Actinic keratosis (AK) skin lesions from sun damage may lead to skin cancer[1,2,]*

WHEN DANGER LURKS BELOW THE SURFACE

AMELUZ®
[aminolevulinic acid HCl] topical gel, 10%
& BF-RhodoLED®

*Actinic keratosis lesions are premalignant and may lead to squamous cell carcinoma (SCC)—the second most common skin cancer. But they don't always appear on the surface where you can see them. **AK lesions develop below the surface where they may go unnoticed and untreated.**[1-3]

INDICATION

AMELUZ® (aminolevulinic acid hydrochloride) topical gel, 10%, 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.

IMPORTANT SAFETY INFORMATION

AMELUZ® (aminolevulinic acid hydrochloride), topical gel, 10%

Purpose: Photosensitizing agent

Uses: AMELUZ® gel, a porphyrin precursor, in combination with photodynamic therapy using BF-RhodoLED® lamp, is used for lesion-directed and field-directed treatment of actinic keratoses of mild-to-moderate severity on the face and scalp.

Please see Important Safety Information throughout.

About actinic keratosis (AK)

What is AK?

Actinic keratoses are premalignant lesions of the skin that, when left untreated, can potentially develop into squamous cell carcinoma (SCC), the second most common form of skin cancer. AK is primarily caused by chronic sun damage and generally affects people aged 40 or older.[2]

What are the signs of AK?

AK lesions typically form on areas of the body most exposed to the sun—such as the face, scalp, neck, and ears. Different types of AK lesions can have a different clinical appearance. AK lesions on the surface of the skin are frequently scaly, range from normal skin color to reddish brown, and can be identified by sight and/or touch. Because AK originates in the skin layers below the visible surface, lesions can be present but still hidden from view. These AK lesions are known as subclinical lesions.[1,2]

Sun damage is usually spread over a large area where multiple AK lesions can develop over time. For every visible lesion on the surface, there are likely others hidden below. When surface and subclinical lesions cover a particular area, they form a premalignant field.[1,3]

For every AK lesion you can see, there are more you can't see—and they can also be harder to treat.[1,2,4]

IMPORTANT SAFETY INFORMATION *(selected)*

Warnings:

Do not use if you have a:

- Known hypersensitivity to photoactive substances known as porphyrins.
- Known hypersensitivity to soybeans.
- Known hypersensitivity to any component of AMELUZ® (aminolevulinic acid HCl) topical gel, 10%.

AMELUZ®
[aminolevulinic acid HCl] topical gel, 10%
& BF-RhodoLED®

IMPORTANT SAFETY INFORMATION *(selected)*

Ask your Health Care Provider before use if you have:

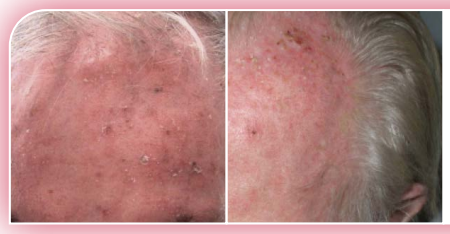
- Porphyria (hereditary disease that is characterized by abnormal production of a red blood pigment called heme).
- Photodermatoses (skin conditions caused by or made worse by exposure to light or ultraviolet radiation).

Please see Important Safety Information throughout.

A potential unseen threat of skin cancer[1-3,*]

You could be at risk

*More than a third of the general population over the age of 51 has at least 1 AK lesion that may be found on their head and scalp.[5] Those with 10 lesions or more are 3 times more likely to develop squamous cell carcinoma (SCC). If left untreated, SCC can grow into a more aggressive form called invasive SCC (iSCC).[6]



