELUZ in combination with PDT. Advise patients to contact their healthcare provider if amnesia occurs after treatment (5.2).
- *Risk of BF-RhodoLED or RhodoLED XL Lamp Induced Eye Injury:* Patients and healthcare providers must wear protective eyewear before operating BF-RhodoLED or RhodoLED XL lamp (5.3).
- *Ophthalmic Adverse Reactions:* Avoid direct contact of AMELUZ with the eyes (5.4).
- *Increased Photosensitivity:* Protect treated lesions from sunlight exposure for 48 hours post treatment (5.5).
- *Risk of Bleeding in Patients with Coagulation Disorders:* Take special care to avoid bleeding during lesion preparation in patients with inherited or acquired coagulation disorders (5.6).
- *Mucous Membrane Irritation:* Avoid direct contact of AMELUZ with the mucous membranes (5.7).

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥10%) were application site erythema, pain/burning, irritation, edema, pruritus, exfoliation, scab, induration, vesicles and paraesthesia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Biofrontera Inc. at 1-844-829-7434 or FDA at 1-800-332-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Concomitant use of the following drugs may enhance the phototoxic reaction to photodynamic therapy: St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones, and tetracyclines (7).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 09/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

AMELUZ, in combination with photodynamic therapy (PDT) using BF-RhodoLED® or RhodoLED® XL lamp, a narrowband, red light illumination source, is indicated for:

- lesion-directed and field-directed treatment of actinic keratoses (AKs) of mild-to-moderate severity on the face and scalp in adults.
- the treatment of superficial basal cell carcinoma (sBCC) in adults.

2. DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

AMELUZ, in conjunction with lesion preparation, is only to be administered by a healthcare provider.

AMELUZ is for topical use only. Not for ophthalmic, oral, or intravaginal use. Avoid using AMELUZ on the eyelid or around the eye *[see Warnings and Precautions (5.4)]*.

AMELUZ treatment, in combination with photodynamic therapy (PDT), is a multi-stage process that requires administration of both AMELUZ and BF-RhodoLED or RhodoLED XL light.

Refer to BF-RhodoLED or RhodoLED XL user manual for detailed lamp safety and operating instructions. Adhere to all safety instructions for both patient and medical personnel while conducting the PDT.

- For treatment of actinic keratoses (AK) of mild-to-moderate severity on the face and scalp: Treat single AK lesions or an entire field affected by multiple AK lesions. Retreat AK lesions that have not completely resolved approximately 3 months after the initial treatment.
- For treatment of superficial basal cell carcinoma (sBCC): Treat one or multiple sBCC lesions with AMELUZ, in combination with PDT, in two sessions spaced 1 to 2 weeks apart. Approximately 3 months after the initial treatment, retreat lesions that have not completely resolved with AMELUZ, in combination with PDT, in two additional sessions, spaced 1 to 2 weeks apart. Perform a follow-up examination 4 to 6 weeks after each treatment cycle to confirm complete response and perform routine skin examinations every 6 to 12 months.

2.2 Recommended Dosage

Apply an approximately 1 mm thick layer of AMELUZ to skin lesion(s). Cover individual lesions (sBCC or AK) or the entire AK field with AMELUZ. Include approximately 5 mm to 10 mm of the surrounding skin. Do not exceed an application area of 60 cm^2. Do not use more than 6 grams of AMELUZ (3 tubes) at one time.

2.3 Administration Instructions

AMELUZ treatment, in combination with PDT, is a multi-stage process:

Step 1. Preparation of Lesions

Before applying AMELUZ, carefully wipe all lesions (sBCC or AK) with an ethanol or isopropanol-soaked cotton pad to ensure degreasing of the skin.

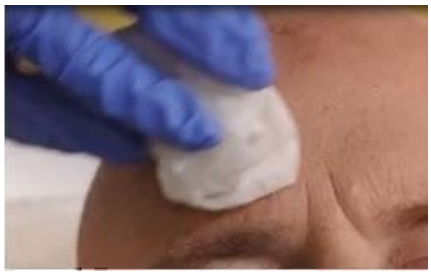


Figure 1A: Degreasing the skin

Thereafter, remove any scaling and crusts and gently roughen all lesion surfaces, taking care to avoid bleeding.

