CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208081Orig1s000

SUMMARY REVIEW

Decisional Memorandum to the File

Date:	May 10, 2016
From:	Kendall A. Marcus, M.D. Director, Division of Dermatology and Dental Products
Subject:	Summary and Recommendations
NDA/BLA #:	208081
Submission Date **PDUFA Goal**	July 10, 2015 May 10, 2016
Proprietary / Generic (USAN) names	AMELUZ (5-aminolevulinic acid hydrochloride)
Dosage forms / strength	Gel, 10%
Proposed Indication(s)	In combination with photodynamic therapy using the BF-RhodoLED lamp for the treatment of actinic keratosis of mild to moderate severity of the face and scalp

1. Introduction

With this New Drug Application (NDA), the applicant seeks marketing approval for AMELUZ (aminolevulinic acid hydrochloride) gel, 10% under Section 505(b)(1) of the Federal Food Drug and Cosmetic Act. The proposed indication is for the treatment of mild to moderate actinic keratoses (AK) on the face and scalp in combination with red light photodynamic therapy (PDT) using the BF-RhodoLED lamp, a narrowband, red light illumination source. This product is considered as a drug-device combination by the Agency.

PDT requires 3 components: (1) a photosensitizer, (2) light with a sufficient amount of energy at a suitable spectrum of wavelengths, and (3) oxygen. In PDT light energy is transferred through the photosensitizer to oxygen, leading to the formation of reactive oxygen species (ROS). ROS oxidize cell membranes and other cellular compounds, causing necrosis or apoptosis of targeted cells.

In Ameluz, the active ingredient, aminolevulinic acid (ALA), is a porphyrin precursor that occurs endogenously as part of the heme biosynthesis pathway. For the treatment of actinic keratoses, ALA functions as a pro-drug and is metabolized to the photoactive substance, protoporphyrin IX (PpIX), in mitochondria. PpIX is a photosensitizer and can be activated by the absorption of energy at several different wavelengths ranging from blue to red light, resulting in an excited state. In the presence of oxygen, reactive oxygen species are formed which causes damage to cellular components, and eventually destroys the (b) (4) cells.

In support of this NDA the applicant conducted the following clinical trials:

- ALA-AK-CT-005: Skin sensitization potential of BF-200 ALA 10%
- ALA-AK-CT-006: Maximal use pharmacokinetics (PK) trial

- ALA-AK-CT-007: Phase 3 efficacy and safety trial
- ALA-AK-CT-003: Phase 3efficacy and safety trial
- ALA-AK-CT-002: Phase 3 efficacy and safety trial including an active control arm (Metvixia®)
- ALA-AK-CT-001: Phase 2b dose finding study

2. Background

Actinic keratoses (AK) are common, sun-induced, potentially premalignant lesions that increase with age. They occur rarely before adulthood. Years of sun exposure are required to induce damage sufficient to cause lesions. AK lesions begin as an area of increased vascularity with the skin surface becoming slightly rough; early lesions may be better recognized by palpation than by inspection. Very gradually, an adherent yellow crust forms; removal of this crust may cause bleeding. Individual lesions vary in size from 3 to 6 mm. The extent of disease varies from a single lesion to involvement of the entire forehead, balding scalp or temples.

The natural history of actinic keratosis can be described as continual flux with new lesions appearing and some of the old lesions remitting. The incidence and remission rates are affected in part by historical and ongoing solar exposure. AK lesions may progress to squamous cell cancers (SCC) over time. While single lesions occur, most patients present with multiple AKs. AKs occur most frequently in the elderly and in men in particular. Males are at highest risk for death or disfigurement from SCC. In one study from Australia, the yearly rate of progression of an AK lesion to invasive SCC in an average risk person was between 8 and 24 per 10,000. In the United States, destruction/removal of AK lesions is the most commonly performed outpatient dermatologic procedure.

A broad spectrum of treatment modalities are available for the treatment of AK lesions; these include excisional surgery, laser treatment, chemical peels, dermabrasion, cryotherapy, photodynamic therapy in combination with photosensitizing cream and systemic and topical treatments. Approved topical treatments include 5-fluorouracil cream, imiquimod cream, diclofenac gel, aminolevulinic acid solution, methyl-aminolevulinic cream, salicylic acid ointment and ingenol mebutate gel.

