ACTINIC KERATOSIS

A PRACTICAL APPROACH:
Field Treatment of AKs with PDT

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A Practical Approach: Field Treatment of AKs with PDT

Why it’s essential to treat visible and invisible actinic keratosis lesions and how PDT fits into the treatment armamentarium.

WITH BRIAN BERMAN, MD; NEAL BHATIA, MD; JOEL L. COHEN, MD; MICHAEL GOLD, MD; GARY GOLDENBERG, MD; AND ANDREA WILLEY, MD

Actinic keratoses (AKs) are among the more common lesions that dermatologists treat. Although considered pre-cancerous, data show a link between AKs and squamous cell carcinoma (SCC) and field cancerization, making early diagnosis and treatment important.1,2

“We commonly refer to actinic keratoses with our patients as pre-cancers—some people refer to them as keratinocyte intraepidermal neoplasia, or an evolving, or on the spectrum of an evolving, skin cancer,” says Joel L. Cohen, MD. "But we don’t know which of these red, rough, and scaly lesions are going to go on to the next step to progress to a skin cancer. There are studies out there showing varying rates of that. But nevertheless, we do treat these AKs because we simply don’t know.”

Gary Goldenberg, MD, says it is imperative that these lesions are treated, citing scientific evidence showing how normal non-sun exposed skin can progress to squamous cell carcinoma in a linear progression of multiple mutations in the keratinocytes from normal to actinic keratosis to in situ carcinoma to invasive carcinoma.1

Dr. Goldenberg describes a 2009 Veterans Affairs study that looked at the role AKs may play in the overall burden of keratinocyte carcinomas (KC). In total, 7,784 AKs were identified on the face and ears of 169 participants. The risk of progression of AK to primary SCC (invasive or in situ) was 0.60 percent at one year and 2.57 percent at four years. Approximately 65 percent of all primary SCCs and 36 percent of all primary BCCs diagnosed in the study cohort arose in lesions that previously were diagnosed clinically as AKs. The majority of AKs (55 percent) that were followed clinically were not present at the one-year follow-up, and the majority (70 percent) were not present at the five-year follow-up. In this study, the authors concluded that the results suggested that AKs may play a greater role in the overall burden of keratinocyte carcinomas than previously documented.3

It is known that anywhere between 0.025 and 16 percent of AKs can progress to invasive SCC—extrapolation studies suggest the risk of progression is approximately eight per-
cent, with risk varying with age, gender, chronic UV exposure, and location of AKs, says Neal Bhatia, MD. And one retrospective review study of biopsy-proven AKs at eventual site of SCC showed that the time range for conversion from AK to SCC is two to 65 months, with a mean range of 24.6 months.

The spontaneous regression rate of AKs is estimated to be 15-25 percent in a one-year period, compared to the occurrence rate of invasive SCC, which is five to 20 percent over follow-up periods of 10 to 25 years with a 0.1 percent and 0.24 percent transformation rate from AK to SCC in one year. And, Dr. Bhatia adds, 82.4 to 100 percent of patients with invasive SCC arising on sun-exposed areas have a history of AK.

Based on this data and what we know anecdotally, Dr. Bhatia says, it’s possible to reduce the risk of skin cancer by treating what we see as well as what is on the way.

THE CASE FOR FIELD TREATMENT

The issue with actinic keratoses, explains Brian Berman, MD, is that if you see a few, there’s a very high likelihood that the surrounding area that has no visible AKs already has changes that are consistent with actinic keratoses, or what are considered sub-clinical AKs.

Michael Gold, MD agrees. “As dermatologists we always recommend treating AKs and treating them early because we know that there is a malignant potential for all of these lesions to become squamous cell carcinomas. The earlier the treatment, the best chance to avoid a diagnosis of malignancy,” he says. “We can treat individual lesions, which is what we do when we use liquid nitrogen or curettage an AK lesion, but we know when we do this we are missing pre-clinical AKs—those that are forming or just under the skin surface. We are also not taking into account that all of these lesions occur on actinically damaged skin, so the potential for new AKs to develop in these areas is also increased as compared to those who have not had the same sun exposure. So that is where the field concept developed—treating the visible and the pre-clinical AKs at the same time.”