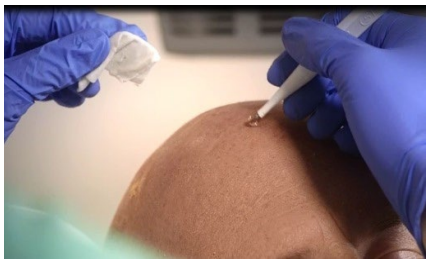


Figure 1B: Removal of scales and crusts (debridement)

Step 2. Application of AMELUZ

Apply AMELUZ using glove protected fingertips or a spatula. Use enough AMELUZ to cover individual lesions (sBCC or AK) or the entire AK field:

- Lesion-directed AK treatment: Apply AMELUZ approximately 1 mm thick to one or more individual AK lesions and include approximately 5 mm of the surrounding healthy skin.
- Field-directed AK treatment: Apply AMELUZ approximately 1 mm thick to the treatment field. Apply AMELUZ to the lesions and the skin between the lesions. Additionally, cover at least 5 mm of the surrounding healthy area.
- Lesion-directed sBCC treatment: Apply AMELUZ approximately 1 mm thick to one or more individual sBCC lesions and include approximately 10 mm of the surrounding healthy skin.

Do not exceed an application area of 60 cm^2 and do not use more than 6 grams of AMELUZ (3 tubes) at one time. AMELUZ can be applied to healthy skin around the lesions. Avoid application near mucous membranes such as the eyes, nostrils, mouth, and ears (keep a distance of at least 10 mm from these areas). In case of accidental contact with mucous membranes, thoroughly rinse with water *[see Warnings and Precautions (5.7)]*.

Allow AMELUZ to dry for approximately 10 minutes before applying occlusive dressing.

Figure 2: Drug application

Step 3. Occlusion for 3 Hours

Cover the area where AMELUZ has been applied with a light-blocking, occlusive dressing. Following 3 hours of occlusion, remove the dressing and wipe off any remaining gel.

Figure 3: Occlusion

Step 4. Illumination with Red Light

For patient and medical personnel, wear suitable protective eyewear during illumination. Avoid staring directly into the light source *[see Warnings and Precautions (5.3)]*.

Illuminate the treatment area with the BF-RhodoLED or RhodoLED XL lamp immediately after removing the occlusive dressing and any remaining gel. BF-RhodoLED and RhodoLED XL lamps are red light sources with a narrow spectrum around 635 nm that deliver a light dose of approximately 37 J/cm^2. Calibration by the operator is not needed; the illumination time is calculated automatically. Physical measures such as cooling with an air stream or nebulized water may help reduce pain during illumination.

Either the BF-RhodoLED or RhodoLED XL lamp can be used:

- BF-RhodoLED has an effective treatment area of 6 cm x 16 cm when an area of 8 cm x 18 cm is illuminated. Position the lamp head 5 cm to 8 cm from the skin's surface. Larger areas can be illuminated in several steps.
- RhodoLED XL has a curved configuration with an effective treatment area up to 23 cm x 29 cm. Position the lamp head of the RhodoLED XL 11 cm to 14 cm from the skin's surface. The smallest recommended number of panels to be used are 3 adjacent panels (see chapter 8.4.6 of RhodoLED XL user manual). For full-face illumination all 5 panels can be used.

Healthy untreated skin surrounding the lesions does not need protection during illumination.

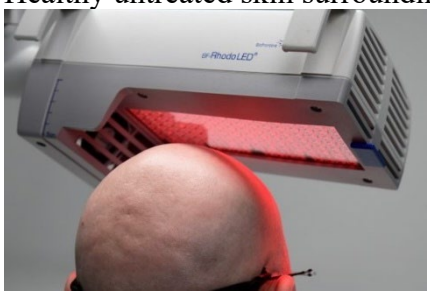


Figure 4A: Illumination with BF-RhodoLED

Figure 4B: Illumination with RhodoLED XL (examples with 3 and 5 panels)

If for any reason the lesions cannot be illuminated within 3 hours after AMELUZ application, rinse off the gel with saline and water. For 2 days, protect the lesion sites and surrounding skin from sunlight or prolonged or intense light (e.g., tanning beds, sun lamps).

3. DOSAGE FORMS AND STRENGTHS

Topical gel: 10% aminolevulinic acid hydrochloride as a white-to-yellowish gel in 2-gram tubes.

