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Topical PDT Photosensitizers (5-ALA and MAL) Therapeutic Cheat Sheet[1,2]

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TRADE NAME[3,4]

- LEVULAN KERASTICK® (aminolevulinic acid HCl for topical solution, 20%)
- AMELUZ® (aminolevulinic acid HCl topical gel, 10%)
- Metvix®/Metvixia (methyl aminolevulinate 16% or 160 mg/g cream)

MECHANISM OF ACTION[5]

- 5-ALA and MAL (methyl ester derivative of ALA) enter cells and the heme biosynthesis pathway for conversion into protoporphyrin IX (or PpIX, immediate precursor of heme)
- Final step in heme biosynthesis pathway requires ferrochelatase to insert Fe2+ into PpIX, forming heme. Usually a slow process, but in neoplastic and hyperproliferative cells, the pathway is dysregulated, causing faster buildup of PpIX in tissue
- Upon visible-light absorption and subsequent activation of PpIX, the metabolite reaches an excited state and transfers energy to molecular oxygen creating a singlet oxygen and reactive oxygen species (ROS)
- These ROS cause oxidative damage to cellular components killing target cells through apoptosis, necrosis, and autophagy
- Methyl ester makes MAL more lipophilic, giving deeper and more selective penetration into skin, which is why it is often used with deeper-penetrating red wavelength light therapy

FDA-APPROVED FOR[3,4]

- Levulan Kerastick (ALA 20% solution) - Minimal to moderately thick actinic keratoses (AKs) of the face, scalp, or upper extremities.
  - Approved for use with BLU-U Blue Light Photodynamic Therapy Illuminator
  - Formulation: plastic tube with two glass ampules — one with 1.5 mL solution vehicle, the other with dry ALA HCl solid — crushed and mixed to form the 20% solution
- Ameluz (ALA 10% gel) – Mild to moderate actinic keratoses (AKs) on the face and scalp and superficial basal cell carcinomas (sBCC) in adults.
  - Approved for use with photodynamic therapy (PDT) using BF-RhodoLED, a narrowband, red light illumination source
  - Formulation: 10% gel (white-to-yellowish), supplied in 2-gram tubes
- Metvix/Metvixia (MAL 16% or 160 mg/g cream)
  - FDA approved in 2004 for thin-to-moderately-thick AKs of the face and scalp but was withdrawn from the US market in 2012 for commercial reasons; it continues to be widely used in Europe, Australia, Canada, and Latin America for AK, Bowen disease, and superficial/nodular BCC.

OFF-LABEL DERMATOLOGIC USES[6-12]

- Facial Flat Warts
- Genital Condyloma Acuminata
- Acne Vulgaris
- Hypertrophic Scars
- Hidradenitis Suppurativa
- Genital Vitiligo
- **ALA-derived protoporphyrin IX absorbs strongly in both the blue (~410 nm, the Soret band) and red (~635 nm) ranges, so ALA can be photoactivated by either wavelength. HOWEVER, FDA approval required fixed drug-plus-device pairing, with Kerastick to blue light and Ameluz to red light devices. Using either for the alternative light source is considered off label.

INSTRUCTIONS FOR USE[13,14]

Both the Levulan Kerastick and Ameluz are provider-administered photosensitizers for photodynamic therapy (PDT). Standard FDA-approved PDT protocols include specific incubation and light illumination times. However, numerous alternative protocols have been developed and studied with comparable efficacy, improved patient tolerability, and more streamlined/shorter procedures.

Levulan Kerastick (aminolevulinic acid HCl for topical solution, 20%)

- STEP 1: Clean/degrease the skin with alcohol.
- STEP 2: Crush Kerastick containing ampules of both ALA dry solid and solution, to mix.
- STEP 3: Apply the solution directly to the target lesions by dabbing gently with the wet applicator tip. Enough solution should be applied to uniformly wet the lesion surface, including the edges without excess running or dripping.
- STEP 4: Incubate under light-blocking occlusion (per protocol)
- STEP 5: Illuminate with Blue Light PDT (per protocol)

Ameluz (aminolevulinic acid HCl topical gel, 10%)

- STEP 1: Clean/degrease the skin with alcohol, then gently roughen all lesions.
- STEP 2:
  - **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. Additionally, cover approximately 5 mm of the surrounding healthy area
- STEP 3: Allow gel to dry for 10 minutes before applying light-blocking occlusive dressing.
- STEP 4: Incubate under light-blocking occlusion (per protocol), then remove dressing and wipe off any remaining gel
- STEP 6: Illuminate with the Red Light PDT (per protocol)

PDT Protocols:

