

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208081Orig1s000

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: March 16, 2016

To: Belainesh Robnett
Regulatory Project Manager
Division of Dermatology and Dental Products (DDDP)

From: Tara Turner, Pharm.D., MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Pharm.D., BCPS, RAC, Team Leader, OPDP

Subject: **NDA 208081**
AMELUZ[®] (aminolevulinic acid hydrochloride) gel, 10%, for topical use

On July 21, 2015, DDDP consulted OPDP to review the draft Package Insert (PI) and carton and container labeling for AMELUZ[®] (aminolevulinic acid hydrochloride) gel, 10%, for topical use (Ameluz) for the original NDA submission.

OPDP reviewed the proposed substantially complete version of the PI provided by DDDP via e-mail on March 2, 2016 and March 11, 2016. OPDP's comments on the PI are based on the March 11, 2016 version. OPDP also reviewed the proposed carton and container labeling submitted to the electronic document room by the sponsor on July 10, 2015. OPDP's comments on the PI and carton and container labeling are provided below.

Thank you for your consult. If you have any questions about OPDP's comments, please contact Tara Turner at 6-2166 or at Tara.Turner@fda.hhs.gov.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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/s/

TARA P TURNER
03/16/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, Office of Drug
Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: March 11, 2016 **Consult Received:** September 28, 2015

From: Carol H. Kasten, MD, Medical Officer
Maternal Health Team, Division of Pediatric and Maternal Health
Office of Drug Evaluation IV (ODE IV)

Through: Tamara Johnson, MD, MS, Team Leader
Maternal Health Team
Division of Pediatric and Maternal Health, ODE IV

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health, ODE IV

To: Division of Dermatology and Dental Products

Drug: Ameluz® (aminolevulinic acid HCl) Gel, 10%, for topical use with
the BF-RhodoLED® lamp photodynamic therapy, NDA 208-081

Sponsor: Biofrontera Bioscience GmbH

Proposed Indication: "For the treatment of actinic keratoses of mild to moderate severity
of the face and scalp (b) (4) ,,"

Subject: Labeling Review

Consult Request: "We welcome your feedback on the PLLR section."

INTRODUCTION

Biofrontera Bioscience GmbH submitted this original application (NDA 208-081) on July 10, 2015 for the combination drug/device product Ameluz[®] (aminolevulinic acid) 10% Gel administered in combination with red light photodynamic therapy (PDT) using the BF-RhodoLED[®] lamp, for (b) (4) treatment of actinic keratoses (AKs) of mild to moderate severity on the face and scalp. The cover letter states the application is a 505(b)(1) submission; however, the decision of the Division of Dermatology and Dental Products (DDDP) is that this application must be submitted as a 505(b)(2) application because as the applicant references published literature for the non-clinical data section.¹ DDDP consulted the Division of Pediatric and Maternal Health Staff - Maternal Health Team (DPMH-MHT) on September 28, 2015 to review and provide recommendations for the Pregnancy (Subsection 8.1) and Lactation (Subsection 8.2) of the Ameluz labeling.

BACKGROUND

Mechanism of Action

This combination drug/device product consists of a topical gel of 10% 5-Aminolevulinic acid (ALA) and the BF-RhodoLED system which emits light in the red light spectrum (635 nm). ALA is an endogenous compound that is part of the heme biosynthesis pathway that produces protoporphyrin IX (PpIX), other porphyrins and heme. Topical application of ALA is thought to lead to ALA accumulation in the treated skin cells. The applicant hypothesizes that increased quantities of intracellular ALA results in increased quantities of PpIX in treated cells via the heme biosynthesis pathway. It is thought that when activated via the BF-RhodoLED system, PpIX induces a toxic intracellular reaction via electron transfers to oxygen and generation of free radicals. This process may be the mechanism leading to intracellular membrane damage reported by the applicant.²

Endogenous ALA

According to Perez, et al,³ the typical quantity of ALA consumed daily in food is approximately 1-2 mg, although the type of diet was not specified. The body is reported to synthesize about 600 mg per day of ALA and maintains a plasma ALA concentration of approximately 92 nmol/L (± 39), diet not reported.

Drug

The ALA formulation used in this drug product (Ameluz[®]), is a nanoemulsion gel of 10% aminolevulinic acid HCl. The dosage and administration instructions state if a treated lesion has not completely resolved after 3 months the lesion should be retreated. The applicant provided data comparing the pre-treatment ALA level in the systemic circulation (plasma) with that following treatment with the drug/device at maximal use conditions. The C_{max} of ALA was reached at three hours following application and was 2.5 times that of the ALA baseline concentration. This elevated total systemic exposure was discussed at length and additional data were reviewed with the Division. The

¹ See Mid-Cycle Meeting Minutes held December 4, 2015. (not submitted in DARRTS)

² Aminolevulinic Acid from Clinical pharmacology online©, www.clinicalpharmacology-ip.com Elsevier. Gold Standard. Revision date: June, 2015. Accessed January 24, 2016.