AK lesions on the head and scalp

TALK TO YOUR HEALTHCARE PROVIDER IF YOU THINK YOU HAVE AK

IMPORTANT SAFETY INFORMATION *(selected)*

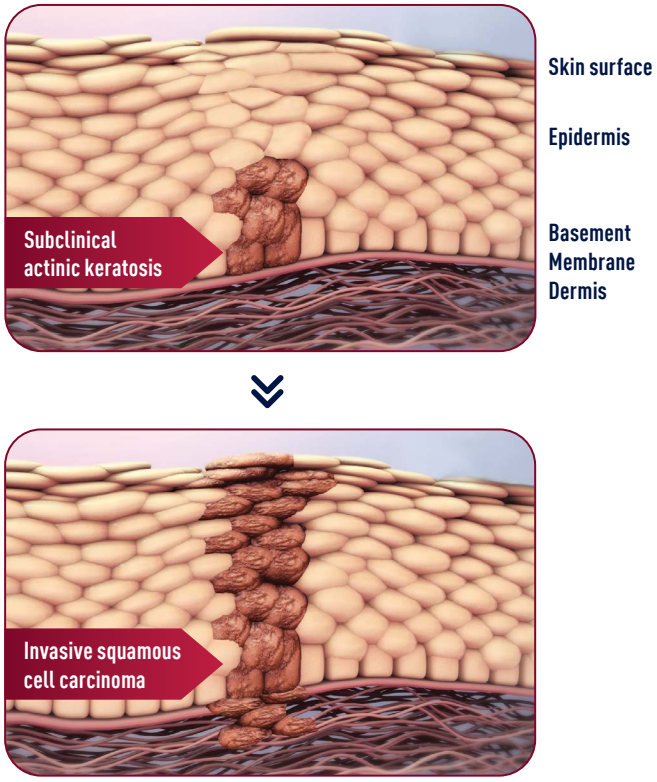
When using this product:

- ***Ophthalmic Adverse Reactions:*** Avoid applying AMELUZ® (aminolevulinic acid HCl) topical gel, 10% into the eyes. Wash eyes with water in case of accidental contact.
- ***Mucous Membrane Irritation:*** Avoid direct contact of AMELUZ® with the mucous membranes. Wash with water in case of accidental contact.

AMELUZ®
[aminolevulinic acid HCl] topical gel, 10%
& BF-RhodoLED®

AK may change before you see it

It's not uncommon for subclinical AK lesions to progress to iSCC.[7]
Potential progression risk reported as being between **0.025% and 16%.**[8]



VISIT AMELUZ.COM TO LEARN MORE ABOUT ACTINIC KERATOSIS

IMPORTANT SAFETY INFORMATION *(selected)*

When using this product:

- ***Risk of Eye Injury:*** Patients and health care providers must wear protective eyewear while operating BF-RhodoLED® lamp.
- ***Risk of Bleeding:*** Special care should be taken to avoid bleeding during lesion preparation in patients with inherited or acquired coagulation disorders. Bleeding must be stopped before application of the gel.

Please see Important Safety Information throughout.

Choose a therapy that treats the field[9,†]

†AMELUZ® is indicated for the lesion-directed and field-directed treatment of actinic keratoses of mild-to-moderate severity on the face and scalp. Treatment area should not exceed 20 cm^2.

AMELUZ® (aminolevulinic acid HCl) topical gel, 10% delivers results

In a clinical study of photodynamic therapy (PDT) with AMELUZ® and BF-RhodoLED® (N=55)

91% of patients were 100% cleared after 12 weeks[2,10,‡]

Placebo (12 weeks after the last treatment) (N=32)

22% of patients achieved 100% clearance with placebo[2,10,‡]

‡Results from a phase 3 clinical trial with 87 patients presenting 4 to 8 mild-to-moderate AK lesions on the face/forehead and/or bald scalp treated with AMELUZ® or placebo and the BF-RhodoLED® lamp. Patients received a maximum of 2 PDTs and were examined 12 weeks and 12 months after the last treatment.[2,9]

IMPORTANT SAFETY INFORMATION *(selected)*

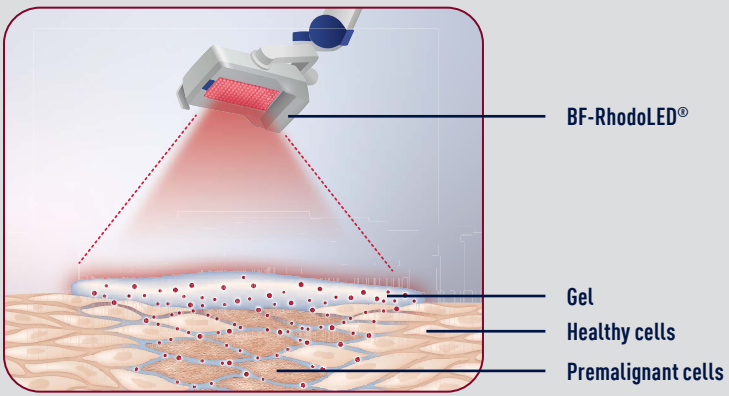
When using this product:

