CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208081Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **May 10, 2016**

From: **Hitesh Shroff, Ph.D.**
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: **CMC Review #1 of NDA 208081**

Subject: Final Recommendation for NDA 208081

At the time when the CMC Review #1 was completed on March 31, 2016, it had noted the following pending issues:

- The label/labeling issues were not resolved.
- Final "Acceptable" recommendation from the Office of Process and Facilities was not issued.
- The CDRH consult reviews for BF-RhodoLED lamp were not completed from the Office of Compliance and Office of Device Evaluation.

Because of these deficiencies, the NDA was not recommended for approval from the ONDP perspective.

On April 14, 2016, the immediate container label was revised. The package insert and the carton label were also revised and submitted on April 28, 2016. The CMC sections of the package insert, immediate container label and carton label were reviewed by Dr. Hitesh Shroff and found acceptable (**Attachment – 1).**

On May 10, 2016, the Office of Process and Facilities issued the overall "Approval" recommendation for the facilities involved in this NDA (**Attachment – 2)**.

On March 17, 2016, the Office of Device Evaluation, CDRH, has made an Approval recommendation of the BF-RhodoLED lamp red light system for photodynamic therapy in combination with Ameluz gel (see the Review conducted by Dr. Richard P. Felten, dated March 17, 2016)

On May 09, 2016, the Office of Compliance, CDRH, has issued a final approval recommendation for the applicant's Quality System Requirements for the device based on the review conducted by Dr. Crystal Lewis.

Recommendation:

This NDA is now recommended for Approval from the ONDP perspective.

Application Technical Lead's Assessment and Signature

The NDA is recommended for Approval from quality

perspective. Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
May 10, 2016

Hitesh N. Shroff -A

Digitally signed by Hitesh N. Shroff -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -A
Date: 2016.05.10 14:12:01 -04'00'

Attachment 1:

1. *Package Insert*

(a) "Highlights" Section

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AMELUZ safely and effectively. See full prescribing information for AMELUZ.

AMELUZ® (aminolevulinic acid hydrochloride) gel, 10%, for topical use
Initial U.S. approval: 1999

----------DOSAGE FORMS AND STRENGTHS----------
Gel: 10% (3).

(b) "Full Prescribing Information" Section

#3. Dosage Form and Strength

3. DOSAGE FORMS AND STRENGTHS

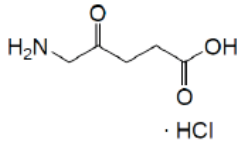
Each gram of AMELUZ gel, 10% contains 100 mg of aminolevulinic acid hydrochloride (equivalent to 78 mg of aminolevulinic acid).

#11. Description

11. DESCRIPTION

AMELUZ (aminolevulinic acid hydrochloride) gel, 10% for topical use is a non-sterile white-to-yellowish gel. The gel formulation contains a nanoemulsion.

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, molecular weight is 167.59 and molecular formula is $C_5H_9NO_3 \cdot HCl$. The structural formula of aminolevulinic acid hydrochloride is represented below:



Each gram of AMELUZ contains 100 mg of aminolevulinic acid hydrochloride (equivalent to 78 mg aminolevulinic acid) 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.

#16 How Supplied/storage and Handling

16. HOW SUPPLIED/STORAGE AND HANDLING

AMELUZ (aminolevulinic acid hydrochloride) gel, 10% is a white-to-yellowish gel. The drug product is supplied in an aluminum tube with a white, high density polyethylene (HDPE) screw cap. Each tube contains 2 g of gel.

NDC 70621-101-01 2 g tube

Store AMELUZ in a refrigerator, 2°C– 8°C (36°F - 46°F). Excursions permitted to 15°C – 30°C (59°F -86°F).

After opening, AMELUZ can be stored for up to 12 weeks in a refrigerator at 2°C – 8°C (36°F - 46°F) if the tube is tightly closed.

1 Page of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reviewer's Assessment and Signature:

The final label and labeling submitted on April 14 and April 28, 2016 are satisfactory from ONDP perspective.

Reviewer's Signature:
Hitesh Shroff, Ph.D.
Branch V
Division of New Drug Products II/ONDP

Hitesh N. Shroff -A

Digitally signed by Hitesh N. Shroff -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -A
Date: 2016.05.10 14:05:11 -04'00'

Secondary Review Comments and concurrence:

Supervisor's Signature:
Moo-Jhong Rhee, Ph.D.
Branch V
Division of New Drug Products II/ONDP

Moojhong Rhee -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Moojhong Rhee -S, 0.9.2342.19200300.100.1.1=1300041261
Date: 2016.05.10 14:09:19 -04'00'

Attachment 2:

Facilities:

Memorandum	**Department of Health and Human Services** **Public Health Services** **Food and Drug Administration** **Center for Drug Evaluation and Research**
Date:	**May 10, 2016**
From:	**Vipul Dholakia, Ph.D., Consumer Safety Officer** **Division of Inspectional Assessment/ Branch 3**
Through:	**Juandria Williams, Quality Assessment Lead** **Division of Inspectional Assessment/Branch 3**
To:	**CMC Review #1 of NDA 208-081**
Subject:	**Facility Final Recommendation**

The OPQ Review # 1 for NDA 208-081 was closed March 31, 2016. The Facility Review was not finalized at that time because the review of the inspection reports of the Drug Substance manufacturing facility, [redacted] (b) (4); Drug Product manufacturing facility, [redacted] (b) (4); Control Testing Laboratory, [redacted] (b) (4) and Device manufacturing facility, Biofrontera Pharma GmbH, Germany were pending. Reviews of these inspection reports are completed and the above mentioned facilities are acceptable.

Signature: Vipul Dholakia

Vipul Dholakia -S
Digitally signed by Vipul Dholakia -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Vipul Dholakia -S, 0.9.2342.19200300.100.1.1=2000342958
Date: 2016.05.10 10:50:57 -04'00'

Juandria Williams -S
Digitally signed by Juandria Williams -S
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Date: 2016.05.10 11:40:15 -04'00'

ASSESSMENT OF THE FACILITIES

Revised on 05/09/2016

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

S.2.1 Manufacturer(s)

35. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
(b) (4)		**CSN:** API manufacturing, (b) (4) (b) (4)	High No Inspection History	Last Inspection (b) (4) OAI to VAI	Acceptable

Reviewer's Assessment:

(b) (4): The firm is responsible for manufacturing API Aminolevulinic Acid Hydrochloride. This site did not have any inspection history and was not inspected by FDA before. Based on no inspection history, initial risk was identified as high and a pre-approval inspection was required. This facility operates as an Intermediate and Finished Active Pharmaceutical Ingredient (API) manufacturer and currently has two (2) pending Agency applications for the US market, NDA 208-081 and (b) (4). The facility currently manufactures Intermediates and APIs for the domestic (b) (4) market. The initial GMP and Pre-approval inspection of API manufacturer was conducted in (b) (4) and covered Quality, Laboratory, Materials, Facilities and Equipment, Production, and limited coverage of Packaging and Labeling.

At the conclusion of this inspection, Form FDA 483 was issued for the significant deficiencies related to production batch records found in trash area, investigation not completed for OOS results, laboratory worksheets not controlled, periodic requalification of analytical reference standard not performed, rust paint/chipping observed on the manhole of the reactor, not all raw material supplier qualified, purified water system component not labeled and identified and training for production personnel was found inadequate. These observations did not have any direct impact on the manufacture operation of API, Aminolevulinic acid. This inspection was initially classified as OAI and based on the firm's responses CDER reviewer downgraded it to VAI,

and the facility is considered acceptable for manufacturing API, Aminolevulinic Acid Hydrochloride.

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

P.3.1 Manufacturer(s)

36. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
(b) (4)		**OIN:** DP manufacturing, (b) (4) (b) (4) packaging & labeling	High No Inspection History	Last Inspection (b) (4) VAI	Acceptable
		CTL: (b) (4) testing of finished product	LOW	Last Inspection (b) (4) NAI	Acceptable
		CTL: (b) (4) analysis of the finished product	High No Inspection History	Last Inspection (b) (4) OAI to VAI	Acceptable
Biofrontera Pharma GmbH, Germany	3011764519	**DKA:** Device manufacturing – Red light lamp	High No Inspection History	Recent Inspection on May 2-6, 2016 NAI	Acceptable

Reviewer's Assessment:

(b) (4) The firm is a contract manufacturer for the finished drug product 5-Aminolevulinic acid hydrochloride (Ameluz Gel). This site did not have any inspection history and was not inspected by FDA before. Based on no inspection history, initial risk was identified as high. This product is approved and marketed in Europe. The initial GMP and Pre-approval inspection of this facility was performed from (b) (4) and was classified as VAI. Minor observations were identified related to supplier controls and qualifications, inadequate SOPs for training, maintenance and sampling. There were no issues for the Pre-approval coverage of the application. In this inspection quality, materials, equipment & facilities, production, laboratory controls and packaging & labeling systems were covered. As the objectionable conditions were considered minor, had no impact on the Pre-approval of the current application, and there were no outstanding concerns related to readiness for manufacture, equipment or integrity of data submitted in the application that could impact the approvability of the facility.

Based on the current compliance status and the inspectional coverage, this facility is at low risk in performing the manufacturing operations and is acceptable for manufacturing the finished product 5-Aminolevulinic Acid Gel 5%.