Aminolevulinic acid hydrochloride is currently marketed in the United States (US) as a 20% topical solution (Levulan Kerastick®; NDA 20965). Levulan Kerastick® (aminolevulinic acid hydrochloride), 20% for Topical Solution plus blue light illumination using the BLU-U Blue Light Photodynamic Therapy (PDT) Illuminator is indicated for the treatment of minimally to moderately thick actinic keratoses of the face or scalp. It was approved in 1999.

3. CMC

For complete details, please refer to Office of Product Quality's (OPQ) Integrated Quality Assessment completed by the Quality Review Team.

AMELUZ gel, 10% for topical use is a non-sterile white to-yellowish gel. The active pharmaceutical ingredient in the drug product is aminolevulinic acid hydrochloride (ALA HCl). 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, its molecular weight is 167.59 and its molecular formula is C5H9NO3.HCl.

Each gram of AMELUZ gel contains 100 mg of ALA HCl 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.

The specification of AMELUZ gel, 10% includes tests for appearance, drug substance identification and assay, sodium benzoate assay, viscosity, pH, impurities, particle size distribution, minimal fill and microbial contamination. The identity, strength, purity and quality of the drug product are assured by adequate raw material controls, validated manufacturing process and drug product specification.

The CMC review team concluded that the applicant has submitted sufficient information to assure the identity, strength, purity and quality of the drug substance and drug product. The Office of Process and Facilities made a final overall manufacturing inspection "Approvable" recommendation for the facilities involved in this application. From the OPQ perspective, this NDA is ready for approval at this time in its present form per 21 CFR 314.125 (b)(6) and 21 CFR 314.125 (b)(13).

4. Nonclinical Pharmacology/Toxicology

Please refer to the review prepared by Barbara Hill, PhD, the Pharmacology/Toxicology team leader, for full details. This NDA is considered approvable from a pharm/tox perspective. The NDA is considered to be a 505(b)(1) NDA because the sponsor owns all the necessary nonclinical data necessary to support this drug application.

The sponsor demonstrated that there is a negligible systemic increase in plasma levels of ALA above background endogenous levels and no increase in PpIX plasma levels (a biomarker of systemically absorbed ALA) under maximal clinical use conditions for Ameluz. The need for reproductive toxicity studies and a systemic carcinogenicity study were waived based on the level of systemic exposure demonstrated under maximal clinical use conditions. Maternal use of Ameluz is not expected to result in fetal exposure to the drug and breastfeeding is not expected to result in exposure of the child to the drug due to the negligible systemic absorption of ALA following topical administration of Ameluz under clinical maximal use conditions. The need for a dermal carcinogenicity study for Ameluz was waived due to the clinical conditions of use (single application followed by another single application after 3 months, if needed).

The target organ of toxicity identified in a 14-day repeat dose intravenous dog toxicity study was the liver. A repeat dose dermal minipig study was conducted with once monthly topical administration of ALA gel, 10% or vehicle gel for 3 months with and without red light exposure. The results from this study were the expected effects based on the pharmacologic mechanism of photodynamic therapy. Mild to moderate erythema and eschar formation were noted at ALA gel, 10% treated sites. The symptoms were more pronounced at ALA gel, 10% treated sites exposed to red light. No increase in local toxicity was noted after repeat dose administration and the recovery process appeared to be quicker from the second application through the fourth application of ALA gel, 10% plus red light treated sites. Histopathological evaluation of treated skin sites 28 days after the last ALA gel, 10% treated site exposed to red light demonstrated complete recovery.

An ICH battery of genotoxicity studies were conducted with ALA hydrochloride (HCl). ALA HCl 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). The in vitro genotoxicity studies were conducted without red light exposure. Literature data indicates a low genotoxicity potential of ALA when combined with UVA light exposure. The observed DNA damage is probably caused by the oxidative free radicals formed when ALA derived PpIX is exposed to light of the correct wavelength. This is the desired pharmacologic effect that is utilized for the treatment of actinic keratosis lesions.