- ***Allergic reactions:*** AMELUZ® may cause allergic reactions before photodynamic therapy. AMELUZ® should be washed off and suitable treatment started. The allergic reactions can potentially include severe courses like sudden, severe allergic reaction with breathing difficulty, swelling, lightheadedness, fast heartbeat, sweating and loss of consciousness.
- ***Transient Amnestic Episodes:*** Photodynamic therapy may cause transient amnestic episodes (temporary loss of memory). If observed, the therapy must be stopped immediately. If observed after treatment, contact your health care provider. in case of accidental contact.

AMELUZ® [aminolevulinic acid HCl] topical gel, 10% & BF-RhodoLED®

How AMELUZ® and BF-RhodoLED® work together

AMELUZ® penetrates the epidermis of your skin to reach the premalignant cells that cause AK. It is then converted into the light-activated agent called PpIX. The red light of BF-RhodoLED® illuminates these cells and activates the agent, setting off a reaction that destroys the premalignant cells that cause AK—while leaving healthy skin cells mostly intact.[2,9,11,12]



IMPORTANT SAFETY INFORMATION *(selected)*

When using this product:

- ***Concomitant use*** of the following medications may increase the intensity of adverse reactions after light exposure related to photodynamic therapy: St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones, and tetracyclines.

Please see Important Safety Information throughout.

The treatment process

Therapy with AMELUZ® (aminolevulinic acid HCl) topical gel, 10% and BF-RhodoLED® is a multi-step process

Your healthcare provider will prepare the skin and apply AMELUZ® (application area should not exceed 20 cm^2).

After waiting the recommended time (3 hours) to allow AMELUZ® gel to penetrate the targeted cells, your healthcare provider will illuminate the area with BF-RhodoLED® lamp for 10 minutes.

Your healthcare provider's staff will provide protective eyewear that must be worn during your BF-RhodoLED® lamp treatment.

IMPORTANT SAFETY INFORMATION *(selected)*

Directions:

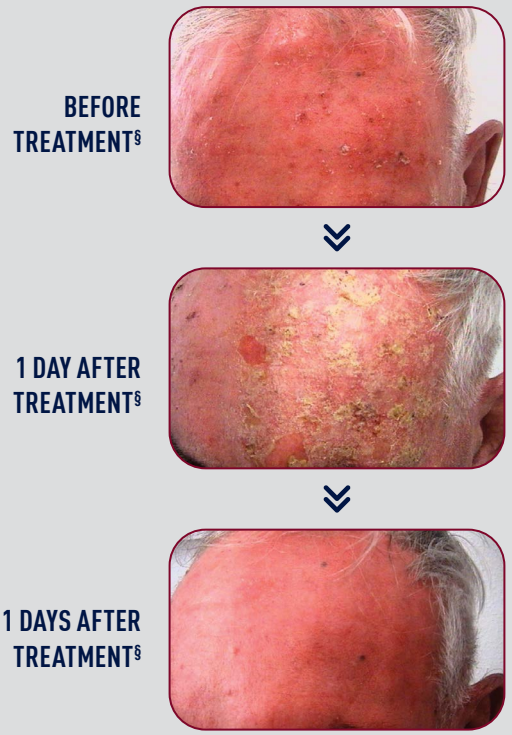
- AMELUZ® is administered only by a health care provider.
- AMELUZ® is for topical use only.
- Photodynamic therapy with AMELUZ® involves preparation of lesions, application of the product, occlusion and illumination with BF-RhodoLED®
- Retreat lesions that have not completely resolved 3 months after the initial treatment.

AMELUZ®
[aminolevulinic acid HCl] topical gel, 10%
& BF-RhodoLED®

After treatment with AMELUZ® and BF-RhodoLED® lamp

For 48 hours after treatment, you should avoid exposing treated areas of the skin to sunlight and artificial sources of UV radiation (e.g., tanning beds or sunlamps).