(b) (4) This facility provides contract services for microbial (90%) and analytical (10%) testing services for pharmaceuticals and medical devices. There is no manufacturing conducted at this site.

This contract testing laboratory was inspected in (b) (4) and was classified as NAI and no objectionable condition was identified. In the previous inspection performed in (b) (4), only one observation for not performing method verification of USP and other monographs methods used in analytical work for samples representing products for USA markets. This item was corrected and site was acceptable.

Based on the GMP history, inspectional coverage and current compliance status as a control testing laboratory of finished drug product, this site is at low risk and is acceptable.

(b) (4)

This facility is a contract testing laboratory providing purity analysis of the finished drug product. The (b) (4) only involvement in this NDA product is to perform one specialized impurity test using HPLC/MS on finished drug product BF 200 ALA 10% Gel filed under NDA 208-081. The initial GMP and pre-approval inspection of this laboratory was performed on (b) (4) and was classified as OAI. At the conclusion of the inspection, a few deficiencies were identified related to deviations from written specifications, standards were not recorded, suitability of the test methods not verified, laboratory records do not include complete record of all data and routine inspection of automatic and electronic equipment not performed. During this inspection quality, material, facility and equipment and laboratory systems were inspected and CTL profile was covered.

The review of EIR, 483 observations and the responses was performed by CDER/OPQ/OPF and the responses were found adequate. Based on the review the inspection classification was downgraded to VAI from OAI and the facility is acceptable.

Biofrontera Pharma GmbH, Germany, (DKA), FEI: 3011764519: This facility is responsible for the manufacturing, testing and release of the red light lamp BF-RhodoLED device. This site has no inspectional history and therefore, pre-approval inspection of this device site was recommended by CDRH. This site was inspected for the device from May 2 - 6, 2016 and no objectionable conditions were observed. This site is considered acceptable for the manufacture of BF RhodoLED Lamp.

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

All Facilities listed in this application are acceptable.

Vipul Dholakia, Ph.D., OPQ/OPF/DIA/Branch 3

May 9, 2016

Secondary Review Comments and Concurrence:

I concur with the overall recommendation.

Juandria Williams, PhD; DIA/B3

May 9, 2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service
Food and Drug Administration (FDA) Center for Devices and
Radiological Health (CDRH) Office of Compliance, Division of
Manufacturing & Quality (DMQ) Respiratory, ENT, General Hospital,
Ophthalmic Device Branch (REGO)

DATE: September 22, 2015 **(Updated April 28, 2016)**

TO: Juandria Williams, CDER/DIA/OPF
Juandria.Williams@fda.hhs.gov

Grace McNally, CDER/OPQ/OPF/DIA/IABIII
Grace.McNally@fda.hhs.gov

Office of combination products at combination@fda.gov

RPM: Juandria Williams

Through: LT Viky Verna, Combination Product Branch Lead, REGO, DMQ, OC, CDRH, OMPT

Viky Verna -S

Digitally signed by Viky Verna -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Viky Verna -S, 0.9.2342.19200300.100.1.1=2000495623
Date: 2016.05.09 16:58:16 -04'00'

From: Crystal Lewis, REGO, DMQ, OC, CDRH. WO-66, Room 3452

Applicant:

Biofrontera Pharma GmbH
Hemmelrather Weg 201
D-51377 Leverkusen
FEI# 3011764519

Application# NDA 208081

Consult # ICC#1500405

Product Name: Ameluz

Consult Instructions: This consult was received from the CDER to identify relevant device constituent facilities and determine their acceptability to support the supplement.

Documentation Review: No Additional Information Required

Final Recommendation: Approval

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA 208081.

PRODUCT DESCRIPTION

The BF-RhodoLED is a lamp used in photodynamic therapy (PDT). It is used with Ameluz, 5-aminolevulinic acid 10% gel for the treatment of mild to moderate actinic keratoses (AKs). This is a (b) (4) treatment for the face, scalp, (b) (4). Affected areas are treated with Ameluz gel and an incubation of three hours occurs with a light-tight occlusion. The area is then illuminated with the BF-RhodoLED lamp from a five to eight centimeter distance. Photochemical processes are triggered by the illumination, generating toxic compounds, which then destroy neoplastic cells.