- Longer incubation times raise complete clearance (23.5% at 0.5 h vs 73.5% at 4 h with red light at 37 J/cm^2) but also increased local skin reactions (26% at 0.5 h vs 66% at 4 h).
- A 2026 narrative review concluded that short- and no-incubation "painless" protocols achieve clearance comparable to conventional PDT with significantly improved tolerability and streamlined workflow, though larger trials are still needed to standardize them.
  - *Bullock TA, Maytin EV. Painless Photodynamic Therapy: Emerging Protocols and Light Delivery Systems for the Treatment of Actinic Keratoses. Photodermatol Photoimmunol Photomed. 2026 Jan;42(1):e70068. doi: 10.1111/phpp.70068. PMID: 41351497.*
- *Choosing Red light vs Blue Light:*
  - Blue light (~405–420 nm)
    - Is absorbed most strongly by protoporphyrin IX (its Soret peak) but penetrates only ~1–2 mm, so it delivers intense, efficient activation confined to the epidermis.
    - Ideal for thin, superficial actinic keratoses.
  - Red light (~630–635 nm)
    - Hits a weaker PpIX absorption peak and is a less efficient activator, but longer wavelengths scatter less and are absorbed less by hemoglobin/melanin, so red penetrates deeper (>2 mm, up to ~4–6 mm)
    - Better for thicker, hyperkeratotic, or field disease and off-label superficial skin cancers.
  - For typical thin-to-moderate AKs, efficacy is comparable between wavelengths, so lesion depth, device availability, and tolerability drive the choice.

		Incubation time	Illumination time/dose
Red Light PDT	*Standard Red Light Protocol	3 hours with occlusion	~10 minutes; Auto-calculated by lamp
	Shorter-incubation "painless" Red Light15	30 minutes	37 J/cm ~7-10 mins
	Low irradiance/ reduced fluence16	3 hours	Same total dose (37 J/ cm^2) at ~25% irradiance, longer time
	Continuous low-level (Phosistos fabric device, P-PDT)17	30 minutes	Continuous low-irradiance light for a longer, sustained session
	Modified high-dose painless PDT (M-PDT)18	30 minutes	Red light at doubled total dose (288 vs 144 J/cm^2); the higher dose extends illumination time relative to conventional PDT
	Daylight (red-spectrum) PDT	None	2-hour daylight light-exposure
Blue Light PDT	*Standard Blue Light Protocol	14–18 hours (face/ scalp) or 3 hours with occlusion (upper extremities).	1000-second (16 minutes 40 seconds)
	"Conventional" PDT	1 hour	1000-second (16 minutes 40 seconds)
	"Simultaneous" Blue Light19	None	30, 45, or 60 minutes
	No-incubation double-cycle protocol20	None	Two back-to-back 16 min 40 s cycles (33 min 20 s total).

*Only FDA-approved protocols. All others are off-label.

ADMINISTRATION CONSIDERATIONS[13,14]

- **Levulan Kerastick**
  - If for any reason the patient cannot be given illuminator treatment during the prescribed time after applying topical solution, advise patient to wear appropriate protective apparel (e.g., wide-brimmed hat, long sleeve shirt, gloves) to shade the treated actinic keratoses from sunlight or other bright light sources until at least 40 hours after the application of topical solution.
- **Ameluz**
  - Physical measures such as cooling with an air stream or nebulized water may help reduce pain during illumination.
  - If for any reason, the lesions cannot be illuminated within 3 hours after 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).
  - Do not exceed an application area of 60 cm^2, and do not use more than 6 grams (3 tubes) at one time.
  - Retreat lesions that have not completely resolved 3 months after the initial treatment.
- Both provider and patient should wear protective eyewear
- Post-treatment photoprotection: Advise the patient to avoid sunlight and prolonged or intense light exposure on the treated and surrounding skin for approximately 48 hours after treatment.

SIDE EFFECTS[3,4]

- The most common side effects are local application site-reactions that are expected with response to phototoxic PDT therapy and generally resolve within days to a few weeks
  - Application-site stinging/burning – reported by at least 50% of Levulan-treated subjects; usually subsides within 1 minute to 24 hours after light is turned off. Can be managed with local cooling, pauses, or analgesia.
  - Other - Erythema, edema, scaling/crusting, itching, erosion, hypo-/hyperpigmentation, oozing/vesiculation, and dryness
- Less Common/Rare – Wheals, pustules, ulceration, bleeding, blistering, tenderness, dysesthesia
- Systemic (uncommon) – with Ameluz - headache, chills, eyelid edema, transient amnestic episodes and hypersensitivity (including anaphylaxis) are labeled precautions

GENERAL PRECAUTIONS[3,4,21,22]:

- After application of 5-ALA, treated skin becomes photosensitive and requires protection for 40 hours after initial application
  - Sunscreen does not protect against visible-light phototoxicity, need to use physical barriers (wide-brimmed hat, long sleeves, gloves).
  - Avoid concomitant photosensitizing drugs – St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulfonamides, quinolones, and tetracyclines – for 24 hours before and after 5-ALA use
- Contraindicated in
  - Patients with acute or chronic porphyria due to risk of uncontrolled phototoxicity and potential ineffectiveness
  - Patients with hypersensitivity to porphyrins or ALA (for Ameluz specifically, hypersensitivity to soybean phosphatidylcholine)
  - Patients with photodermatoses
- There is a risk of HSV/VZV reactivation following PDT therapy
- For topical use only – not for ophthalmic, oral, or intravaginal use; avoid contact with mucosal surfaces
- Pediatrics – safety and effectiveness are not established

PREGNANCY AND BREASTFEEDING[3,4]

- Pregnancy Category C
- No data collected from animal reproduction studies, studies in pregnant women, or of levels of metabolites in breastmilk. As per FDA, should be given to a pregnant woman only if clearly needed.

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