ALA gel, 10% without red light exposure was not a dermal irritant or ocular irritant in rabbits. ALA gel, 10% without red light exposure was not a sensitizer in the murine LLNA assay.

The toxicity profile of ALA gel, 10% has been adequately characterized by the nonclinical studies conducted by the sponsor. The toxicity profile elicited by ALA gel, 10% in the presence of red light exposure was what is anticipated for PDT.

5. Clinical Pharmacology

Please refer to the review by Chinmay Sukla, Ph.D., the clinical pharmacology reviewer from the Office of Clinical Pharmacology/DCP III for full details. The clinical pharmacology review team considers this NDA approvable.

The applicant assessed pharmacokinetics (PK) of ALA and PpIX via serial sampling in the maximal use PK trial and in a Phase 2b dose-finding study.

The maximal use PK trial enrolled 12 adult subjects with at least 10 mild or moderate AK lesions on the face and forehead. The clinical staff applied 2 g of vehicle gel or ALA 10% gel (1 tube) at a thickness of about 1 mm to the lesions and the surrounding areas covering about 20 cm^2. The application area was covered with an occlusive dressing for about 3 hours after which the excess gel from the treatment area was wiped off and the

treatment area was illuminated with the BF-RhodoLED® lamp. The lamp has an emission at around 635 nm and a light dose of approximately 37 J/cm². Each subject first received a vehicle gel treatment with PDT and after a wash-out period of 7 days, the subject received an ALA 10% gel treatment with PDT. The same AK lesions/areas were treated in both periods.

Systemic concentrations of ALA were quantifiable in all subjects. The mean ± SD baseline concentrations of ALA and PpIX were 20.16 ± 16.53 ng/mL and 3.27 ± 2.40 ng/mL, respectively. After application of the vehicle gel, the mean plasma concentrations of ALA were similar to baseline. After application of ALA 10% gel, the mean plasma concentrations of ALA increased compared to baseline. The baseline corrected mean ± SD Cmax (maximum concentration), AUC0-t (area under the concentration time curve) and median tmax (time at which Cmax occurred) were 27.19 ± 20.02 ng/mL, 142.83 ± 75.50 ng*h/mL, and 3.00 h, respectively. Baseline corrected systemic concentrations of PpIX was estimated only in one subject due to the values being negative in other subjects. The baseline corrected Cmax and AUC0-t in the single subject was 0.29 ng/mL and 0.07 ng*h/mL, respectively.

In summary, exogenous application of ALA10% gel resulted relatively small increase (~2.5 fold) in mean systemic 5-ALA concentration for a duration of up to approximately 6 hours.

6. Microbiology

No microbiologic studies were conducted in support of this application.

7. Clinical/Statistical

Please refer to the reviews completed by Denise Cook, M.D., the clinical reviewer, and Carin Kim, Ph.D., the biostatistical reviewer, for full details of the efficacy review. They consider this NDA approvable from an efficacy perspective.

In support of the efficacy of AMELUZ gel, 10% for the treatment of mild to moderate AK on the face and scalp in combination with red light PDT using the BF-RhodoLED lamp, the applicant submitted results from three Phase 3 trials (Trials 02, 03, 07). Of note, none of the trials were conducted in the United States: the trials were conducted across 38 centers in Germany, 2 centers in Australia and 1 center in Switzerland.

The trials enrolled adult male or female subjects with 4-8 clinically confirmed AK target lesions of mild to moderate intensity within the face or bald scalp excluding eyes, nostrils, ears and mouth. Lesions were assessed as mild to moderate based on grading as described by Olsen et al.[1] (1991). The Olsen scale is provided in Table 1 below:

Table 1: Olsen Scale[1] for Actinic Keratoses Lesion Intensity

[1]Olsen EA et al. A double-blind, vehicle-controlled study evaluating masoprocol cream in the treatment of actinic keratoses on the head and neck. Jour Amer Aca Derm 24 (1991) 5(1)L738-743.