The standard of care and most commonly used treatment for actinic keratoses in the US is still cryotherapy with liquid nitrogen—it has been around forever, it is simple to do, and reimbursement is decent for this procedure, Dr. Gold says. Some physicians will use curettage if there is suspicion of

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**Red or Blue?**

Dr. Berman completed a split-face study to investigate blue vs. red light when using the more recently FDA-approved ALA 10% (Ameluz). Ahead he discusses the findings.

“According to the FDA, the way you are supposed to use Ameluz, you apply it under occlusion where you have prior treatment of these actinic keratoses with light curettage or abrasion of them. So, you have to do this procedure, then apply the gel under occlusion. And then you wait three hours before you expose the area to red light. The original ALA 20% (Levulan) was approved for use with blue light, and we know ALA can absorb energy from blue light or from red light.

“We studied 40 patients and did a bilateral examination of actinic keratoses on the left and right side of the face of these patients, and randomized the sides of their face to get either the Ameluz, or the other side, Levulan. But, when we used the Ameluz, we did not use it according to the FDA-approved protocol—that is, we did not do any abrasion of the lesions. We did not use it under occlusion either. Then, rather than using the red light, both sides of the face were exposed to high intensity blue light.

“Generally rates of AK reduction achieved using topical creams for AKs are about 80 percent reduction in AKs from baseline. In this case—and it was a small number of patients (40 patients)—we saw rates of the percent reductions into the mid-90s for both the Levulan- and the Ameluz-treated sides, even though the Ameluz was being used without abrasion of the AKs prior to the exposure, without being applied under occlusion, and with blue light activation rather than red light. In this case, the two formulations were fairly equal in respect to efficacy. With such a small sample size of 40 patients, it’s impossible to determine statistically significant differences between 95 (Ameluz) and 94 (Levulan) percent reduction rates.

“However, it turned out that the tolerability was better on the side of the face that was treated with Ameluz with statistically significantly higher local skin reactions on the side treated with Levulan than that treated with Ameluz. So, we determined that treating with Ameluz activated with blue light, the combination for the patient is good, because they get equivalent efficacy and greater tolerability than Levulan, with respect to local skin reactions, and that’s good news for a physician who doesn’t have the red light equipment.

“In terms of the benefits of red light, technically red light goes deeper, so if this were being used off-label to treat acne or non-melanoma skin cancers with PDT, then you may want a deeper wavelength to activate the ALA.

“And when used as was done in the clinical trials for FDA approval, with occlusion, with the abrasion of lesions prior to the application, and using red light, Ameluz compared to the Levulan, appears to have a greater efficacy.”
malignancy. If a patient has an isolated lesion, liquid nitrogen can be very effective, Dr. Cohen says, but he adds that it’s important to educate patients about AKs to help them understand that our goal is to decrease the number of subclinical lesions they have and that although they may not be able to see them, it’s clear that they have sun damaged skin and other visible features of subclinical AKs. He explains that field therapy vs. a destructive modality can help to clean up the overall photodamage and treat both the visible and invisible lesions.

This concept of subclinical lesions does need to be explained to patients, Dr. Gold adds. Most patients don’t understand that they may only have four to 10 lesions on their face, but that there may be 20 underneath the skin, especially if they are presenting with AKs for the first time.

“My job is to prevent patients from needing to see a surgeon,” Dr. Goldenberg explains, comparing field therapy to preventative medicine. When you treat the entire field, you’re also helping to prevent new lesions from developing as well as helping prevent the development of AK to a skin cancer that needs to be surgically removed.

There are several effective topical field therapy options, including 5-fluorouracil (5-FU) (Carac, Efudex, Fluoroplex, Tolak), chemical peels, diclofenac sodium (Solaraze), imiquimod (Aldara, Zyclara), and ingenol mebutate (Picato). They have all been shown to reduce the number of AKs from baseline, give or take, by about 80 percent, says Dr. Berman, but the main issues with the use of topicals are the local skin reactions from these various products and the number of applications that are required to exert their efficacy. Agreeing that these topical therapies are efficacious and beneficial in the field management of AKs, Dr. Goldenberg notes that patients should be counseled and made aware of potential issues associated with these topical therapies, including redness, scaling, and crusting, and resulting downtime.