³ Perez M, Rodriguez B, et al., 5-Aminolevulinic Acid (5-ALA): Analysis of Preclinical and Safety Literature. Food and Nutrition Sciences, 2013, 4, 1009-1013. <http://dx.doi.org/10.4236/fns.2013.410131>

conclusion reached was the total maternal exposure to ALA is considered negligible.⁴ Additional drug product data included that no “obvious difference in PpIX concentrations” was observed under maximal use conditions.⁵ The applicant states that the light dose delivered is approximately 37 J/cm² within 10 minutes.

Other combination drug/device products that have been approved for treatment of AK lesions are:

- Levulan[®] Kerastick^{®6} uses ALA 20% and the blue light emitting Kerastick device approved for the treatment of minimally to moderately thick actinic keratoses of the face or scalp.
- Metvixia⁷ uses methyl aminolevulinate (16.8%), cream and a red light emitting device (Aktelite, CL-128[®]) and was approved for use to treat AK lesions on the face and scalp. Metvixia has been discontinued not for issues of safety or efficacy.

Disease - Actinic Keratosis

AK lesions are prevalent, occurring in approximately 10 to 25% of people living in North America.⁸ These figures are approximate and there are no data on the prevalence of AK in pregnant women, the indicated population for this review. AK is a precancerous skin lesion which is most common in sun exposed areas of the body in older individuals.^{9,10,11} The conversion rate of AK lesions to invasive cutaneous squamous cell carcinoma is approximately 6 to 10% over a 10 year period.¹² There are multiple treatment modalities for AK including topical application of cytotoxic drugs such as 5-fluorouracil,¹³ cryosurgery, electrosurgery, dermabrasion and excision.

⁴ From the February 26, 2016 Ameluz labeling version: “The mean $\pm$ SD area under the concentration time curve (AUC₀₋₄) and maximum concentration (C_{max}) for baseline corrected ALA (n=12) were 142.83 $\pm$ 75.50 ng.h/mL and 27.19 $\pm$ 20.02 ng/mL, respectively.”

⁵ Biofrontera Report: Influence of 5-ALA on Pregnancy, Lactation and Reproductive potential. Dated October 20, 2015.

⁶ NDA 20-965 approved 1999.

⁷ NDA 21-415 approved 2004.

⁸ Guenther L, Barber K, et al., Non-melanoma Skin Cancer in Canada Chapter 1: Introduction to the Guidelines. J Cutaneous Med Surg 2015, Vol. 19(3) 205–215. DOI: 10.1177/1203475415588652

⁹ Kaur R, Alikhan A, Maibach H. Comparison of topical 5-fluorouracil formulations in actinic keratosis Treatment. J Dermat Treatmt 2010;21:267–271. DOI: 10.3109/09546630903341937

¹⁰ Urman C, Loo DS. Common Skin Disorders. In: Williams B, Chang A, Ahalt C, Chen H, Conant R, Landefeld C, Ritchie C, Yukawa M. eds. Current Diagnosis & Treatment: Geriatrics, Second Edition. New York, NY: McGraw-Hill; 2014. Accessed January 31, 2016.

<http://accessmedicine.mhmedical.com/content.aspx?bookid=953&Sectionid=53375673>.

¹¹ Flohil S, van der Leest R, et al. Prevalence of Actinic Keratosis and Its Risk Factors in the General Population: The Rotterdam Study. J Investigat Dermat 2013;133:1971–1978;doi:10.1038/jid.2013.134

¹² See Urman C, et al.

¹³ Efudex, NDA 16-831; Carac, NDA 20-985, Tolak, NDA 22-259. J Investigat Dermat 2013;133:1971–1978; doi:10.1038/jid.2013.134

Database Review

No reviews of ALA could be found in the reproductive toxicology databases Reprotox,¹⁴ TERIS¹⁵ or in LactMed,¹⁶ the toxicology database which curates reviews of drugs and lactation. However, a brief review was found in Shepard's¹⁷ that described the findings of one publication.¹⁸ Rats were orally administered ALA during organogenesis and in the prenatal/postnatal period. In the Shepard's review it was reported that no adverse effects on pregnancy or lactation were observed except at a dose of 180 mg per kg per day at which reduced fetal weight was observed. This reviewer could not locate the publication and cannot ascertain if the reduced fetal weight was associated with maternal toxicity; nor can this reviewer estimate the human dose multiples used.