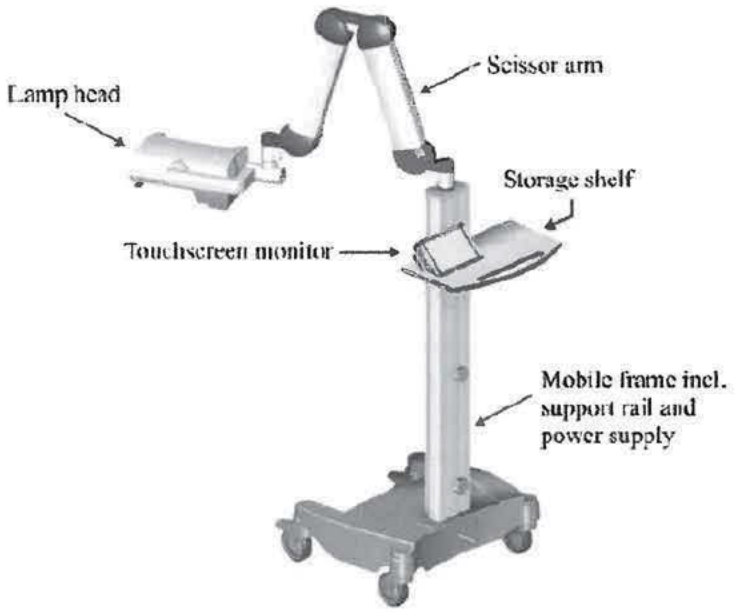


Figure 1- BF-RhodoLED® - key components

REGULATORY HISTORY

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

1. Biofrontera Pharma GmbH
   Hemmelrather Weg 201
   D-51377 Leverkusen
   FEI# 3011764519

This manufacturing site is responsible for the final manufacturing, testing and release of the red light lamp BF-RhodoLED device constituent part. An analysis of the firm's inspection history revealed no inspection history. Therefore, an inspection is required for the firm. This document will be updated once an inspection has been completed and the inspection results become available.

Update (Date: 5/9/16):
A medical device inspection was performed (b) (4). The inspection covered medical device requirements and was classified NAI.

2. (b) (4)

This manufacturing site is responsible for the manufacturing and packaging of the active pharmaceutical ingredient (API). Quality control of starting materials and reagents used for manufacturing, in-process controls, final testing and batch release of the final drug substance is performed at this facility. Also, stability testing occurs at this facility. The firm is not responsible for activities involving the device constituent part. Therefore, an inspection is not required for the firm.

3. (b) (4)

This site covers the manufacturing of bulk finished drug product, primary packaging, labelling and secondary packaging. No further information was provided regarding the packaging for this product. This facility is also responsible for quality controls including starting materials and finished drug product. No inspectional history was found for (b) (4) An inspection is not required because the firm is not responsible for the manufacturing of the device constituent part.

4. (b) (4)

This manufacturing site is responsible for the microbiological analysis of the finished product. The most recent inspection was performed (b) (4) An inspection is not required because the firm is not responsible for activities involving the device constituent parts.

5. (b) (4)

(b) (4)

This manufacturing site is responsible for the purity analysis of the finished drug product. No inspectional history was found for (b) (4)
An inspection is not required because the firm is not responsible for activities involving the device constituent part.

DOCUMENTATION REVIEW

(b) (4)

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Acceptance Activities
The firm's documentation for Acceptance Activities was not found. Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.80(b),(c),(d).

Update (Date: 4/28/16):
SOP-LO-014 describes the firm's purchasing procedures from approved contractors confirming incoming products meet specification. Further, incoming products are tested per SOP-LO-015, which include specifications for material and components used for the manufacture of the BF-RhodoLED device.

The device master record includes work instructions in AA-MD-011 and tests that confirm the safety and functionality of the BF-RhodoLED device. Once the release data and documentation are reviewed, the head of QC releases the finished medical device for distribution.

RECOMMENDATION
The application for NDA 208081 is approvable from the perspective of the applicable Quality System Requirements.

(1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.
(2) The recommended pre-approval inspections were performed and deemed acceptable.

DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=PIV, serialNumber=D72A10D821086C4471A26DA1685901084990C04D872A8243E7
Date: 2016.05.09 17:02:48 -04'00'

Crystal Lewis

Prepared: CLewis: 08/27/2015; 04/28/2016

Reviewed: VVerna: 08/28/2015; 9/18/2015; 9/22/2015; 9/22/2015; 3/11/16; 5/9/2016

CTS No.: ICC1500405;

NDA 208081

Review Cycle Meeting Attendance:

Month/Day/Year

Month/Day/Year

Month/Day/Year

March 17, 2016

Review NDA 208081, Consult memo

Submitted by Biofrontera Bioscience GmbH

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

Richard P. Felten -A
2016.03.17 10:59:46 -04'00'

Biofrontera Bioscience GmbH submitted the BF-RhodoLED Light System to NDA 208081 as the activation light source for the photosensitizing drug Ameluz. Biofrontera is requesting approval for this combination drug/device system for "treatment of actinic keratosis of mild to moderate severity on the face and scalp (b) (4) ."