4. CONTRAINDICATIONS

AMELUZ is contraindicated in patients with:

- Known hypersensitivity to porphyrins.
- Known hypersensitivity to any of the components of AMELUZ, which includes soybean phosphatidylcholine *[see Warnings and Precautions (5.1)]*.
- Porphyria. AMELUZ use may cause uncontrolled phototoxic effects *[see Warnings and Precautions (5.5)]*.
- Photodermatoses. PDT may worsen the phototoxic or photoallergic reactions *[see Warnings and Precautions (5.5)]*.

5. WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Several cases of hypersensitivity were reported during postmarketing use of AMELUZ prior to PDT illumination *[see Adverse Reactions (6.2)]*. If hypersensitivity reactions occur, clean the

area of skin where AMELUZ was applied and institute appropriate therapy. Inform patients and their caregivers that AMELUZ may cause hypersensitivity, potentially including severe cases (anaphylaxis).

5.2 Transient Amnestic Episodes

Transient amnestic episodes have been reported during postmarketing use of AMELUZ in combination with PDT. Inform patients and their caregivers that AMELUZ in combination with PDT may cause transient amnestic episodes. Advise them to contact the healthcare provider if the patient develops amnesia after treatment.

5.3 Risk of BF-RhodoLED- or RhodoLED XL Lamp-Induced Eye Injury

BF-RhodoLED or RhodoLED XL lamp may cause eye irritation, glare, vision blurred, visual impairment or injury. Before operating the lamp, personnel must refer to the user manual for specific warnings, cautions, and instructions. Eye exposure to the BF-RhodoLED or RhodoLED XL light must be prevented. Protective eye equipment must be used by patients, healthcare providers, and any person present during the illumination period. Avoid staring directly into the light source.

5.4 Ophthalmic Adverse Reactions

Eyelid edema and dry eyes have occurred after PDT with AMELUZ. PDT with AMELUZ can cause ophthalmic adverse reactions. Avoid direct contact of AMELUZ with the eyes. Rinse eyes with water in case of accidental contact.

5.5 Increased Photosensitivity

AMELUZ increases photosensitivity. Avoid sunlight, prolonged or intense light (e.g., tanning beds, sun lamps) on lesions and surrounding skin treated with AMELUZ for approximately 48 hours following treatment, whether exposed to illumination or not. Concomitant use of AMELUZ with other known photosensitizing drugs may increase the risk of phototoxic reaction to PDT *[see Drug Interactions (7)]*.

5.6 Risk of Bleeding in Patients with Coagulation Disorders

AMELUZ has not been tested on patients with inherited or acquired coagulation disorders. Take special care to avoid bleeding during lesion preparation in such patients *[see Dosage and Administration (2.3)]*. Any bleeding must be stopped before application of AMELUZ.

5.7 Risk of Mucous Membrane Irritation

AMELUZ can cause mucous membrane irritation. AMELUZ is intended for topical use only. Avoid direct contact of AMELUZ to the mucous membranes. Rinse with water in case of accidental contact.

6. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Hypersensitivity *[see Warnings and Precautions (5.1)]*.
- Transient Amnestic Episodes *[see Warnings and Precautions (5.2)]*.
- Risk of BF-RhodoLED or RhodoLED XL Lamp Induced Eye Injury *[see Warnings and Precautions (5.3)]*.

- Ophthalmic Adverse Reactions *[see Warnings and Precautions (5.4)]*.
- Increased Photosensitivity *[see Warnings and Precautions (5.5)]*.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Subjects with Mild-to-Moderate Actinic Keratosis

The safety and efficacy of AMELUZ in combination with PDT using a narrow spectrum source was evaluated in three double-blind and placebo-controlled phase 3 trials (Trials 1, 2, and 3), enrolling a total of 299 subjects that were treated with narrow band light. Trial subjects were adults greater than or equal to 49 years of age, and the majority had Fitzpatrick skin type I, II, or III. No subjects had Fitzpatrick skin type V or VI. Approximately 86% of subjects were male, and all subjects were White *[see Clinical Studies (14.1)]*.

For all three trials, the enrolled subjects had mild to moderate AKs (Olsen grade 1 and 2) with 4 to 8 lesions on the face and scalp. Overall, 212 AMELUZ-treated subjects (n=32, n=55, and n=125) and 87 subjects receiving placebo (n=16, n=32, n=39) were illuminated with BF-RhodoLED or similar narrow spectrum lamps. For these trials, the maximal dose was one tube of AMELUZ (2 g) and the size of the application area was up to 20 cm^2.