“So it’s a mixture of tolerability and whether patients are going to be compliant with use in order to achieve the efficacy that’s in the literature. The number of applications of the various creams and gels range from as few as two days total, two applications, in the case of ingenol mebutate 0.05%, all the way up to 180 applications according to the FDA indication for Diclofenac 3%,” Dr. Berman says. “And the problem is that patients are often not compliant with any medication and likely would not apply any medication 180 times religiously. Even if the efficacy is there, if it requires 180 applications, patients will not achieve that efficacy.”

In terms of compliance and user-friendliness, Dr. Berman suggests ingenol mebutate with its two- or three-day dosing pattern would be best. But it is associated with some risk of local skin reactions, so may not be suitable for some patients. With 5-FU, patients will need seven to 28 applications—there are four different FDA-approved variations. And imiquimod, which Dr. Berman says is a highly effective immune response modifier, still requires twice-weekly application for up to 16 weeks or about 32 applications with the classic 5% imiquimod or 28 for the 3.75% formulation. The 3.75% cream is available in a metered-dose pump—one to two pumps are applied once nightly for two weeks of treatment, followed by two weeks of no treatment (rest period), and then followed by another two weeks of treatment, which does offer a shorter total treatment duration, increased tolerability, and the ability to treat a larger area, adds Dr. Goldenberg.

“But what it really comes down to, in addition to the compliance and the user friendliness and the degree of local skin reactions, is whether or not the insurance company of the patient will actually pay for these products. There’s a lot of science behind these treatments,” Dr. Berman says. “But if you can’t get it, it doesn’t matter how effective the treatments are.”

It’s about accessibility and tolerability when choosing which topical cream to prescribe for AKs. If a patient has difficulty getting the topical creams or if the patient has a very large number of AKs on the scalp and face, photodynamic therapy field treatment may be the right choice. Dr. Cohen says at his practice, they offer patients a choice regarding field therapy—asking if patients prefer to use a cream at home or want to come into the office to do something, and not have to have the homework. Some people have used topical therapies in the past, like 5FU or imiquimod or ingenol mebutate, and they know that it can result in crusty and irritated skin that can look unsightly for a while.

“For patients who have used 5-FU before, some are willing to deal with those kinds of side effects for up to several weeks, but some patients say, ‘I will never do anything like that again.’ They think about doing ingenol mebutate for a few days. Or, we may think about treating with a shortened therapy, or with imiquimod for two weeks on, two weeks off, two weeks on,” Dr. Cohen says. “But some people are really clear. They would rather come into the office, have us do a PDT treatment, and then they’ll stay indoors and away from any outdoor light for the next couple of days. And that’s very clear cut.”

With an in-office treatment you know your patients are getting the treatment and appropriately so, adds Dr. Berman.

“I’m a skin cancer surgeon, so most of the patients I treat have had skin cancer,” says Andrea Willey, MD. “They often have significant sun damage and a history of skin cancer, so a field therapy is indicated. Because of its efficacy and the ability to complete the treatment in a few hours, PDT is often the preferred treatment for patients with field cancerization.”
PHOTODYNAMIC THERAPY

“We know from years of study that PDT, using ALA and a blue or red light, and methyl ALA, using a red light, can make dramatic changes in one’s skin, as the photosensitizers are absorbed by AKs and actinically damaged skin—clearing both conditions nicely” Dr. Gold explains. “In fact, PDT has been shown to have a very acceptable cosmetic effect, not always seen with any other modality. PDT fits in nicely when we can document numerous AKs to be treated, when other modalities have failed to control the AKs, and when patients are tired of having liquid nitrogen applied to their skin or tired of being cut.”

PDT came to the US in the late 1990s, notes Dr. Gold, and in 2000, 20% aminolevulinic acid (ALA) solution (Levulan Kerastick) was FDA approved to treat non-hyperkeratotic AKs of the face and scalp with a blue light source (Blu-U). The original FDA indication was for the individual treatment of these AKs. Clinical studies since then have shown full-face and scalp treatment, as well as treatment of the extremities in a full-field manner, have resulted in an effective treatment option for these lesions,9,10 says Dr. Gold.