Literature Review

There are no publications describing the use of the combined drug/device Ameluz in the indicated population during pregnancy. There is one publication which describes PDT using an ALA solution in five pregnant women with intravaginal or perineal condyloma accumulata (CA).¹⁹ This reference is discussed for general information purposes and does not contain human data in the indicated population. The CA lesions in these pregnant women were treated with a combination of 20% ALA and a helium neon laser light source emitting red light at a wavelength of 635 nm for PDT. The patients underwent three to four PDTs at intervals of 7 to 15 days. It was reported that one patient's lesions were completely cleared after three PDTs. The remaining four pregnant women had complete clearing of their CA lesions after four PDTs. All five of the women delivered what were described as normal infants and no severe adverse events were reported.²⁰

DISCUSSION

PLLR

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "Content and Format of Labeling for Human Prescription Drug and

¹⁴ Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed January 24, 2016.

¹⁵ TERIS is the TERatology Information Service located at University of Washington. It is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women. http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/ Accessed January 24, 2016

¹⁶ LACTMED®: The LactMed database is a National Library of Medicine database with information on drugs and lactation. Accessed January 24, 2016.

¹⁷ © 2016 Shepard's: A Catalog of Teratogenic Agents: An updated, automated version of Shepard's Catalog of Teratogenic Agents is distributed with TERIS. Accessed January 24, 2016.

¹⁸ Miyanari, S, Ishizuka M: Effects of 5-aminolevulinic acid phosphate on fertility and early embryonic development to implantation, embryo-fetal development and pre-and postnatal development including maternal function in rats via oral administration. *Jpn Pharmacol Ther* 2011;39:595-610.

¹⁹ Yang Y, Zou X, *et al*. Clinical experience - Photodynamic therapy of condyloma acuminata in pregnant women. *Chin Med J* 2012;125(16):2925-2928.

²⁰ See Yang Y, *et al*.

Biological Products; Requirements for Pregnancy and Lactation Labeling,”²¹ also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule²² format to include information about the risks and benefits of using these products during pregnancy and lactation.

Pregnancy Data

As this is a 505(b)(2) application relying on published literature for the non-clinical reproductive toxicology information, there are no Animal Data to include in subsection (8.1). In the reproductive toxicology databases there was only one review related to ALA administration during pregnancy. The Shepard’s review described one animal study which reported no adverse effects on pregnancy or lactation from oral ALA administration except at a dose of 180 mg/kg which was associated with reduced fetal growth. There was no information on the presence or absence of maternal toxicity and no human dose multiple was provided. This prenatal animal study of the effects of oral ALA administration is not comparable to topical administration of a 10% ALA nanoemulsion gel illuminated with the Ameluz device. Therefore, this animal study does not provide information for the Ameluz pregnancy labeling.

Studies of systemic absorption of a topically applied drug are important to assess a product’s safety. The applicant provided data on the systemic exposure in adults to ALA and PpIX following Ameluz treatment under maximal use conditions. These data were reviewed with the Division and the conclusion was reached that the data demonstrated negligible systemic exposure. The applicant reported no evidence of serious toxicity from use of Ameluz in their clinical studies. The teratogenic risk from use of the Ameluz drug/device appears to be very low and may be hypothetical.

Lactation Data

There was no review of topical administration of ALA followed by PDT with the Ameluz drug device in the LactMed database in any population of lactating women. The data provided by the applicant demonstrates some absorption of ALA occurs from use of the Ameluz drug/device to treat AK, although the systemic exposure to ALA is negligible. The PLLR requires the following:

“For drugs absorbed systemically by the mother, unless breastfeeding is contraindicated during drug therapy, the Risk Summary must include the following risk and benefit statement at the end of the Risk Summary.

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for (name of drug) and

²¹ Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

²² Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006).

any potential adverse effects on the breastfed child from (name of drug) or from the underlying maternal condition.”²³

DPMH attended meetings on December 4, 2015 and February 5, 2016. At the latter meeting DPMH presented their labeling recommendations on Ameluz.

CONCLUSIONS

A review of the applicant’s data and the published literature found no information on the use of the Ameluz (10% ALA) with the BF-RhodoLED lamp in pregnant or lactating women.

- The teratogenic risk from prenatal exposure to Ameluz and the BF-RhodoLED lamp appears to be very low as the exposure from systemic absorption of the drug (ALA, 10%) is negligible based on review of additional data and discussions with the Division.
- The risk to the breastfed infant from maternal treatment with Ameluz and the BF-RhodoLED lamp is likely very low as the maternal exposure is negligible.