Local skin reactions at the application site were observed in about 99.5% of subjects treated with AMELUZ and narrow spectrum lamps. The most frequent adverse reactions during and after PDT were application site erythema, pain, burning, irritation, edema, pruritus, exfoliation, scab, induration, and vesicles.

Most adverse reactions occurred during illumination or shortly afterwards, were generally of mild or moderate intensity, and lasted for 1 to 4 days in most cases; in some cases, however, they persisted for 1 to 2 weeks or even longer. Severe pain/burning occurred in up to 30% of subjects. In one case, the adverse reactions required interruption or discontinuation of the illumination.

Table 1 presents the incidence of common (≥1%, <10%) and very common (≥10%) adverse reactions at the application site in Trials 1, 2, and 3.

Table 1: Application Site Adverse Reactions Occurring at ≥1% of the AMELUZ Group and More Frequently than the Vehicle Group in Subjects with Mild-to-Moderate Actinic Keratosis (Trials 1, 2, and 3)

Application Site Adverse Reaction	AMELUZ n=212	Vehicle n=87
Erythema	195 (92%)	34 (39%)
Pain/Burning	195 (92%)	26 (30%)
Irritation	153 (72%)	17 (20%)
Edema	75 (35%)	3 (3%)
Pruritus	72 (34%)	14 (16%)
Exfoliation	41 (19%)	4 (5%)
Scab	41 (19%)	2 (2%)

Induration	26 (12%)	0 (0%)
Vesicles	25 (12%)	1 (1%)
Paresthesia	18 (9%)	2 (2%)
Hyperalgesia	13 (6%)	0 (0%)
Reaction	8 (4%)	2 (2%)
Discomfort	7 (3%)	0 (0%)
Erosion	6 (3%)	0 (0%)
Discharge	4 (2%)	0 (0%)
Bleeding	3 (1%)	0 (0%)
Pustules	3 (1%)	0 (0%)

In Trials 1, 2, and 3, common (≥1%, <10%) adverse reactions not at the application site in AMELUZ-treated subjects were headache, skin exfoliation, chills and eyelid edema.

In Trials 1, 2, and 3, less common (≥0.1%, <1%) application site adverse reactions in AMELUZ-treated subjects were hemorrhage and swelling. Adverse reactions not at the application site were blister, feeling hot, pruritus, pyrexia, scab, nervousness, pain, petechiae, rash pustular, skin erosion and ulcer.

In two open-label clinical trials to evaluate safety and tolerability, 116 subjects with actinic keratosis (AK) on the face and scalp were treated with three tubes (6 g) of AMELUZ applied to a 60 cm² area in combination with PDT. Most adverse reactions observed were consistent with those reported in trials using one tube (2 g) of AMELUZ on a 20 cm² area (Trials 1, 2, and 3) (see Table 1). Additional reactions which occurred in ≥1% of subjects when three tubes (6 g) of AMELUZ were applied to a 60 cm² area included dry eyes, photosensitivity, and application site discoloration, dryness, papules, and fissures.

The frequencies of certain adverse reactions at the application site in these trials—exfoliation, itching, scabbing, and erosion—were more than 10% higher with the larger dose (three tubes, 6 g) and treatment area (60 cm²) compared to the frequencies observed in the trials for the smaller dose (one tube, 2 g) and area (20 cm²). Severe application site pain was reported in 41% of the subjects treated with three tubes (6 g) on a 60 cm² area. Most cases were reported during PDT illumination. A total of 15% of subjects discontinued illumination due to adverse reactions.

Adverse Reactions in Subjects with Superficial Basal Cell Carcinoma

The safety and efficacy of AMELUZ, in combination with PDT using the BF-RhodoLED lamp, was evaluated in a randomized controlled trial enrolling 187 adults (Trial 4) with superficial basal cell carcinoma (sBCC). Subjects received AMELUZ or vehicle followed by exposure to BF-RhodoLED red light. All subjects were White and the majority had Fitzpatrick skin type I, II, or III *[Clinical Studies (14.2)]*.

Most of the enrolled subjects had one sBCC lesion. Approximately 48% of the lesions were located on the neck and/or trunk and 45% of the lesions were located on the extremities.

All subjects treated with AMELUZ and BF-RhodoLED lamp developed at least one adverse reaction at the application site. The most common adverse reactions during and after AMELUZ treatment in combination with PDT were application site pain that may be severe, erythema, pruritus, edema, paraesthesia, scab, induration, and exfoliation.