The protocol-specified primary efficacy endpoint for all three trials was the overall patient complete response assessed 12 weeks after the last photodynamic therapy (PDT). The overall complete responder was defined as a patient in whom all treated lesions were cleared, including patients receiving the second treatment, if necessary. Efficacy results for the primary endpoint were statistically significant for all three trials (p-value< 0.0001).

Different lamps were used in the Phase 3 clinical trials used to demonstrate efficacy of AMELUZ in combination with PDT. The applicant provided comparison testing of several "Narrowband Lamp Systems", including the BF-RhodoLED, the Aktilite CL-128 and the Omnilux EL1258S. The spectral output, peak wavelength, peak power and the output power stability across a 10-minute treatment time were evaluated for all three lamps. Based on the data provided, the CDRH reviewer, Richard Felton, concluded that the clinical data obtained from using any of these three lamps can be considered equivalent, since the light interaction and activation processes from each lamp on PpIX would be considered identical. Please refer to the completed review by Dr. Felton for full details.

Trial 02 was a randomized, observer-blind, multinational trial to evaluate the safety and efficacy of AMELUZ Gel, 10%, in comparison with Metvix® (methyl aminolevulinate) Cream, and Vehicle, for the treatment of AK with PDT. Subjects were randomized in a 3:3:1 ratio to the following arms: AMELUZ Gel, 10%, Metvix® Cream, and Vehicle arm. In this trial the light sources used were both broad band [WaldmannPDT 1200 L (600-750 nm)/Hydrosun/PhotoDyn 505 (580-1400 nm) or narrow band Aktilite CL 128 (630 nm) or Omnilux PDT 1200 L (633 nm)].

Trials 03 and 07 were randomized, double-blind, vehicle-controlled, inter-individual, 2-armed, multicenter trials. Subjects were randomized in a 2:1 ratio to the following arms: AMELUZ Gel, 10% and Vehicle. The light sources used for Trial 03 were both red light sources; the broad band light source Hydrosun/PhotoDyn 750 (580-1400 nm) and the narrow band light source Aktilite CL 128 (630 nm). The light source used for Trial 07 was BF-RhodoLED lamp (narrowband, red light illumination source).

In all three trials, preparation of the lesions for PDT included removal of all scabs, crusts and hyperkeratotic parts by curettage and cleansing of the skin sites with alcohol (ethanol or isopropanol). For each subject, the assigned trial formulation was applied to the target AK lesions and covered with occlusive tape material for 3 hours. Thereafter, the remnants of these applied formulations were removed carefully and PDT was administered. The clearance of AK lesions was assessed 12 weeks after the first PDT. All lesions that were not completely cleared were treated with a second PDT. For all subjects, two follow-up visits (6 months and 12 months after the last PDT) were scheduled.

The demographics and baseline disease characteristics were generally balanced across the treatment arms for all trials. The majority of the subjects were male (approximately 86%) and all subjects were Caucasian. The mean age of subjects was approximately 70 years (range 49 years to 87 years). Most subjects had moderate AK severity based on the Olsen scale (82%), Fitzpatrick skin type I, II or III (90%).The majority of subjects (72%) had the AK on the face and/or forehead.

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 Gel and a narrow band spectrum lamp. The efficacy results for AMELUZ Gel when used with narrow spectrum PDT in Trials 02, 03 and 07 are represented in Table 2 below:

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 12 weeks after the last PDT entered a 6 to 12-month follow-up period. Eighty-eight subjects (88/212; 42%) who were treated with AMELUZ Gel needed a second treatment. In Trials 02, 03, and 07, the subjects who received AMELUZ Gel with the narrowband PDTs and achieved complete clearance 12 weeks after the last PDT, had recurrence rates of 14%, 11%, 25% at 6 months and 40%, 22%, and 37% at 12 months. Recurrence was defined as the percentage of subjects with at least one recurrent lesion during the follow-up period in subjects with completely cleared lesions 12 weeks after the last PDT.

8. Clinical/Safety

Please refer to the review completed by Denise Cook, M.D., the clinical reviewer, for full details of the safety review. This NDA is considered approvable from a safety perspective.