Dr. Bhatia also notes that dermatologists have learned that the original (and on label) drug incubation time, which was 14-18 hours with 20% ALA, is not needed in most cases. Clinical studies have shown that short-contact ALA drug incubation—from one to three hours—works with the same efficacy as the longer drug incubation time periods.11

A second ALA was FDA approved in 2016. Aminolevulinic acid hydrochloride (BF-200 ALA, Ameluz) was FDA approved for PDT using the BF-RhodoLED lamp, a narrowband, red light illumination source, for lesion-directed and field-directed treatment of AKs of mild to moderate severity on the face and scalp. This approval was based on results from 779 patients with four to eight mild to moderate AK lesions. The results obtained from these studies demonstrated that BF-200 ALA was significantly superior to the standard of care, with a complete patient response rate of 91 percent when paired with BF-RhodoLED PDT lamp.12

In addition, Ameluz showed positive long-term effects with low recurrence over the course of 12 months.13 And in a pivotal Phase 3 trial performed on entire treatment fields, BF-200 ALA demonstrated long-lasting skin rejuvenation effects in sun-damaged, but asymptomatic, skin regions.14

Ameluz differs from Levlun in that it’s a gel formulation rather than a liquid, Dr. Berman says. “It’s a different concentration, it’s 10% rather than 20%, and it’s in a nano formulation, which is better for penetration,” he says.

Dr. Bhatia explains that the nanoemulsion delivery of Ameluz optimizes the transport of the ALA through the stratum corneum and allows penetration of ALA without permeation into the dermis.12

“We use a lot of Ameluz in our office,” Dr. Cohen says. “In terms of the way that it’s actually formulated, it’s easy to apply and see the area you’ve covered. The patients have done well with it.”

Dr. Willey says both FDA-approved ALA formulations have been shown to be effective for the treatment of AKs, but the newer ALA 10% gel is a litter easier and faster to apply. Ameluz is indicated for use with a red light, which does penetrate deeper than blue light, however Dr. Gold says he has found that the ALA is effective with either light source for treating AKs and that clinical studies have shown results are virtually the same with either light source. (See sidebar “Red or Blue”)

Dr. Willey uses both red and blue light in her office, and notes significant aesthetic benefits following treatment with red light PDT compared to other field therapies for AKs.

PDT TREATMENT PROTOCOL

All physicians have a unique treatment approach based

Crack the Code

Dr. Bhatia says the insurance reimbursement process for PDT has improved as long as the appropriate codes are used. Importantly, all PDT codes should be billed with the appropriate J code:

• 20% ALA (Levlun): J7308
• 10% ALA (Ameluz): J7345

And the correct CPT code must be used:

• CPT Code 96567: Photodynamic therapy by external application of light to destroy premalignant and/or malignant lesions of the skin and adjacent mucosa (eg, lip) by activation of photosensitive drug(s), each phototherapy exposure session. This code should now ONLY be used when a physician or other QHP does not directly participate in the PDT treatment delivery.
• CPT Code 96573: Photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitizing drug(s), per day.
• CPT Code 96574: Debridement of premalignant hyperkeratotic lesion(s) (ie, targeted curettage abrasion) followed with photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitizing drug(s), per day.

To use CPT Code 96573 and 96574, the physician/QHP MUST apply the photosensitizer AND initiate the light illumination.
on their years of experience treating AKs. There are general treatment guidelines, says Dr. Bhatia.

- Patients should wash the area to be treated with soap and water and then use an alcohol-soaked 4x4 gauze pad to remove any remaining debris and oil.
- The photosensitizer is then evenly applied to the entire treatment area and a second coat may be applied after the first has dried completely.
- Then, the photosensitizer needs to incubate for 30 minutes to four hours, followed by activation of the photosensitizer by the appropriate light source.
- After treatments, patients should wash the treated area again with soap and water to remove any residual photosensitizer.
- Patients should be instructed to avoid direct sunlight for 48 hours.
- Treatment may be repeated, as needed, for two to three weeks.

“There is no question that prepping the skin with something prior to PDT is beneficial to the skin. Some use micro-dermabrasion, some use topicals in advance, and most use an acetone scrub before the procedure to enhance the penetration of the ALA,” Dr. Gold says. “Post-treatment, there is no set ‘this or that’—and that is the joy of PDT itself—everything can be customized to the patient based on their needs, their lifestyle, and how much they can tolerate and do in between clinic visits.”