Table 2: Application Site Adverse Reactions Occurring at ≥1% of the AMELUZ Group and More Frequently than in the Vehicle Group in Subjects with sBCC (Trials 4)

	AMELUZ N = 145		Vehicle N = 42	
Application Site Adverse Reaction				
Pain	138	(95%)	12	(29%)
Erythema	100	(69%)	15	(36%)
Pruritus	73	(50%)	11	(26%)
Edema	42	(29%)	5	(12%)
Paraesthesia	35	(24%)	5	(12%)
Scab	30	(21%)	2	(5%)
Induration	25	(17%)	3	(7%)
Exfoliation	25	(17%)	6	(14%)
Discoloration	13	(9%)	1	(2%)
Vesicles	12	(8%)	1	(2%)
Dysaesthesia	3	(2%)	0	(0%)
Haemorrhage	3	(2%)	0	(0%)
Dryness	2	(1%)	0	(0%)
Hyperaesthesia	2	(1%)	0	(0%)
Swelling	2	(1%)	0	(0%)

Less common (≥0.1%, <1%) application site adverse reactions were atrophy, hypoesthesia, inflammation, ulcer and fatigue. Less common adverse reactions not at the application site were vision blurred, visual impairment, headache, and solar lentigo.

AMELUZ in combination with PDT was also evaluated in another clinical trial (Trial 5) that included 110 adults with sBCC and safety findings were consistent with those observed in Trial 4.

Sensitization Potential of Aminolevulinic Acid

In a clinical trial designed to investigate the sensitization potential of aminolevulinic acid with 216 healthy subjects, 13 subjects (6%) developed allergic contact dermatitis after continuous exposure for 21 days with doses of aminolevulinic acid that were higher than the recommended dose for the treatment of AK or sBCC.

6.2 Postmarketing Experience

The following adverse reactions have been reported during post-approval use of AMELUZ. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: dermatitis allergic.
Nervous system disorders: transient amnestic episodes.
Eye disorders: eye irritation, diplopia, ocular hyperemia, photophobia.
Immune System disorders: hypersensitivity.

7. DRUG INTERACTIONS

There have been no formal studies of the interaction of AMELUZ with other drugs. It is possible that concomitant use of other known photosensitizing drugs, such as St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones and tetracyclines, may enhance the phototoxic reaction to PDT *[see Warnings and Precautions (5.3)]*.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The available data on topical aminolevulinic acid use in combination with PDT in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Animal reproduction studies were not conducted with aminolevulinic acid. Systemic absorption of aminolevulinic acid in humans is low following topical administration of AMELUZ under maximal clinical use conditions *[see Clinical Pharmacology (12.3)]*. It is not expected that maternal use of AMELUZ will result in fetal exposure to the drug.

The background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a risk of birth defects, loss, and other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

No data are available regarding the presence of aminolevulinic acid in human milk, or the effects of aminolevulinic acid on the breastfed infant or on milk production. However, breastfeeding is not expected to result in exposure of the infant to the drug due to the low systemic absorption of aminolevulinic acid in humans following topical administration of AMELUZ under maximal clinical use conditions *[see Clinical Pharmacology (12.3)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AMELUZ and any potential adverse effects on the breastfeeding infant from AMELUZ or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of AMELUZ have not been established in pediatric patients. AK and sBCC are not conditions generally seen in the pediatric population.

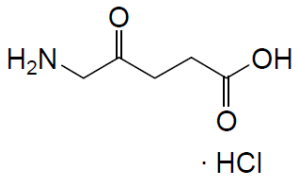
8.5 Geriatric Use

Of the 529 subjects exposed to AMELUZ in randomized, multicenter clinical trials, 72% (382/529) of the subjects were 65 years old and over. No overall differences in safety or effectiveness were observed between these subjects and younger adult subjects, but greater sensitivity of some older individuals cannot be ruled out.

11. DESCRIPTION

AMELUZ (aminolevulinic acid hydrochloride) topical gel, 10% is a non-sterile white-to-yellowish gel. The gel formulation contains a nanoemulsion.