The applicant submitted data from three pivotal trials, Trials 02, 03 and 07 to establish the safety of their product in the treatment of mild to moderate actinic keratoses on the face and scalp in combination with narrowband PDT. Additional safety data are available from the maximal use PK trial and a dermal safety study. All of the trials were conducted with the final-to-be-marketed formulation.

A total of 384 subjects were exposed to Ameluz in Phase 3 clinical trials. Of these subjects, 201 underwent one Ameluz application followed by PDT. A total of 183 subjects had a second Ameluz application followed by PDT for unsuccessfully treated or recurrent AK lesions.

Common (≥1%, <10%) adverse reactions not limited to the application site were chills, headache and skin exfoliation. Uncommon (≥ 0.1%) adverse reactions at the application site in AMELUZ Gel, 10% group were hemorrhage and swelling. The adverse reactions not limited to the application site were eye edema, eyelid edema, feeling hot, pain, pyrexia, ulcer, hyperalgesia, nasopharyngitis, rash pustular, nervousness, blister, dermatitis allergic, petechiae, pruritus, scab, and skin erosion.

AMELUZ Gel is approved outside of the US in Germany, Sweden, Norway, Denmark, The Netherlands, Austria, Slovenia, Spain, and the UK. In ex-US postmarketing adverse event reporting systems there have been spontaneous reports of 320 adverse events in 128 patients. Of these, the applicant assessed that a causal relationship to AMELUZ could be suspected in 185 of these events. The majority of the cases were localized to the treatment area: erythema and pain have been the most common reported related adverse events. Less frequent events were exfoliation, erosion, scab, pustules, edema, hemorrhage, inflammation, application site reactions, application site swelling, vesicles and skin discoloration. At non-application sites there have been reports of blister, eyelid edema, erythema, pain, pyrexia, and swelling. There have been very occasional reports of eye disorders including eye irritation, diplopia, ocular hyperemia, photophobia, and blurred vision. Erythema, swelling, application site inflammation, skin discoloration, eye irritation, diplopia, ocular hyperemia, photophobia, and blurred vision were added to the post-market experience section of labeling.

9. Advisory Committee Meeting

No regulatory issues were identified during the review of this application that required input from an advisory committee.

10. Pediatrics

Actinic keratoses are caused by chronic ultraviolet radiation exposure and occur almost exclusively in adults. The applicant was granted a waiver for all pediatric age groups on the grounds that pediatric studies would be impossible or highly impracticable because there are too few children with the disease/condition to study.

11. Other Relevant Regulatory Issues

A total of three investigator sites were inspected in support of this NDA. No deficiencies were found that would preclude reliance upon the data that was submitted. The reader is referred to the Clinical Inspection Summary by Roy Blay, Ph.D.; Good Clinical Practice Assessment Branch; Division of Clinical Compliance Evaluation; Office of Scientific Investigations; dated March 4, 2016.

12. Labeling

The applicant submitted proposed labeling in the format that complies with the Physicians' Labeling Rule. Professional and patient labeling were reviewed and labeling was finalized following minor modifications.

Labeling includes contraindications to use in patients with porphyrias, photodermatoses or any known hypersensitivities to components of AMELUZ, which includes soybean phosphatidylcholine. It also includes warnings and precautions instructing patients and providers to wear protective eyewear during PDT, protection of treated lesions from sun or intense light exposure for 48 hours post-treatment and avoidance of direct contact of AMELUZ with the eyes or mucous membranes.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action: I concur with the recommendations of the multi-disciplinary review team to approve.

Risk-benefit assessment: Efficacy of AMELUZ was established in three adequate and well-controlled clinical trials. Safety of the product is demonstrated through data from the clinical development program as well as postmarketing experience with the 10% gel formulation approved outside of the US. Product labeling adequately describes appropriate use as well as adverse reactions associated with use of AMELUZ in combination with PDT.

Postmarketing Risk Evaluation and Management Strategies: Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product. A Risk Evaluation and Mitigation Strategy (REMS) is not required.

Postmarketing requirements (PMR): None

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/s/

KENDALL A MARCUS
05/10/2016