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----------
Dosage and Administration (2.2, 2.3) 3/2024

----------INDICATIONS AND USAGE----------
AMELUZ, a porphyrin precursor, in combination with photodynamic therapy using BF-RhodoLED or RhodoLED XL lamp, is indicated for the lesion-directed and field-directed treatment of actinic keratoses (AK) of mild-to-moderate severity on the face and scalp (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 or the entire AK-field with AMELUZ. Include approximately 5 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 3 months after the initial treatment (2.2).

----------DOSAGE FORMS AND STRENGTHS----------
Gel: 10% (3).

----------CONTRAINDICATIONS----------
- 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 allergic 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 or confusion 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, and vesicles (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 medications 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: 10/2024

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.

2. DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

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

AMELUZ is for topical use only. Not for ophthalmic, oral, or intravaginal use.

Treat single lesions or an entire field affected by multiple lesions with AMELUZ, in combination with red light photodynamic therapy (PDT). PDT 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.

2.2 Recommended Dosage

Apply an approximately 1-mm thick layer of AMELUZ to skin lesion(s). Cover individual lesions or the entire AK-field with AMELUZ. Include approximately 5 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.

Retreat lesions that have not completely resolved after 3 months after the initial treatment.

2.3 Administration Instructions

PDT is a multi-stage process:

Step 1. Preparation of Lesions

Before applying AMELUZ, carefully wipe all lesions 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.

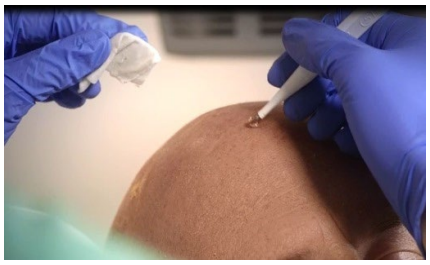


Figure 1B: Removal of scales and crusts

Step 2. Application of AMELUZ

Apply AMELUZ using glove protected fingertips or a spatula. Use sufficient amount of gel to cover individual lesions or the entire field:

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

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. The gel 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 1 cm from these areas). In case of accidental contact with mucous membranes, thoroughly rinse with water *[see Warnings and Precautions (5.7)]*.

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

Figure 2: Drug application

Step 3. Occlusion for 3 Hours

Cover the area where the gel 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 occlusion 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 x 16 cm when an area of 8 x 18 cm is illuminated. Position the lamp head 5-8 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 x 29 cm. Position the lamp head of the RhodoLED XL 11-14 cm from the skin's surface. This usually allows a full-face illumination with the use of 5 panels. The smallest recommended number of panels to be used are 3 adjacent panels (see chapter 8.4.6 of RhodoLED XL user manual).

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

Figure 4A: Illumination with BF-RhodoLED

Figure 4B: Illumination with RhodoLED XL

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 allergic reactions occur, clean the area of skin where the product was applied and institute appropriate therapy. Inform patients and their caregivers that AMELUZ may cause hypersensitivity, potentially including severe courses (anaphylaxis).

5.2 Transient Amnestic Episodes

Transient amnestic episodes have been reported during postmarketing use of AMELUZ in combination with photodynamic therapy. Inform patients and their caregivers that AMELUZ in combination with photodynamic therapy 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, 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 patient, 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 agents 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 the gel.

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.

The clinical program for AMELUZ included 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.

For all three phase 3 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 randomized, multicenter trials which evaluated a maximal dose of one tube of AMELUZ (2 g) and an application area up to 20 cm^2.

Table 1: Incidence of Adverse Reactions Occurring at ≥1% of the AMELUZ Group and More Frequently than the Vehicle Group in Actinic Keratosis Trials 1, 2, and 3 at the Application Site

Adverse reaction	Vehicle n=87	AMELUZ n=212
Adverse reactions at the application site		
Erythema	34 (39%)	195 (92%)
Pain/Burning	26 (30%)	195 (92%)
Irritation	17 (20%)	153 (72%)
Edema	3 (3%)	75 (35%)
Pruritus	14 (16%)	72 (34%)
Exfoliation	4 (5%)	41 (19%)
Scab	2 (2%)	41 (19%)
Induration	0 (0%)	26 (12%)
Vesicles	1 (1%)	25 (12%)
Paresthesia	2 (2%)	18 (9%)
Hyperalgesia	0 (0%)	13 (6%)
Reaction	2 (2%)	8 (4%)
Discomfort	0 (0%)	7 (3%)
Erosion	0 (0%)	6 (3%)
Discharge	0 (0%)	4 (2%)
Bleeding	0 (0%)	3 (1%)
Pustules	0 (0%)	3 (1%)

Common (≥1%, <10%) adverse reactions not at the application site for AMELUZ maximal dose of one tube (2 g) and application area up to 20 cm^2 were headache, skin exfoliation, chills and eyelid edema.

Less common (≥0.1%, <1%) adverse reactions at the application site for AMELUZ maximal dose of one tube (2 g) and application area up to 20 cm^2 were hemorrhage and swelling. The adverse reactions not at the application site were blister, feeling hot, pruritus, pyrexia, scab, nervousness, pain, petechiae, rash pustular, skin erosion and ulcer.

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 doses normally used in the treatment of AK.

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. Most adverse reactions observed were consistent with those reported in trials using one tube (2 g) of AMELUZ on a 20 cm² area (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 by 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.

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: allergic dermatitis, application site inflammation, application site discoloration.
Eye disorders: eye irritation, diplopia, ocular hyperemia, photophobia, and blurred vision.
General disorders and administration site conditions: fatigue.
Immune System disorders: hypersensitivity.
Nervous system disorders: dysaesthesia, transient amnestic episodes.

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 agents 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

There are no available data on AMELUZ use in pregnant women to inform a drug associated risk. Animal reproduction studies were not conducted with aminolevulinic acid. Systemic absorption of aminolevulinic acid in humans is negligible 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. 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, the effects of aminolevulinic acid on the breastfed infant or on milk production. However, breastfeeding is not expected to result in exposure of the child to the drug due to the negligible 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 child from AMELUZ or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 have not been established. AK is not a condition generally seen in the pediatric population.

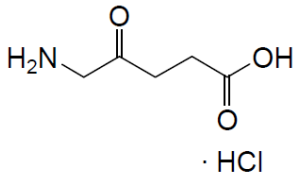
8.5 Geriatric Use

Of the 384 subjects exposed to AMELUZ in randomized, multicenter clinical trials, 83% (318/384) of the subjects were 65 years old and over. No overall differences in safety or effectiveness were observed between these subjects and younger 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 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 in the treatment of actinic keratosis are 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.

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

The efficacy and safety of AMELUZ in combination with PDT using a narrow spectrum (red light lamp) source were evaluated in three randomized, multicenter trials (Trials 1, 2, and 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 2.

Table 2: 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.

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 – 8°C (36°F – 46°F). Excursions permitted to 15°C – 30°C (59°F – 86°F).

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

17. PATIENT COUNSELING INFORMATION

Inform patients of the following:

Hypersensitivity

Hypersensitivity has been reported with use of AMELUZ. Inform patients and their caregivers that AMELUZ may cause hypersensitivity potentially including severe courses (anaphylaxis) *[see Warnings and Precautions (5.1)]*.

Transient amnestic episodes

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)]*.

Photosensitivity

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

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

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 Clinical Trial Experience (6.1)]*

PATENT INFO

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