Aminolevulinic acid, a porphyrin precursor, is a white to off-white crystalline solid. It is readily soluble in water, methanol, and dimethylformamide. Its chemical name is 5-amino-4-oxo-pentanoic acid hydrochloride, molecular weight is 167.59 and molecular formula is $C_5H_9NO_3 \cdot HCl$. The structural formula of aminolevulinic acid hydrochloride is represented below:



Each gram of AMELUZ contains 100 mg of aminolevulinic acid hydrochloride (equivalent to 78 mg aminolevulinic acid) as the active ingredient and the following inactive ingredients: xanthan gum, soybean phosphatidylcholine, polysorbate 80, medium-chain triglycerides, isopropyl alcohol, dibasic sodium phosphate, monobasic sodium phosphate, sodium benzoate and purified water.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Photoactivation following topical application of AMELUZ occurs when aminolevulinic acid (prodrug) is metabolized to protoporphyrin IX (PpIX), a photoactive compound which accumulates in the skin. When exposed to red light of a suitable wavelength and energy, PpIX is activated resulting in an excited state of porphyrin molecules. In the presence of oxygen, reactive oxygen species are formed which causes damage to cellular components and eventually destroys the cells. AMELUZ photodynamic therapy of AK and sBCC lesions utilizes photoactivation of topically applied AMELUZ resulting from BF-RhodoLED or RhodoLED XL illumination, which provides a red light of narrow spectrum and a light dose of approximately 37 J/cm^2.

12.2 Pharmacodynamics

The pharmacodynamics of AMELUZ is unknown.

12.3 Pharmacokinetics

Aminolevulinic acid acts as a prodrug to the photoactive metabolite, protoporphyrin IX (PpIX).

Pharmacokinetics (PK) of aminolevulinic acid and PpIX were evaluated in two trials:

In the first trial, a single dose of one entire tube of AMELUZ (2 grams) was applied under occlusion for 3 hours followed by PDT to a total area of 20 cm^2 in 12 adult subjects with mild to moderate AK with at least 10 AK lesions on the face or forehead. The mean ± SD baseline plasma aminolevulinic acid concentration was 20.16 ± 16.53 ng/mL. In most subjects, an up to

2.5-fold increase of aminolevulinic acid plasma concentrations was observed during the first 3 hours after AMELUZ application. The mean ± SD area under the concentration time curve (AUC_{0-t}) and maximum concentration (C_{max}) for baseline corrected aminolevulinic acid (n=12) were 142.83 ± 75.50 ng·h/mL and 27.19 ± 20.02 ng/mL, respectively. The median T_{max} (time at which C_{max} occurred) was 3 hours.

The mean ± SD baseline plasma PpIX concentration was 3.27 ± 2.40 ng/mL (n=12). The majority (about 55%) of the PpIX concentrations were below the limit of quantification (LOQ = 1 ng/mL) and baseline corrected values were negative in all subjects except for one. The baseline corrected AUC_{0-t} and C_{max} in the single subject was 0.07 ng·h/mL and 0.29 ng/mL, respectively.

In the second trial, a single dose of three entire tubes of AMELUZ (6 grams) was applied under occlusion for 3 hours followed by PDT to a total area of 60 cm^2 in 16 adult subjects with mild to severe AK with at least 12 AK lesions on the face and scalp. The mean ± SD baseline plasma aminolevulinic acid concentration was 13.53 ± 1.58 ng/mL. In most subjects, an up to 2.5-fold increase of aminolevulinic acid plasma concentrations was observed during the first 3 hours after AMELUZ application. The mean ± SD area under the concentration time curve (AUC_{0-t}) and maximum concentration (C_{max}) for baseline corrected aminolevulinic acid (n=16) were 134.24 ± 87.97 ng·h/mL and 33.85 ± 21.85 ng/mL, respectively. The median T_{max} (time at which C_{max} occurred) was 3 hours.

The mean ± SD baseline plasma PpIX concentration was 1.93 ± 0.42 ng/mL (n=15). The mean ± SD baseline corrected C_{max} of PpIX was 0.67 ± 0.78 ng/mL (n=13) with a median T_{max} of 4 hours. The baseline corrected PpIX concentrations in 14 of 15 subjects were < 1 ng/mL.

PK was not assessed in subjects with sBCC.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to evaluate the carcinogenic potential of AMELUZ or aminolevulinic acid have not been performed.