RECOMMENDATIONS

The following are the DPMH Maternal Health Team recommendations for the proposed labeling for Ameluz. DPMH refers to the final NDA action for final labeling.

Language was provided in the following sections of the Ameluz labeling:

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 ALA. Systemic absorption of ALA 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.

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 ALA in human milk, the effects of ALA on the breast fed 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 ALA in humans following topical administration of AMELUZ under maximal clinical

²³ (§ 201.57(c)(9)(ii)(A)(3)).

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.

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/s/

CAROL H KASTEN
03/11/2016

TAMARA N JOHNSON
03/11/2016

LYNNE P YAO
03/14/2016

Clinical Inspection Summary

Date	March 3, 2016
From	Roy Blay, Ph.D.
To	Belainesh Robnett Denise Cook, M.D., Gordana Diglisic, M.D. Division of Dermatology and Dental Products
NDA/BLA #	208081
Applicant	Biofrontera Bioscience GmbH
Drug	Aminolevulinic acid HCl gel, 10% with BF-RhodoLED lamp
NME (Yes/No)	No
Therapeutic Classification	Standard
Proposed Indication(s)	Treatment of actinic keratosis of mild to moderate severity on the face and scalp (b) (4)
Consultation Request Date	August 31, 2015
Summary Goal Date	March 7, 2016
Action Goal Date	April 25, 2016
PDUFA Date	May 10, 2016

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Mensing, Jenne, and Karl were inspected in support of this NDA. None of these sites were issued a Form FDA 483. The final classification of the inspections for Drs. Mensing and Karl was No Action Indicated (NAI).

The EIR for the inspection of Dr. Jenne has not been received yet. Knowledge of the status of this inspection is based on communications with the field investigator. Preliminary classification of this inspection is NAI pending receipt and evaluation of the EIR. An inspection summary addendum will be generated if conclusions change after review of the EIR.

The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

2. BACKGROUND

The investigational drug, aminolevulinic acid HCl gel, 10% with BF-RhodoLED lamp, was the subject of Protocol ALA-AK-CT002 entitled “A randomized, observer blind, multinational phase III study to evaluate the safety and efficacy of a nanoemulsion gel formulation BF-200 ALA, in comparison with Metvix® and placebo, for the treatment of actinic keratosis with photodynamic therapy”. The primary efficacy variable was the overall subject complete response assessed 12 weeks after the last PDT. A total of 600 subjects in 32 centers were enrolled in four countries with a study duration between April 8, 2008 and August 21, 2009. The sites below were chosen because only foreign data was available and the sites represented relatively high numbers of enrollees. The sponsor interpreted the findings of the study to indicate that topical application of BF-200 ALA with PDT was effective in the treatment of AK.

3. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects	Inspection Date	Final Classification
118 Mensing, Hartwig Dermatologisches Ambulatorium Heegbarg 4 22391 Hamburg, Germany	ALA-AKCT002/ 46	14-17 Dec 15	NAI
115 Jenne, Lars Gemeinschaftspraxis im Sellspeicher Wall 55 24103 Kiel, Germany	ALA-AKCT002/ 39	30 Nov-4 Dec 15	Pending. Interim classification: NAI
116 Karl, Lars Hautarztpraxis Riga-Ring 15 59494 Soest, Germany	ALA-AKCT002/ 35	19-23 Oct 15	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Mensing, Hartwig**a. What was inspected:**

At this site for Protocol ALA-AK-CT002, 47 subjects were screened, 46 subjects were enrolled, and all 46 subjects completed the study. Source data was compared to line listings. The records of all 46 subjects were reviewed. Records reviewed included, but were not limited to, financial disclosure, delegation of duties, inclusion/exclusion criteria, drug randomization, sponsor, IRB and CRO communications, laboratory results, adverse events, concomitant medications, and test article storage and accountability.

b. General observations/commentary:

Signed informed consent was obtained from all enrolled subjects prior to study entry. A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

c. Assessment of data integrity:

The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Jenne, Lars**a. What was inspected:**

At this site for Protocol ALA-AK-CT002, 39 subjects were enrolled, and 35 subjects completed the study. Records reviewed included, but were not limited to, source documentation, case report forms, adverse events, and sponsor monitoring reports.

b. General observations/commentary:

A Form FDA 483 was not issued at the conclusion of the inspection.

c. Assessment of data integrity:

The EIR has not been received to date. The final classification is pending and the interim classification is NAI. An inspection summary addendum will be generated if conclusions change after review of the EIR.

