

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) gel, 10%, for topical use

Initial U.S. approval: 1999

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

AMELUZ gel, a porphyrin precursor, in combination with photodynamic therapy using BF-RhodoLED lamp, is indicated for the lesion-directed and field-directed treatment of actinic keratoses 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).
- Photodynamic therapy with AMELUZ involves preparation of lesions, application of the product, occlusion and illumination with BF-RhodoLED (2.2).
- Retreat lesions that have not completely resolved 3 months after the initial treatment (2.2).
- See BF-RhodoLED user manual for detailed lamp safety and operating instructions (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-----

- *Risk of Eye Injury:* Patients and healthcare providers must wear protective eyewear before operating BF-RhodoLED lamp (5.1).
- *Photosensitivity:* Protect treated lesions from sunlight exposure for 48 hours post treatment (5.2).
- *Risk of Bleeding:* Special care should be taken to avoid bleeding during lesion preparation in patients with inherited or acquired coagulation disorders (5.3).
- *Ophthalmic Adverse Reactions:* Avoid direct contact of AMELUZ with the eyes (5.4).
- *Mucous Membranes Irritation:* Avoid direct contact of AMELUZ with the mucous membranes (5.5).

-----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 1-884-829-7434 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, sulfonyleureas, phenothiazines, sulphonamides, quinolones, and tetracyclines (7).

See 17 for PATIENT COUNSELING INFORMATION

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FULL PRESCRIBING INFORMATION: CONTENTS*

1. INDICATIONS AND USAGE
2. DOSAGE AND ADMINISTRATION
 - 2.1 Important Administration Information
 - 2.2 Dosage and Administration Instructions
3. DOSAGE FORMS AND STRENGTHS
4. CONTRAINDICATIONS
5. WARNINGS AND PRECAUTIONS
 - 5.1 Risk of BF-RhodoLED Lamp Induced Eye Injury
 - 5.2 Increased Photosensitivity
 - 5.3 Risk of Bleeding in Patients with Coagulation Disorders
 - 5.4 Ophthalmic Adverse Reactions
 - 5.5 Risk of Mucous Membranes Irritation
6. ADVERSE REACTIONS
 - 6.1 Clinical Trial Experience
 - 6.2 Postmarketing Experience
7. DRUG INTERACTIONS
8. USE IN SPECIFIC POPULATIONS
 - 8.1 Pregnancy
 - 8.2 Lactation

- 8.4 Pediatric Use
- 8.5 Geriatric Use
10. OVERDOSAGE
 - 10.1 AMELUZ Overdose
 - 10.2 Red Light Overdose following AMELUZ Administration
11. DESCRIPTION
12. CLINICAL PHARMACOLOGY
 - 12.1 Mechanism of Action
 - 12.3 Pharmacokinetics
13. NONCLINICAL TOXICOLOGY
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14. CLINICAL STUDIES
16. HOW SUPPLIED/STORAGE AND HANDLING
17. PATIENT COUNSELING INFORMATION
 - 17.1 Photosensitivity
 - 17.2 Common Adverse Reactions

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

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

AMELUZ[®] gel, in combination with photodynamic therapy (PDT) using BF-RhodoLED[®] 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 light. Retreat lesions that have not completely resolved after 3 months after the initial treatment.

Refer to BF-RhodoLED user manual for detailed lamp safety and operating instructions. Both patient and medical personnel conducting the PDT should adhere to all safety instructions.

2.2 Dosage and 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 crust

Step 2. Application of AMELUZ

Use glove protected fingertips or a spatula to apply AMELUZ. Apply gel approximately 1 mm thick and include approximately 5 mm of the surrounding skin. Use sufficient amount of gel to cover the single lesions or if multiple lesions, the entire area. Application area should not exceed 20 cm² and no more than 2 grams of AMELUZ (one tube) should be used 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 these areas, thoroughly rinse with water. 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

During illumination, patient and medical personnel need to wear suitable protective eyewear.

Immediately after removing occlusion and any remaining gel, illuminate the treatment area with BF-RhodoLED[®], a red light source with a narrow spectrum around 635 nm that delivers a light dose of approximately 37 J/cm² within 10 minutes. Calibration by the operator is not needed; the illumination time is calculated automatically. Position the lamp head 5-8 cm from the skin's surface. When an area of 8 x 18 cm is illuminated, the effective treatment area is 6 x 16 cm. Larger areas can be illuminated in several steps.

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

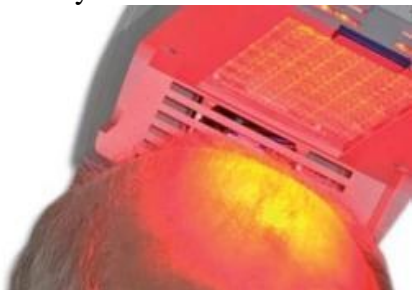


Figure 4: Illumination

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

Each gram of AMELUZ gel, 10% contains 100 mg of aminolevulinic acid hydrochloride (equivalent to 78 mg of aminolevulinic acid).

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.
- Porphyria. AMELUZ use may cause uncontrolled phototoxic effects [*see Warnings and Precautions (5.2)*].
- Photodermatoses. PDT may worsen the phototoxic or photoallergic reactions [*see Warnings and Precautions (5.2)*].