Aminolevulinic acid revealed no evidence of mutagenic or clastogenic potential based on the results of three in vitro genotoxicity tests (Ames assay, HPRT test in V79 cells, and Human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (mouse micronucleus assay). These genotoxicity studies were conducted without exposure to light. There is a literature report that indicates that aminolevulinic acid may cause genotoxic effects in the presence and in the absence of activating light. These genotoxic effects are likely caused by the formation of reactive oxygen species.

Animal fertility studies have not been conducted with aminolevulinic acid because of the negligible systemic absorption of aminolevulinic acid in humans following topical administration of AMELUZ under maximal clinical use conditions.

14. CLINICAL STUDIES

14.1 Clinical Trials in Subjects with Mild-to-Moderate Actinic Keratosis

The efficacy and safety of AMELUZ, in combination with PDT using a narrow spectrum (red light lamp) source, for the treatment of mild-to-moderate AK were evaluated in three randomized, multicenter trials (Trial 1, Trial 2, and Trial 3). Trials 2 and 3 were vehicle-controlled and double-blind. Trial 1 was double-blind with respect to vehicle and observer-blind regarding the active comparator arm. All clinical trials included a follow-up assessment after 6 and 12 months.

In these trials, 212 subjects with 4 to 8 mild to moderate AK lesions on the face/forehead and/or bald scalp were treated with up to one tube (2 grams) of AMELUZ on an application area up to 20 cm^2 and a narrow band spectrum lamp. Subjects ranged from 49 to 87 years of age (mean 71 years), and 92% had Fitzpatrick skin type I, II, or III. No subjects had Fitzpatrick skin type V or VI. Approximately 86% of subjects were male, and all subjects were White.

All sessions were comprised of lesion preparation to roughen the surface and remove crusts, application of AMELUZ with occlusion for 3 hours, and removal of the residual gel. Subsequently, the entire treatment area was illuminated with a narrow spectrum red light source, a lamp of either 630 nm or 633 nm and a light dose of approximately 37 J/cm^2. In Trial 3, illumination was performed with BF-RhodoLED, a red light source with a narrow spectrum around 635 nm and a light dose of approximately 37 J/cm^2.

In all trials, the lesions that were not completely cleared 12 weeks after the initial treatment were treated a second time with an identical regimen. In the trials, 42% (88/212) of subjects needed a second treatment.

The primary endpoint for all trials was complete clearance 12 weeks after the last PDT. The results of Trials 1, 2 and 3 are presented in Table 3.

Table 3: Complete Clearance 12 Weeks After the Last Narrow Spectrum PDT in Subjects with Actinic Keratoses in Trials 1, 2 and 3

	AMELUZ	Vehicle
Trial 1	106/125 (85%)	5/39 (13%)
Trial 2	27/32 (84%)	2/16 (13%)
Trial 3	50/55 (91%)	7/32 (22%)

Subjects who achieved complete clearance at 12 weeks after the last PDT entered a 12-month follow-up period. In the three trials, subjects who received AMELUZ with the narrowband PDT and achieved complete clearance 12 weeks after the last PDT had recurrence rates of 14%, 11%, and 25%, respectively (at 6 months) and 40%, 22%, and 37%, respectively (at 12 months). Recurrence was defined as the percentage of subjects with at least one recurrent lesion during the 6-month or 12-month follow-up period in subjects with completely cleared lesions 12 weeks after the last PDT.

14.2 Clinical Trials in Subjects with Superficial Basal Cell Carcinoma

The efficacy and safety of AMELUZ, in combination with PDT using the BF-RhodoLED lamp, for the treatment of superficial basal cell carcinoma (sBCC) were evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (Trial 4 [NCT03573401]).

In this trial, 187 subjects with at least 1 histologically confirmed sBCC lesion on the face/forehead, bald scalp, extremities and/or neck/trunk were treated. Most of the enrolled

subjects had one sBCC lesion. Approximately 48% of the lesions were located on the neck and/or trunk and 45% of the lesions were located on the extremities. For each subject, one lesion was defined as Main Target Lesion (preselected for surgical excision and histological analysis 12 weeks after start of the last PDT cycle). Additional lesions in the same illumination area were treated but not excised. Subjects ranged from 33 to 89 years of age (mean 63 years), and 95% had Fitzpatrick skin type I, II, or III. No subject had Fitzpatrick skin type V or VI. All subjects were White, with 2% of Hispanic or Latino ethnicity. Approximately 57 % of subjects were male.