3. Karl, Lars**a. What was inspected:**

At this site for Protocol ALA-AK-CT002, 39 subjects were screened, 35 subjects were enrolled, and 31 subjects completed the study. Source data was compared to line listings. The records of 19 subjects were reviewed. Records reviewed included, but were not limited to, financial disclosure, inclusion/exclusion criteria, blinding/randomization, efficacy endpoints adverse events, protocol deviations, sponsor, IRB and CRO communications, laboratory certifications, concomitant medication, test article accountability

b. General observations/commentary:

Signed informed consent was obtained from all enrolled subjects prior to study entry. A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

c. Assessment of data integrity:

The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

{ See appended electronic signature page }

Roy Blay, Ph.D.
Good Clinical Practice Enforcement Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: { See appended electronic signature page }

Janice Pohlman, M.D., M.P.H.
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Kassa Ayalew, M.D., M.P.H.
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DDDP/Division Director/Kendall Marcus

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DDDP/MO/Denise Cook

Review Division /Project Manager/Belainesh Robnett

OSI/Office Director/David Burrow

OSI/DCCE/ Division Director/Ni Khin

OSI/DCCE/Branch Chief/Kassa Ayalew

OSI/DCCE/Team Leader/Janice Pohlman

OSI/DCCE/GCP Reviewer/Roy Blay

OSI/GCP Program Analysts/Yolanda Patague/Joseph Peacock

OSI/Database PM/Dana Walters

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/s/

ROY A BLAY
03/04/2016

JANICE K POHLMAN
03/04/2016

KASSA AYALEW
03/04/2016

LABEL, LABELING, AND PACKAGING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	January 28, 2016
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 208081
Product Name and Strength:	Ameluz (aminolevulinic acid) Gel, 10%
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Biofrontera Pharmaceuticals
Submission Date:	July 10, 2015
OSE RCM #:	2015-1650
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

This review responds to a request from the Division of Dermatology and Dental Products (DDDP) to evaluate the container label and carton labeling for Ameluz gel (NDA 208081), submitted on July 10, 2015, for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – n/a
ISMP Newsletters	D – n/a
FDA Adverse Event Reporting System (FAERS)*	E – n/a
Other	F – n/a
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The applicant is proposing to market Ameluz in 2 g tubes for use by healthcare professionals only, as the product is used in combination with photodynamic therapy using the BF-RhodoLED® lamp.

We note that the established name is not presented within parenthesis as per draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors¹. In addition, the carton labeling indicates that the product should be used within 3 months after opening; however, the carton does not provide a means to keep track of the 3 months use date. DMEPA recommends adding the statement “Discard after: __/__/__”. Finally, the NDC number is presented with a placeholder “XXXXX-XXX-XX”.

4 CONCLUSION & RECOMMENDATIONS

We recommend the following be implemented prior to approval of this NDA.

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

4.1 RECOMMENDATIONS FOR THE BIOFRONTERA PHARMACEUTICALS

A. General (container label and carton labeling)

1. Revise the established name to be presented within parenthesis.

Ameluz

(aminolevulinic acid HCl) Gel, 10%

2. Revise the NDC placeholder with the actual NDC number.

B. Carton Labeling

1. Relocate the statement “For use with BF-RhodoLED lamp” from the side panel to the principal display panel after the route of administration statement. For example: “For Topical Use Only with BF-RhodoLED lamp”.
2. Revise the statement “Use contents within 3 months after opening.” to include the phrase “Discard after: __/__/__”. This will allow healthcare providers to keep track of the 3 months use date.
3. Revise the storage statement to use bold font for the first part of the statement. For example: “**Store refrigerated 2°-8°C (36°-46°F)**, excursions permitted to 15°-30°C (59°-86°F).”

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ameluz that Biofrontera Pharmaceuticals submitted on July 10, 2015.

Table 2. Relevant Product Information for Ameluz	
Initial Approval Date	n/a
Active Ingredient	Aminolevulinic acid
Indication	In combination with photodynamic therapy using the BF-RhodoLED® lamp, is indicated for the treatment of actinic keratoses of mild to moderate severity of the face and scalp (b) (4)
Route of Administration	Topical
Dosage Form	Gel
Strength	10%
Dose and Frequency	Apply gel approximately 1 mm thick to the lesion or field, and to include approximately 5 mm of surrounding skin. Prepare area to be treated, apply gel, occlude treated area and illuminate after 3 hours as recommended.
How Supplied	2 g aluminum tubes
Storage	2° – 8°C (36° - 46°F). Excursions permitted to 15° – 30°C (59° -86°F)
Container Closure	(b) (4) aluminum tube and high density polyethylene cap.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On January 20, 2016, we searched the L:drive and AIMS using the terms, Ameluz, to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any relevant reviews.