5. WARNINGS AND PRECAUTIONS

5.1 Risk of BF-RhodoLED Lamp Induced Eye Injury

BF-RhodoLED 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 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 [*see Dosage and Administration (2)*].

5.2 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)*].

5.3 Risk of Bleeding in Patients with Coagulation Disorders

AMELUZ has not been tested on patients with inherited or acquired coagulation disorders. Special care should be taken to avoid bleeding during lesion preparation in such patients [see *Dosage and Administration (2)*]. Any bleeding must be stopped before application of the gel.

5.4 Ophthalmic Adverse Reactions

Eyelid edema has occurred with AMELUZ application. AMELUZ can cause ophthalmic adverse reactions. AMELUZ is intended for topical use only. Do not apply AMELUZ into the eyes. Rinse eyes with water in case of accidental contact.

5.5 Risk of Mucous Membrane Irritation

AMELUZ can cause mucous membrane irritation. AMELUZ is intended for topical use only. Do not apply 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:

- Risk of BF-RhodoLED Lamp Induced Eye Injury [see *Warnings and Precautions (5.1)*].
- Increased Photosensitivity [see *Warnings and Precautions (5.2)*].
- Risk of Bleeding in Patients with Coagulation Disorders [see *Warnings and Precautions (5.3)*].
- Ophthalmic Adverse Reactions [see *Warnings and Precautions (5.4)*].
- Risk of Mucous Membranes Irritation [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 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 Caucasian.

For all 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, 87 placebo-treated subjects (n=16, n=32, n=39) and 212 AMELUZ-treated subjects (n=32, n=55, and n=125) were illuminated with BF-RhodoLED or similar narrow spectrum lamps.

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.

The incidence of common ($\geq 1\%$, $< 10\%$) and very common ($\geq 10\%$) adverse reactions in randomized, multicenter trials at the application site are presented in Table 1.

Table 1: Incidence of Adverse Reactions Occurring at $\geq 1\%$ of the AMELUZ Group and More Frequently than the Vehicle Group in the Actinic Keratosis Trials 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%) | 10 (5%) |
| 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 ($\geq 1\%$, $< 10\%$) adverse reactions not limited to the application site were chills, headache, and skin exfoliation.

Uncommon ($\geq 0.1\%$, $< 1\%$) adverse reactions at the application site for AMELUZ were hemorrhage and swelling. The adverse reactions not limited to the application site were eyelid edema, feeling hot, pain, pyrexia, ulcer, hyperalgesia, rash pustular, nervousness, blister, petechiae, pruritus, scab and skin erosion.

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.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been reported during post-approval use of AMELUZ outside the United States. 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: erythema, swelling, application site inflammation and skin discoloration.

Eye disorders: eye irritation, diplopia, ocular hyperemia, photophobia, and blurred vision.

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, sulfonyleureas, phenothiazines, sulphonamides, quinolones and tetracyclines may enhance the phototoxic reaction to PDT [see *Warnings and Precautions (5.1)*].

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 estimated 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.

10. OVERDOSAGE

10.1 AMELUZ Overdose

AMELUZ overdose following topical administration has not been reported. If AMELUZ is accidentally ingested, monitoring and supportive care is recommended. The patient should be advised to avoid incidental sunlight exposure for 48 hours after ingestion.

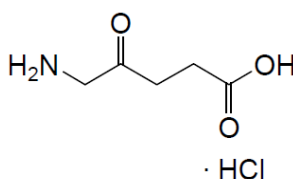
10.2 Red Light Overdose following AMELUZ Administration

There is no information on overdose of red light from the BF-RhodoLED following AMELUZ application.

11. DESCRIPTION

AMELUZ (aminolevulinic acid hydrochloride) gel, 10% for topical use 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-oxopentanoic 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, propylene glycol, 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 illumination, which provides a red light of narrow spectrum and a light dose of approximately 37 J/cm².

12.3 Pharmacokinetics

Pharmacokinetics (PK) of aminolevulinic acid and PpIX was evaluated in a trial of 12 adult subjects with mild to moderate AK with at least 10 AK lesions on the face or forehead. 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 cm². The mean \pm SD baseline plasma aminolevulinic acid and PpIX concentrations were 20.16 \pm 16.53 ng/mL and 3.27 \pm 2.40 ng/mL, respectively. 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 \pm 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 \pm 75.50 ng.h/mL and 27.19 \pm 20.02 ng/mL, respectively. The median Tmax (time at which C_{max} occurred) was 3 hours.

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. PK of aminolevulinic acid and PpIX following treatment on the scalp was not evaluated.

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 AMELUZ 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 Caucasian.

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/cm². 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/cm².

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

| | Narrow Spectrum PDT | |
|---------|---------------------|------------|
| | 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.

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

16. HOW SUPPLIED/STORAGE AND HANDLING

AMELUZ (aminolevulinic acid hydrochloride) 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

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

17.1 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) and Drug Interactions (7)*].

17.2 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.

AMELUZ and BF-RhodoLED are registered trade marks of Biofrontera Pharma GmbH.

PATENT INFO

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