The BF-RhodoLED light system incorporates 128 LED's with a peak output of 635 nm. The output fluence for treatment is fixed at 37 J/cm^2 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. The company has stated that the output characteristics have been fixed for the US market however for the European market these can be adjusted. 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.

To support their application Biofrontera provided 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 test lamps include the Hydrosun PhotoDyn; Omnilux EL1258S; and the Aktilite CL-128. In terms of spectral output the peak output for the BF-RhodoLED is 635 nm; for the Aktilite CL-128 it is 628 nm; and for the Omnilux it is 630 nm. Because of the narrowness of these peak outputs these three light systems can be considered as "Narrowband Lamp Systems". 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. All of the devices listed above as being "Narrowband Laser Systems" have wavelengths that are within the spectral absorption band for protoporphyrin IX which is the targeted photosensitizer within the actinic keratotic lesion. Thus clinical data obtained using any of these three lamps can be equivalent since the light interaction and activation processes from each lamp on protoporphyrin IX would be considered identical.

The Hydrosun PhotoDyn does not meet the criteria of narrowband lamp system since its output is from 550 nm to 739 nm, therefore, any clinical outcomes using this lamp cannot be considered

as providing similar effects as the clinical effects seen from using "Narrowband Lamp Systems" for the treatment of actinic keratosis.

Review of the revised User Manual provided for the BF-RhodoLED lamp system has identified no issues with the device labeling and instructions for use. Use of this manual is acceptable.

I have provided comments to Nancy Xu related to device sections of the drug labeling and the device sections of the drug labeling are acceptable.

From a device perspective there are no outstanding issues related to the BF-RhodoLED lamp system. Based on my review of the device information submitted in this NDA I would recommend Approval from the device perspective.

I concur.

Neil R Ogden -S
2016.03.18 10:55:31 -04'00'

Chief GSBD1

I concur

Jennifer R. Stevenson -A
2016.03.18 15:20:11
-04'00'

Deputy Director, DSD

Recommendation: This 505(b)(1) application is **not** deemed ready for approval as of this review in its present form, per 21 CFR 314.125 (b)(6) and (13).

NDA 208081
Review # 1

Drug Name/Dosage Form	Aminolevulinic acid hydrochloride
Strength	10%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Biofrontera Bioscience GmbH
US agent, if applicable	Cardinal Health

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original submission	07/10/2015
Amendment	07/22/2015
Amendment	08/17/2015
Amendment	10/21/2015
Amendment	10/30/2015
Amendment	12/22/2015
Amendment	02/01/2016
Amendment	03/01/2016
Amendment	03/03/2016

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Roger Farr	ONDP Branch II/DLA
Drug Product	Hitesh Shroff	ONDP Branch V/DNDP II
Process	Kejun Cheng	OPF Branch VIII/DIII
Microbiology	Eric Adeeku	OPF Branch I/DIV
Facility	Vipulchandra Dholakia	OPF Branch III/DIAV
Biopharmaceutics	Vidula Kolhatkar	ONDP Branch II/DB
Regulatory Business Process Manager	Ankara "Nikki" Yokum	OPRO Branch II/DI
Application Technical Lead	Hitesh Shroff	ONDP Branch V/DNDP II
Laboratory (OTR)	N/A	N/A
ORA Lead	Paul Perdue	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	Rannan Bloom	OPQ/ONDP

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	09-11-2015	Reviewed by R. Farr, Ph.D.
	Type III			N/A	N/A	N/A
	Type IV			Adequate	06-02-2011	No significant changes reported since last review.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A	N/A	N/A

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH/ODE	Pending			John Felton
CDRH/OC	Pending			Lewis Crystal
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The Office of Process and Facilities has not made a final overall "Approval" recommendation for the facilities involved in this application. (See **Attachment A**).

The label/labeling issues have not been completely resolved as of this review.

CDRH consult reviews for BF-RhodoLED lamp have not been completed from the Office of Compliance and Office of Device Evaluation.

Therefore, from the OPQ perspective, this NDA is ***not*** ready for approval at this time in its present form per 21 CFR 314.125 (b)(6) and 21 CFR 314.125 (b)(13), until above issues are satisfactorily resolved. (see **List of Deficiencies on p. 101**)

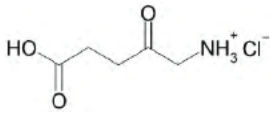
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Quality Assessments

A. Drug Substance [Aminolevulinic acid hydrochloride] Quality Summary

The active pharmaceutical ingredient in the drug product is Aminolevulinic acid hydrochloride. It is manufactured by (b) (4). The detailed CMC information is provided in (b) (4) DMF (b) (4). A LoA is provided to reference CMC information in DMF (b) (4) to support this application. It was reviewed on 09/11/2015 and found to be adequate.