All subjects received at least one PDT cycle consisting of two PDTs sessions 7 to 14 days apart. Each session was performed with up to one tube (2 grams) of AMELUZ or vehicle and the BF-RhodoLED lamp. Sessions were comprised of lesion preparation (degreasing with alcohol, and careful debridement to remove scales or crusts), application of AMELUZ or vehicle with occlusion for 3 hours, and removal of the residual gel. Subsequently, the treatment area was illuminated with the BF-RhodoLED lamp at approximately 37 J/cm^2.

Subjects clinically diagnosed as partial responders or non-responders 12 weeks after the start of the first PDT cycle received a second PDT cycle (52 %, 97/184; 62/145 (42.8%) in the in the AMELUZ group and 35/42 (83.3%) in the vehicle group).

The primary efficacy endpoint was the composite clinical and histological complete response of the Main Target Lesion 12 weeks after the start of the last PDT cycle. Clinical response was based on clinical assessment only. Histological response was determined by biopsy.

Efficacy results for the primary and key secondary endpoints are presented in Table 4.

Table 4: Efficacy Results at 12 Weeks After the Start of the Last PDT Cycle in Subjects with sBCC in Trial 4

	AMELUZ (n=145)	Vehicle (n=42)
Primary Endpoint		
Main Target Lesion composite clinical and histological response, n(%)	95 (66%)	2 (5%)
Key Secondary Endpoints:		
Main Target Lesion histological response	110 (76%)	8 (19%)
Main Target Lesion clinical response	121 (83%)	9 (21%)
Subject complete clinical response [1]	119 (82%)	9 (21%)
Subject complete response [2]	93 (64%)	2 (5%)

[1] Subject complete clinical response defined as all (main and additional) target lesions assessed as clinically clear 12 weeks after the start of last PDT cycle.
[2] Subject complete response defined as main target lesion clinically and histologically clear as well as all additional target lesions assessed as clinically clear 12 weeks after the start of last PDT cycle.

At 12 weeks after start of the last PDT cycle, 26/119 (22%) subjects in the AMELUZ group were clinically cleared at target lesions but had histologically confirmed residual sBCC.

16. HOW SUPPLIED/STORAGE AND HANDLING

AMELUZ (aminolevulinic acid hydrochloride) topical gel, 10% is a white-to-yellowish gel. The drug product is supplied in an aluminum tube with a white, high-density polyethylene (HDPE) screw cap. Each tube contains 2 g of gel.

NDC 70621-101-01	2 g tube
NDC 70621-101-10	Cardbox containing one 2 g tube
NDC 70621-101-20	Cardbox containing ten 2 g tubes

Store AMELUZ in a refrigerator, 2°C to 8°C (36°F to 46°F). Excursions permitted to 15°C to 30°C (59°F to 86°F).

After opening, AMELUZ can be stored for up to 12 weeks in a refrigerator at 2°C to 8°C (36°F to 46°F) if the tube is tightly closed.

17. PATIENT COUNSELING INFORMATION

Hypersensitivity

Inform patients and their caregivers that AMELUZ may cause hypersensitivity, potentially including severe cases (anaphylaxis) *[see Warnings and Precautions (5.1)]*.

Transient Amnestic Episodes

Inform patients that transient amnestic episodes have been reported with use of AMELUZ in combination with photodynamic therapy. Advise patients and their families or caregivers to contact their healthcare provider if memory impairment, confusion, or disorientation is observed *[see Warnings and Precautions (5.2)]*.

Increased Photosensitivity

Advise patients that following treatment with AMELUZ, avoid exposure to sunlight, and prolonged or intense light on the treated lesion sites and surrounding skin for approximately 48 hours.

Advise patients to avoid certain medications that may enhance the phototoxic reaction to PDT *[see Warnings and Precautions (5.5) and Drug Interactions (7)]*.

Treatment Site Pain

Inform patients that sensations of burning and pain that may be severe commonly occur during and after treatment with AMELUZ in combination with PDT. Advise patients to contact the healthcare provider if symptoms are severe *[see Adverse Reactions (6.1)]*.

Common Adverse Reactions

Inform patients that treatment with AMELUZ in combination with PDT may result in adverse reactions which include local skin reactions at the application site such as erythema, pain/burning, irritation, edema, pruritus, exfoliation, induration, scab, and vesicles *[see Adverse Reactions (6.1)]*.

AMELUZ, BF-RhodoLED and RhodoLED are registered trade marks of Biofrontera Inc.

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