Before and after patient images



§Individual results may vary.

SAFETY

Adverse reactions and the safety of PDT with AMELUZ®

Most common side effects at the application site were:

- skin reddening
- swelling
- scabbing
- pain/burning
- itching
- hardening
- irritation
- scaling of the skin
- blistering

Most side effects occurred during illumination or shortly afterwards, were generally of mild to moderate intensity, and lasted for 1 to 4 days in most cases; in some cases, they persisted for 1 to 2 week or even longer.

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

AMELUZ® (aminolevulinic acid hydrochloride) topical gel, 10%, 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.

IMPORTANT SAFETY INFORMATION

AMELUZ® (aminolevulinic acid hydrochloride), topical gel, 10%
Purpose: Photosensitizing agent

Uses: AMELUZ® gel, a porphyrin precursor, in combination with photodynamic therapy using BF-RhodoLED® lamp, is used for lesion-directed and field-directed treatment of actinic keratoses of mild-to-moderate severity on the face and scalp.

Warnings:
Do not use if you have a:

- Known hypersensitivity to photoactive substances known as porphyrins.
- Known hypersensitivity to soybeans.
- Known hypersensitivity to any component of AMELUZ®.

Ask your Health Care Provider before use if you have:

- Porphyria (hereditary disease that is characterized by abnormal production of a red blood pigment called heme).
- Photodermatoses (skin conditions caused by or made worse by exposure to light or ultraviolet radiation).

When using this product:

- ***Allergic reactions:*** AMELUZ® may cause allergic reactions before photodynamic therapy. AMELUZ® should be washed off and suitable treatment started. The allergic reactions can potentially include severe courses like sudden, severe allergic reaction with breathing difficulty, swelling, lightheadedness, fast heartbeat, sweating and loss of consciousness.
- ***Transient Amnestic Episodes:*** Photodynamic therapy may cause transient amnestic episodes (temporary loss of memory). If observed, the therapy must be stopped immediately. If observed after treatment, contact your health care provider.
- ***Risk of Eye Injury:*** Patients and health care providers must wear protective eyewear while operating BF-RhodoLED® lamp.
- ***Photosensitivity:*** Avoid sun exposure on the treated lesion sites and surrounding skin for approximately 48 hours following treatment.
- ***Risk of Bleeding:*** Special care should be taken to avoid bleeding during lesion preparation in patients with inherited or acquired coagulation disorders. Bleeding must be stopped before application of the gel.
- ***Ophthalmic Adverse Reactions:*** Avoid applying AMELUZ® into the eyes. Wash eyes with water in case of accidental contact.
- ***Mucous Membrane Irritation:*** Avoid direct contact of AMELUZ® with the mucous membranes. Wash with water in case of accidental contact.

AMELUZ®
[aminolevulinic acid HCl] topical gel, 10%
& BF-RhodoLED®

- ***Concomitant use*** of the following medications may increase the intensity of adverse reactions after light exposure related to photodynamic therapy: St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones, and tetracyclines.

Most common side effects at the application site were:

- skin reddening
- scabbing
- swelling
- scaling of the skin
- irritation
- blistering
- pain/burning
- hardening
- itching

Most side effects 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 they persisted for 1 to 2 weeks or even longer.

Pregnancy Warning: There is no available data on AMELUZ® use in pregnant women to inform a drug associated risk.

Lactation Warning: There is no available data regarding the presence of the active ingredient (aminolevulinic acid hydrochloride) in human milk, or the effects of aminolevulinic acid hydrochloride on the breastfed infant or on milk production.

Pediatric Warning: Safety and effectiveness in pediatric patients below the age of 18 has not been established.

Geriatric Warning: No overall differences in safety or effectiveness were observed between older (65 years and older) and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Directions:

- AMELUZ® is administered only by a health care provider.
- AMELUZ® is for topical use only.
- Photodynamic therapy with AMELUZ® involves preparation of lesions, application of the product, occlusion and illumination with BF-RhodoLED®
- Retreat lesions that have not completely resolved 3 months after the initial treatment.

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.