Some patients do experience stinging or burning during the procedure, but Dr. Cohen cautions that it’s important to have patients maintain the recommended distance from the light source to get the most effective treatment. Fans may be used to help increase comfort. However, there is some indication that fans should not be used specifically while incubating, because that may actually decrease the overall conversion of porphyrin.

In order to make the treatment more comfortable for his patients who do report burning or discomfort, Dr. Cohen has his team spray hypochlorous acid (Levicyn) immediately following the PDT treatment on patients who report burning or discomfort.

Patients should be advised that they may experience some redness after treatment, but it typically resolves quickly.

Dr. Willey uses a unique, off-label approach that she says has been very successful in increasing efficacy and reducing variability in response to treatment—thermal PDT. To start, she also has patients wash the treatment area using a mildly exfoliating cleanser prior to gently swabbing with alcohol. She says it important to remove all oil from the skin to ensure penetration of the ALA.

Next, ALA gel is applied to the treatment area followed by a heating mask to gently warm the skin during incubation. The patients are treated while they are laying down so it feels more like a spa treatment. After the incubation period, the red light is rolled over to the patient for illumination. Patients are given an ice water mister to apply if they have discomfort during light exposure. Patients wash their face after treatment and then moisturize.

“When you use heat, it’s a very predictable reaction,” Dr. Willey explains. In fact, in a study she led on thermal PDT, she found warming the skin after application of ALA is well tolerated, does not increase side effects, and maintained the long-term efficacy of PDT for the treatment of AKs. Mild skin warming may both improve efficacy and reduce variability of response to PDT in practice.15,16

Dr. Willey typically calls patients the day after treatment and if they have any discomfort, she recommends ice, Aquaphor®, and Tylenol. Patients follow up in one week, then one month to determine if they need follow-up treatment.

THE PROMISE OF PDT

PDT offers patients an excellent option for treating and managing AKs, the physicians agree, and with ongoing research regarding best treatment protocols, the potential use of PDT with red light for treating skin cancers, and improved insurance reimbursement (see sidebar “Crack the Code”), there is a lot to be excited about now and for the future of treating AKs.

AMELUZ® (aminolevulinic acid hydrochloride) gel, 10% with BF-RhodoLED® lamp

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Indications and usage
AMELUZ gel, 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.

Doseage and administration
AMELUZ® is applied topically in a thin film by a healthcare professional or by the patient with or without occlusion, depending on the discretion of the treating physician.

Photodynamic therapy with AMELUZ® requires prior education, application of the product, occlusion and illumination with BF-RhodoLED®. The illumination area should not exceed 25 cm² and no more than 2 grams of AMELUZ® (gel base) should be used at one time. Lesions that have not completely resolved shall be retreated 3 months after the initial treatment. Refer to BF-RhodoLED® User manual for detailed weekly safety and operating instructions. Both patient and medical personnel conducting the PDT should adhere to all safety instructions.

Contraindications
AMELUZ is contraindicated in patients with:
- Known hypersensitivity to porphyrins.
- Known hypersensitivity to any of the components of AMELUZ, which includes aminolevulinic acid.
- Porphyria. AMELUZ may cause uncharacteristic phototoxic effects.
- Phototoxicity. PDT may worsen the phototoxic or photodermatosis reactions.

Warnings and precautions

Transient Amelanotic Changes
Transient amelanotic changes have been reported during postmarketing use of AMELUZ in combination with photodynamic therapy. As patients and their caregivers that AMELUZ in combination with photodynamic therapy may cause transient amelanotic episodes. Advise them to contact the healthcare provider if the patient develops abnormal after treatment.

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.

Increased Photosensitivity
AMELUZ increases photosensitivity. Avoid sunlight, prolonged or intense light (e.g., sunbathing, bed lamps or tanning beds) and surrounding skin treated with AMELUZ for approximately 48 hours after 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.

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. Any bleeding must be stopped before application of the gel.

Ophthalmic Adverse Reactions
Spontaneous adverse events occurred with AMELUZ application. AMELUZ can cause adverse ophthalmic reactions. AMELUZ is intended for topical use only. Do not apply AMELUZ to the eyes. Rinse eyes with water in case of accidental contact.

Risk of Mucosa 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.