APPENDIX C. HUMAN FACTORS STUDY

N/A

APPENDIX D. ISMP NEWSLETTERS

N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

APPENDIX F. OTHER SOURCES

N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,² along with postmarket medication error data, we reviewed the following Ameluz labels and labeling submitted by Biofrontera Pharmaceuticals on July 10, 2015.

- Container label
- Carton labeling
- Instructions for Use

G.2 Label and Labeling Images (not to scale)

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

CARLOS M MENA-GRILLASCA
01/28/2016

MISHALE P MISTRY
01/28/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208081 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Established/Proper Name: aminolevulinic acid HCl Dosage Form: gel Strengths: 10%		
Applicant: Biofrontera Bioscience GmbH Agent for Applicant (if applicable): Cardinal Health Regulatory Sciences		
Date of Application: July 10, 2015 Date of Receipt: July 10, 2015 Date clock started after UN: N/A		
PDUFA/BsUFA Goal Date: May 10, 2016		Action Goal Date (if different): April 25, 2016
Filing Date: September 8, 2015		Date of Filing Meeting: August 26, 2015
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☒ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): For (b) (4) treatment of actinic keratosis (AK) of mild to moderate severity on the face and scalp (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		
Type of BLA		☐ 351(a) ☐ 351(k)

<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	
Review Classification:	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
<i>The application will be a priority review if:</i> <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> <i>The product is a Qualified Infectious Disease Product (QIDP)</i> <i>A Tropical Disease Priority Review Voucher was submitted</i> <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i>	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☒ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☒ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 115412				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	☒	☐		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	☒	☐		
Is the review priority (S or P) and all appropriate	☒	☐	☐	Standard

classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>				
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm If yes, explain in comment column.	☐	☒		
If affected by AIP, has OC been notified of the submission? If yes, date notified:	☐	☐		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		
User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: ☒ Not in arrears ☐ In arrears			
User Fee Bundling Policy <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ Yes ☐ No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes, answer the bulleted questions below:	☐	☒		
• Is the application for a duplicate of a listed drug and	☐	☐		

eligible for approval under section 505(j) as an ANDA?																				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	☐	☐																		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>	☐	☐																		
Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes, please list below: <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													☐	☐		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm	☐	☒																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	☐	☐	☒																	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>																				
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☒	☐	☐																	
If yes , # years requested: 3 years																				
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>																				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic	☐	☒	☐																	

use?				
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☐	☒	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	N/A			
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: ☒ legible ☒ English (or translated into English) ☒ pagination	☒	☐		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

☒ navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	☐	☐	☒	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	☒	☐		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	☒	☐		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	☒	☐		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment

Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	☐	☐	☒	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to</i>	☒	☐		PeRC Meeting: December 2, 2015

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

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<i>approval of the application/supplement.</i>				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)?	☒	☐	☐	March 27, 2015
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application?	☐	☐	☒	Agreed-upon iPSP contains full waiver request for pediatric studies
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	☐	☒		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	☒	☐	☐	Proprietary name request submitted August 26, 2015
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	☐	☒	☐	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☒ Other (specify) User Manual for the RhodoLED Lamp			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	☒	☐		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

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If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?⁵	☒	☐	☐	Edits to the PLLR format will be included in the 74-day letter.
Has a review of the available pregnancy and lactation data been included?	☐	☒	☐	This deficiency will be addressed in the 74-day letter.
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	☐	☐	☒	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	☐	☐		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	☒	☐	☐	CDRH, OSI and DPMH
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): October 8, 2014 <i>If yes, distribute minutes before filing meeting</i>	☒	☐		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 26, 2015

BACKGROUND: The NDA 208081 is an original application that provides for the treatment of actinic keratosis (AK) of mild to moderate severity on the face and scalp (b) (4)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Belainesh Robnett	Y
	CPMS/TL:	Barbara Gould/Paul Phillips	N/Y
Cross-Discipline Team Leader (CDTL)	Gordana Diglisic		N
Division Director/Deputy	Kendall Marcus/Jill Lindstrom		Y/N
Office Director/Deputy	Julie Beitz/Amy Egan		N
Clinical	Reviewer:	Denise Cook	Y
	TL:	Gordana Diglisic	N
Social Scientist Review (for OTC products)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OTC Labeling Review (for OTC products)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Microbiology (for antimicrobial products)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Pharmacology	Reviewer:	Chinmay Shukla	Y
	TL:	Doanh Tran	Y
• Genomics	Reviewer:	N/A	N/A
• Pharmacometrics	Reviewer:	N/A	N/A
Biostatistics	Reviewer:	Carin Kim	Y