Other Information:

- Store in a refrigerator, 2°C – 8°C (36°F – 46°F). Excursions permitted to 15°C – 30°C (59°F – 86°F).
- The risk information provided here is not comprehensive. To learn more, talk about AMELUZ® with your health care provider. The FDA approved product labeling can be found at **https://bit.ly/AmeluzPI.**
- You are encouraged to report side effects of AMELUZ®. Please contact Biofrontera Inc. at 1-844-829-7434 or FDA at 1-800-332-1088 or **www.fda.gov/medwatch.**

WHEN DANGER LURKS BELOW THE SURFACE

Treat the actinic keratosis (AK) lesions you can see–and address those you can't see.

Talk to your healthcare provider about using photodynamic therapy with AMELUZ® and the red light of BF-RhodoLED® to treat the threat of mild-to-moderate AK lesions on your face and scalp.[2,9]

AMELUZ®
[aminolevulinic acid HCl] topical gel, 10%
& BF-RhodoLED®

ASK YOUR HEALTHCARE PROVIDER ABOUT PHOTODYNAMIC THERAPY WITH AMELUZ® (aminolevulinic acid HCl) TOPICAL GEL, 10% AND BF-RhodoLED®

IMPORTANT SAFETY INFORMATION *(selected)*

Geriatric Warning: No overall differences in safety or effectiveness were observed between older (65 years and older) and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Please see Important Safety Information throughout.

References: 1. Berman B, Amini S, Valins W, Block S. Pharmacotherapy of actinic keratosis. *Expert Opin Pharmacother.* 2009;10(18):3015-3031. **2.** Reinhold U. A review of BF-200 ALA for the photodynamic treatment of mild-to-moderate actinic keratosis. *Future Oncol.* 2017;13(27):2413-2428. **3.** Stockfleth E. The importance of treating the field in actinic keratosis. *J Eur Acad Dermatol Venereol.* 2017;31(Suppl 2):8-11. **4.** Schmitz L, Brehmer A, Falkenberg C, et al. Treatment-resistant actinic keratoses are characterized by distinct clinical and histological features. *Ital J Dermatol Venerol.* 2021;156(2):213-219. **5.** Flohil C, van der Leest R, Dowlatshahi E, Hofman A, de Vries E, Nijsten T. Prevalence of actinic keratosis and its risk factors in the general population: the Rotterdam Study. *J Invest Dermatol.* 2013;133(8):1971-1978. **6.** de Berker D, McGregor JM, Mohd Mustapa MF, Exton LS, Hughes BR. British Association of Dermatologists' guidelines for the care of patients with actinic keratosis 2017. *Br J Dermatol.* 2017;176(1):20-43. **7.** Fernández-Figueras MT, Carrato C, Sáenz X, et al. Actinic keratosis with atypical basal cells (AK I) is the most common lesion associated with invasive squamous cell carcinoma of the skin. *J Eur Acad Dermatol Venereol.* 2015;29:991-997. **8.** Fuchs A, Marmur E. The kinetics of skin cancer: progression of actinic keratosis to squamous cell carcinoma. *Dermatol Surg.* 2007;33(9):1099-1101. **9.** AMELUZ® [prescribing information]. Woburn, MA: Biofrontera Inc; 2021. **10.** Reinhold U, Dirschka T, Ostendorf R, et al. A randomized, double-blind, phase III, multicentre study to evaluate the safety and efficacy of BF-200 ALA (Ameluz) vs. placebo in the field-directed treatment of mild-to-moderate actinic keratosis with photodynamic therapy (PDT) when using the BF-RhodoLED lamp. *Br J Dermatol.* 2016;175(4):696-705. **11.** Maisch T, Santarelli F, Schreml S, et al. Fluorescence induction of protoporphyrin IX by a new 5-aminolevulinic acid nanoemulsion used for photodynamic therapy in a full-thickness ex vivo skin model. *Exp Dermatol.* 2010;19(8):e302-e305. **12.** Agostinis P, Berg K, Cengel KA, et al. Photodynamic therapy of cancer: an update. *CA Cancer J Clin.* 2011;61(4):250-281.

Biofrontera

120 Presidential Way, Suite 330, Woburn, MA 01801
customer_service@biofrontera.com | biofrontera.us.com | AME-US031V001