Adverse reactions

The following adverse reactions are discussed in greater detail in other sections (see Warnings and Precautions):


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 2052 subjects in placebo-controlled trials (7 Trials 1-7) and 1,569 subjects in open-label trials (Trials 8-13). There were 1,639 subjects who received AMELUZ and 1,603 subjects who received placebo. The most frequent adverse reactions reported during placebo-controlled trials were erythema, edema, and pain.

Adverse reactions occurring during photodynamic therapy in clinical trials are summarized below (see Adverse Reactions). The most common adverse reaction was erythema, which occurred in 82% of patients treated with AMELUZ and 15% of patients treated with placebo.

Incidence of Adverse Reactions Occurring ≥10% of the AMELUZ Group and More Frequently than the Vehicle Group in the Actinic Keratosis Trials at the Application Site

Adverse reactions at the application site

AMELUZ® Gel

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Vehicle n=87</th>
<th>AMELUZ n=212</th>
<th>p-value</th>
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<tr>
<td>Frequency</td>
<td></td>
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<tr>
<td>Erythema</td>
<td>24 (28%)</td>
<td>195 (92%)</td>
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<td>Pain/burning</td>
<td>26 (30%)</td>
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<tr>
<td>Irritation</td>
<td>17 (20%)</td>
<td>163 (77%)</td>
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<tr>
<td>Edema</td>
<td>3 (4%)</td>
<td>75 (35%)</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>14 (17%)</td>
<td>72 (34%)</td>
<td></td>
</tr>
<tr>
<td>Oedema</td>
<td>4 (5%)</td>
<td>41 (19%)</td>
<td></td>
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<tr>
<td>Stab</td>
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<tr>
<td>Pruritus</td>
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<td>Hypersensitivity</td>
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<tr>
<td>Sloughing</td>
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<tr>
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<td>0 (0%)</td>
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<tr>
<td>Fibrillation</td>
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<td>3 (1%)</td>
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</table>

Common (≥1%-<10%) and very common (<0.1%) adverse reactions are tabulated, multicenter trials at the application site are presented in the following table.

Postmarketing Experience

The following adverse reactions have been reported during postapproval 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.

Site and Subcutaneous Tissue Disorders: application site: infection, application site dermographism, Erythema: eye irritation, diplopia, ocular hypertension, photophobia, and blurred vision.

General disorders and administration site conditions: fatigue, Neurological system disorders: dizziness, Transient amelanotic episodes.

Drug interactions

There have been no formal studies of the interaction of AMELUZ with other drugs. It is possible that concurrent use of other known photosensitizing agents such as St. John's wort, griseofulvin, nicotine, bisulfates, sulfonamides, quinolones and tetracyclines may enhance the phototoxic reaction to PDT.

Use in specific populations

Pregnancy

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 application of AMELUZ under normal clinical care conditions. 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 is 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.

Lactation

No data are available regarding the presence of aminolevulinic acid in human milk. The effects of aminolevulinic acid on the breastfed infant are not known. 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 application of AMELUZ under normal clinical care conditions (see Clinical Pharmacology (5.3)). 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 or the mother's clinical need for AMELUZ.

Pediatric Use

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

Special Populations

Of the 2052 subjects exposed to AMELUZ in randomized, multicenter clinical trials, 8.6% (178/2052) of the subjects were 65 years of age 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.

Please visit our full Prescribing Information for AMELUZ® and BF-RhodoLED® lamp available at https://celyxmed.smx.com/products/rhodolamp/patient-information and refer to AMELUZ® User Manual for detailed weekly safety and operating instructions. Both patient and medical personnel conducting the PDT should adhere to all safety instructions.
Take care of sun damage

AMELUZ® [aminolevulinic acid hydrochloride] gel, 10% is a porphyrin precursor: It is used in combination with BF-RhodoLED® photodynamic therapy for lesion and field-directed treatment of mild to moderate actinic keratosis on the face and scalp.

Indications And Usage
AMELUZ® gel, in combination with photodynamic therapy (PDT) using the BF-RhodoLED® lamp, a narrowband, red light illumination source, is indicated for lesion-directed and field-directed treatment of actinic keratosis (AK’s) of mild-to-moderate severity on the face and scalp.

Important Safety Information
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. Please see Brief Summary of Full Prescribing Information on following page. 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.

1 Ameluz® Prescribing Information. For Ameluz® full Prescribing information visit: https://www.dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=650daa9f-aeec-49ce-95b9-5fa20b988afd