	TL:	Mohamed Alosch	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jiaqin Yao	Y
	TL:	Barbara Hill	Y
Statistics (carcinogenicity)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Product Quality (CMC) Review Team:	ATL:	Hitesh Shroff	Y
	RBPM:	Yokum Ankara	Y
• Drug Substance	Reviewer:	Roger Farr	N
• Drug Product	Reviewer:	Hitesh Shroff	Y
• Process	Reviewer:	Kejun Cheng	Y
• Microbiology	Reviewer:	Eric Adeeku	Y
• Facility	Reviewer:	Vipulchandra Dholakia	Y
• Biopharmaceutics	Reviewer:	Vidula Kolhatkar	Y
• Immunogenicity	Reviewer:	N/A	N/A
• Labeling (BLAs only)	Reviewer:	N/A	N/A
• Other (e.g., Branch Chiefs, EA Reviewer)	Kelly Kitchens		Y
	Moo Jong Rhee		N
	Benjamin Lim		N
	Chidambaram Nallaperumal		N
	Paul Dexter		N
	Ghosh Tapash		N
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Tara Turner	Y
	TL:	Janet Anderson	Y
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Carlos Mena-Grillasca	Y
	TL:	Kendra Worthy	N
OSE/DRISK (REMS)	Reviewer:	Robert Pratt	Y
	TL:	N/A	N/A
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	N/A

	TL:	N/A	N/A
Bioresearch Monitoring (OSI)	Reviewer:	Roy Blay	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Other reviewers/disciplines			
CDRH	Reviewer:	Richard Felten Crystl Lewis	Y Y
	TL:		
Other attendees	DDDP :Nancy Xu, Acting Director for Labeling		Y
	OSE/OPE/DPVI: Jessica Weintraub		Y

FILING MEETING DISCUSSION:

GENERAL 505(b)(2) filing issues: - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? - Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO
Electronic Submission comments List comments:	☐ Not Applicable ☒ No comments

CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☒ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments: Biopharmaceutical filing review comments	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments:	☐ Not Applicable ☐ YES ☒ NO

<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Kendall A. Marcus, MD Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): N/A 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAAs completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BELAINESH ROBNETT
09/14/2015

J P PHILLIPS
09/15/2015

**REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Application: NDA 208081

Application Type: New NDA

Name of Drug/Dosage Form: aminolevulinic acid HCl gel, 10% with BF-RhodoLED

Applicant: Biofrontera Bioscience GmbH

Receipt Date: July 10, 2015

Goal Date: May 10, 2016

1. Regulatory History and Applicant's Main Proposals

The following is the regulatory history for this product: Meeting Minutes for Type B (Pre-NDA) meeting (10/8/2014); Agreed Upon iPSP (3/27/2015)

The applicant proposes a new dosage form.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant via email with an attached draft red-lined document during labeling discussions. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by March 9, 2016. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: A horizontal line was added to separate the TOC from the FPI.

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: White spaces between the HL Heading and HL Limitation Statement and the product i

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

Selected Requirements of Prescribing Information

• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit** year.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and

Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Selected Requirements of Prescribing Information

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- NO** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *The FDA number was missing "FDA" and had the numerical equivalent (i.e. 332) . In addition the applicant had periods "." separating the phone number instead of a*

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

NO 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”

Comment: *The numbering in section 8 needs to be corrected for subsections 8.4 Pediatric Use and 8.5 Geriatric Use.*

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: Headings for subsection 8.3 and 8.4 corrected to 8.4 and 8.5.

- N/A** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*]” or “[see *Warnings and Precautions (5.2)*]”.

Comment: The applicant did not include any cross-references in the labeling.

N/A

Selected Requirements of Prescribing Information

34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment: *Labeling contains contraindications.*

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“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.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). 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.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]

Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)]

[m/year]

[section (X.X)]

[m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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/s/

BELAINESH ROBNETT
09/11/2015

August 24, 2015

Consulting Review for NDA 208081

Submitted by Biofrontera Bioscience GmbH

Reviewed by Richard P. Felten, CDRH, ODE, DSD, GSDB 1

This review is limited to the light system portion of this NDA application. The NDA application is for a combination drug/device system that is intended for the use of a light sensitive drug in combination with a light source that is used to activate the light sensitive drug. The proposed indication for use for this combination drug/device system is "Treatment of actinic keratosis of mild to moderate severity on the face and scalp (b) (4)". The photosensitizing drug is aminolevulinic acid gel, HCl 10% (Ameluz). The light source to be used to activate this drug is the BF-RhodoLED system. This review is limited to the BF-RhodoLED light system.