Aminolevulinic acid hydrochloride is a white to off-white crystalline solid. It is soluble in water, methanol and DMSO. Its melting point range is between 151°C-155°C. It has no chiral center or polymorphic forms. Its chemical name is 5-amino-4-oxo-pentanoic acid hydrochloride. It has the following molecular and structural formulas:



$C_5H_9N0_3$·HCl

During the drug product manufacturing the drug substance [redacted] (b) (4)

B. Drug Product [Aminolevulinic acid hydrochloride gel, 10%] Quality Summary

Aminolevulinic acid hydrochloride gelis indicated for the treatment of actinic keratoses of face, scalp [redacted] (b) (4). This is based on photo reaction of porphyrine precursor, aminolevulinic acid hydrochloride with the BF RhodolLED lamp generating reactive oxygen that cause necrosis of target cells..

The drug product is a non-sterile, white to yellowish topical gel. Each gram of gel contains 100 mg of aminolevulinic acid hydrochloride (equivalent to 78 mg of aminolevulinic acid) as an active ingredient and the following inactive ingredients: xanthan gum, soybean phosphatidylcholine, polysorbate 80, medium-chain triglycerides, isopropyl alcohol, monobasic sodium phosphate, dibasic sodium phosphate, propylene glycol, sodium benzoate and purified water.

Aminolevulinic acid hydrochloride gel, 10% is supplied in a 2 g aluminum tube with a white high density polyethylene (HDPE) screw cap.

The drug product manufacturing process is comprised of the following steps.

[redacted] (b) (4)

On the basis of the drug product stability data, the proposed 24-month expiration dating period when it is stored at 2°C-[redacted] (b) (4)°C in the proposed container closure system is deemed justified. The in-use stability of the drug product

confirmed that once opened, it can be stored for up to 12 weeks at 2°C-(b)(4)°C when the tube is tightly closed.

The identity, strength, purity and quality of the drug product are assured by adequate raw material controls, validated manufacturing process and adequate drug product specification.

As of this review, the Office of Process and Facilities has not made a final overall "Approval" recommendation for the manufacturing and testing facilities involved in this application.

The device consult reviews from CDRH (Office of Compliance and Office of Device Evaluation) are also pending.

B. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Ameluz
Non Proprietary Name of the Drug Product	Aminolevulinic acid hydrochloride gel
Non Proprietary Name of the Drug Substance	Aminolevulinic acid hydrochloride
Proposed Indication(s) including Intended Patient Population	Ameluz gel, 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)
Duration of Treatment	Up to two rounds of treaments
Maximum Daily Dose	As needed
Alternative Methods of Administration	None

C. Biopharmaceutics Considerations

1. BCS Classification:
   - Drug Substance: N/A
   - Drug Product: N/A

2. Biowaivers/Biostudies
   - Biowaiver Requests: N/A
   - PK studies: N/A
   - IVIVC: N/A

D. Novel Approaches

N/A

E. Any Special Product Quality Labeling Recommendations

N/A

F. Life Cycle Knowledge Information (see Attachment B)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:
From the quality perspective this NDA is **not** deemed ready for approval at this time in its present form per 21 CFR 314.125(b)(6) and (13), until the label/labeling issues are satisfactorily resolved and the Consult Reviews from CDRH (Office of Compliance and Office of Device Evaluation) also recommend approval.

Hitesh Shroff, Ph.D.
Application Team Lead, Branch V
Division of New Drug Products II

Hitesh N. Shroff -A

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Juandria Williams, PhD; DIA/B3
March 24, 2016

Juandria Williams -S

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ASSESSMENT OF THE BIOPHARMACUETICS

30. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

In the 74-day letter, the Agency recommended that the Applicant develop an in vitro release test (IVRT) methodology and propose in vitro release acceptance criteria (range) for the proposed drug product to be used at release and during stability as a quality control parameter.

Applicant's Response:
The applicant responded on October 30, 2015 and stated that IVRT is not a significant quality control parameter for the following reasons:

- The proposed product is a topically applied drug product with its site of action within the epidermis, where the actinic keratosis lesions are located. The penetration of the active ingredient 5-aminolevulinic acid (5-ALA) into deeper skin layers (dermis), subcutaneous tissues (muscles and joints) or systemic uptake is not relevant for its clinical efficacy. Adsorption by the skin and transdermal availability does not determine the performance of the product.