The BF-RhodoLED light system is described as incorporating 128 LED's with a peak output of 635 nm. The output fluence for treatment is fixed at 37 J/cm² using a fixed treatment time of 10 minutes. The output fluence for successful treatment has been tested with the lamp placed 5-8 cm from the targeted treatment site with the optimal distance being stated as 6 cm. The light output area is 8 x 18 cm with the effective treatment area being 6 x 16 cm. It should be noted that the company has stated in this filing that the fixed output characteristics is limited to US use and that the light output can be adjusted in the European model. The company has demonstrated that light uniformity in terms of light spectra and light energy is essentially the same within the 5-8 cm distance in terms of treatment effectiveness.

As part of this application Biofrontera has included comparison testing of spectral output, peak wavelength and peak power for a number of similar lamps that have been used in treating face and scalp actinic keratosis using similar topical aminolevulinic acid solutions. The spectral output scan does show that the peak output for the BF-RhodoLED is 635 nm which is extremely close to the 628 nm peak output of the Aktilite, CL-128 which was approved for use with topical aminolevulinic acid for treating face and scalp actinic keratosis. As part of this testing the company also examined the output power stability across the 10 minute treatment time and this testing does show stable output for the total treatment time.

The company has provided a User Manual for their lamp. This manual includes cautions and warnings related to device use in terms of physical safety issues related to possible user injury associated with moving the device and adjustments to the movable light emitting arms. The manual includes a discussion of the light output characteristics and how these conform to the absorption characteristics of protoporphyrin IX (PPIX) which is the cellular target for treatment. The theory of treatment is that the topically applied Ameluz gel will be absorbed by the actinic keratosis resulting in an increase in cellular concentration of PPIX which when activated by red

light generates singlet oxygen resulting in cell death of the actinic keratosis. The manual includes recommendation for wearing of protective eyewear by user and patient. The manual provides a detailed step-by-step instruction for use of the lamp to provide light exposure for therapy with accompanying pictures and illustrations showing correct lamp placement. The manual also includes sections on maintenance and cleaning, possible error messages and trouble shooting.

The company has provided software development and validation information. The initial review of this material noted that the information contained in the figures of the individual software sections had not been translated. Mr. Vallee of Cardinal Health, the official contact person for the NDA was contacted by telephone and a request made for the complete translation. A request was also made to have all of the software placed on a single standalone disc since the original disc had software information scattered throughout the file. At this time the corrected disc has been received but a full review of the software has not yet been completed.

Based on the review of the information provided, I recommend that the NDA be filed from a device perspective. The information provided, including the User Manual, has more than adequately described the device, the device characteristics and device directions for use.

This review has identified several issues that I believe need to be addressed:

1. In the User Manual on page 11/25, section 7.2.2 shows the Home Screen which includes a place for lamp settings. The company has stated that the US version has output energy and time fixed. Biofrontera should clarify what is the function of the setting feature in the US model or provide a statement that this feature has been disabled in the US model.
2. On page 4/25, Intended Use, the intended use is given as "...used exclusively in combination Ameluz gel for (b) (4)". I would recommend that the intended use state the specific indication for use that will be granted for Ameluz in this NDA. Since the lamp will be sold as a separate item and it is possible that Ameluz may obtain approval for indications outside the US not granted in the US, the US model's User Manual should clearly state the US approved indication for use.
3. Since the last step in the treatment of actinic keratosis using Ameluz will be light exposure, it seems appropriate that the lamp User Manual should also include any warnings or precautions associated with possible photosensitive side-effects from the treatment. I believe that addition of these precautions to the BF-RhodoLED User Manual would be appropriate since the light exposure is the last step in the treatment process.

A non-review issue that needs to be addressed deals with lamp manufacturing site inspection of the NDA is approved. If this needs to be performed by Office of Compliance in CDRH then the appropriate contact needs to be made between CDER and CDRH. In addition of Office of Compliance in CDRH does perform this inspection it may be necessary to have a separate file describing the BF-RhodoLED lamp manufacturing prepared for CDRH review.

This review did not comment on the adequacy of the comparison testing performed comparing the BF-RhodoLED lamp to several other similar lamps such as the Aktilite CL-128. It was not clear from the information contained in the device section why these comparisons had been made. It should be noted that all of the lamps did appear to have peak outputs well within the absorption curve for protoporphyrin IX and therefore all of the lamps could potentially be used for activation of a topical drug that results in an increase in intracellular protoporphyrin IX.

From a device perspective I recommend Filing of this NDA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BELAINESH ROBNETT
09/10/2015