- The proposed product is a nanoemulsion formulation. (b) (4)

(b) (4)

(b) (4)

(b) (4)

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As shown in adsorption studies with an ex vivo human skin model with nanoemulsion loaded with a fluorescent dye (Study No.: ALA-AK-PT020), the nanovesicles of the proposed product do not penetrate intact into the human skin. The nanoparticles disintegrate at the surface of the stratum corneum and the individual lipid molecules then interact with the lipid barrier of the stratum corneum and penetrate into the latter. The merging of the nanoemulsion with the stratum corneum results in changes in the permeability of the lipid membranes. After fusion with cellular membranes, the nanoemulsion improves the cellular uptake of 5-ALA presumably caused by changes in the permeability of the cell membrane.
The interaction between nanoemulsion and stratum corneum seems highly relevant to the action of the proposed drug product. By adding the gel to the skin, the nanovesicles change their structure by fusion with existing lipid layers, and by doing so enhance drug penetration through the stratum corneum. This situation would be impossible to mimic in an IVRT test with a synthetic membrane.

The particle size of nanovesicles is an important factor influencing the efficacy of dermal drug delivery. Smaller vesicles provide a larger interaction surface between skin and vesicles. The applicant demonstrated that the cellular uptake of 5-ALA dissolved in nanoemulsion BF-200 is inversely proportional to the vesicle size.

Since 5-ALA resides in the aqueous phase of the nanoemulsion gel only, and since the nanovesicles enhance skin penetration through fusion with biological membranes, it is justified not to use an in-vitro release test for the control of product performance. Such a test would define release in a situation that is not relevant to the biological action of the gel. The properties of the nanoemulsion (particle size and particle size distribution) are responsible for the improved penetration of 5-ALA. Both vesicle size and homogeneity of the vesicle size of the nanoemulsion are adequately controlled in the specification of the finished product and during stability.

Reviewer's Assessment: The Agency recommended the applicant to develop IVRT as a quality control tool and support any future changes. This is a recommendation and not a requirement from the Biopharmaceutics perspective.

IVRT is a quality control (QC) tool and may not reflect in vivo performance. Therefore, the applicant's justification that the *test would define release in a situation that is not relevant to the biological action of the gel* is irrelevant to the

recommendation to develop an IVRT method for QC purposes. However, since 5-ALA resides in the aqueous phase of the nanoemulsion gel only, and since the nanovesicles enhance skin penetration through fusion with biological membranes, the applicant's decision to not to use an in-vitro release test for the control of product performance is justified.

The Applicant conducted ex vivo skin permeation studies to evaluate percutaneous absorption of 5-ALA from the proposed product and penetration behavior of the proposed product. The studies were conducted using the nanoemulsion (BF-200), the intended commercial formulation (Formulation B) and an earlier formulation (Formulation A). Formulation A was slightly modified (b) (4) The following table represents the compositions of formulation A and B:

Table 1: Qualitative and quantitative composition of BF-200 ALA gel formulations

Ingredients	Formulation A	Formulation B (intended commercial formulation))
	mg (w/w) per g of gel	
Aminolevulinic acid hydrochloride	(b) (4)	100.000 mg
Xanthan gum		(b) (4)
Soybean phosphatidylcholine		
Polysorbate 80		
Triglycerides, medium-chain		
Isopropyl alcohol		
(b) (4)		
Propylene glycol		
Sodium benzoate		
Purified water		

Study ALA-AK-PT002

As part of the safety evaluation of 5-ALA, the study assessed the rate and extent of absorption of [^{14}C]-5-ALA following topical application of the formulation to fresh human skin. (Formulation A 1% and 3% ALA HCL formulations were tested in addition to the 10% ALA HCl gel). Following topical application of [^{14}C]-5-ALA in 1%, 3% and 10% Gels to full-thickness human skin in vitro, the dislodgeable dose (the mass of test item that is removable from the application site) at 24 h was 96.97%, 100.16% and 101.23% of the applied dose, respectively. The dermal delivery of [^{14}C]-5-ALA was 1.30% (2.65 µg equiv./cm^2), 0.55% (3.38 µg equiv./cm^2) and 0.36% (7.53 µg equiv./cm^2), respectively. Mass balance of [^{14}C]-5-ALA was complete with 100.13%, 102.03% and 102.02% recovered, respectively. The intended commercial formulation is 10%. The Applicant did not provide justification for selection of 10% formulation. Since this study

was not conducted with the intended commercial formulation, the Division of Biopharmaceutics did not evaluate the study in details,

Study ALA-AK-PT005
The in vitro percutaneous absorption of a nanoemulsion formulation radiolabelled [^{14}C]-5-ALA through human skin (Formulation A). Since this study was not conducted on the intended commercial formulation, and this study has no impact on the selection of the to-be-marketed formulation, the Division of Biopharmaceutics did not evaluate this study.

Study ALA-AK-PT009
Evaluation of 5-aminolevulinic acid induced protoporphyrin IX (PpIX) fluorescence in nude mouse skin comparison of BF-200 ALA versus Metvix® (1% and 3% ALA formulations were tested using formulation A, whereas BF-200 ALA 10% were applied using formulation B). The results of the experiments showed that the intensity of PpIX-fluorescence induced by BF-200 ALA or Metvix® was time dependent. But the Applicant has stated that these results are most probably specific for the present model. The advantages of the BF-200 formulation, to penetrate better and deeper into the epithelial layer, is not of relevance in mice because of their thin healthy epithelium consisting of 3 to 4 cell layers.

Study ALA-AK-PT037
Epidermal penetration and PpIX formation of two different 5-aminolevulinic acid formulations in ex vivo human skin (the study compares the penetration of a standardized ALA nanoemulsion containing 10% ALA hydrochloride, Formulation B, to that of a 20% ALA hydrochloride cream formulation).

Photosensitizer formation and epidermal penetration depth represent basic predictors of drug efficacy in Photodynamic Therapy (PDT). The efficacy of 5-aminolevulinic acid (ALA) Photodynamic Therapy (PDT) for epidermal neoplasias is associated with effective formation and distribution of the photosensitizer PpIX. PpIX formation was assessed according to different durations of incubation with both preparations. The nanoemulsion formulation (BF-200 ALA) led to more intense PpIX fluorescence than the 20% ALA cream formulation. Quantitative fluorimetric measurements of PpIX concentrations showed that PpIX increased from l h after BF-200 ALA application and reached 24.8 nM after 12 h, while 8.9 nM PpIX was measured 12 h after application of the standard formulation. After the clinically relevant incubation time of 3 h the PpIX concentration induced by BF-200 ALA was three-fold higher than that induced by the 20% ALA formulation. In spite of the 50% lower ALA content, BF-200 ALA triggers significantly higher PpIX concentrations than the standard 20% ALA formulation, indicating that clinical efficacy with BF-200 ALA may be higher.

The study was conducted using human upper eyelid skin obtained from ten routine blepharoplastic surgeries performed in one dermatological center. Eyelid material was comprised of either one or both upper lids and was subjected to experimental processes immediately. Thickness of the vital layers of the epidermis (stratum basale to stratum granulosum) reached from 31-65 µm (mean: 50 ± 13 µm), while stratum corneum thickness varied between 14.8 - 25.2 µm (mean: 20 ± 4 µm). Test items BF-200 ALA, placebo gel or 20% 5-ALA cream formulation were applied to the epidermis at approximately 1 mm thickness.

Route of administration: Non-occlusive dermal application to the ex vivo skin.
Frequency: Once
Treatment area: Samples of 4 mm diameter

Study ALA-AK-PT020
Penetration behavior of BF-200 in human skin (BF-200 nanoemulsion).

In order to visualize the penetration behavior of the nanovesicles, the lipophilic fluorescent compound 1, 1' - dioctadecyl-3,3,3 ',3 '-tetramethylindocarbocyanine perchlorate (Dil) was encapsulated into BF-200 vesicles. This was applied to explanted full-thickness human skin (1 abdomen and 1 thigh, patients aged 41 to 62 years) obtained from operative tissue. Within a period of 5 hours after surgery the skin was prepared for the penetration study and the test items were applied. Exposure was terminated at 1 h or 24 h post dose and the distribution of fluorescence throughout the skin was determined by fluorescence microscopy. A strong signal relating to the dye used to label the nanovesicles was detected in the stratum corneum at each time-point analyzed. No fluorescence was seen in other skin layers.

Study ALA-AK-PT014
Comparative investigations into the penetration behavior of BF-200 ALA in an ex-vivo porcine skin model (the formulations used in the study include BF-200 ALA (10%) Formulation B, Metvix® 160mg/g Cream (Galderma SA, Paris, France); active ingredient: 16% methyl-(5-amino-4-oxopentanoate) and BF-200 placebo).

Skin was obtained from the backs of 6-month old, female or castrated male pigs (Pietrain breed). The skin, including the subcutis, was obtained immediately after slaughter, before the pigs are scalded. The skin was prepared for the study in four hours. The amount of formulation applied was adjusted so that the same amount of active ingredient per cm^2 was applied in each case. Incubation was performed at 32°C and the incubation times were 0h, 3h, 5h, 8h, and 12h. The study demonstrated that the PpIX-associated fluorescence increased as a function of incubation time (3h to 12h). The results of this study suggested that there is no difference in the uptake of ALA and methyl-ALA by the keratinocytes. However, the data shows that significant differences in intensity of fluorescence and depth of penetration developed at time points greater than 5 hours, and demonstrate the advantages of the BF-200 ALA (10%) formulation over the Metvix cream formulation.

The ex vivo studies, in general, suggest better penetration of 5-ALA using the nanoemulsion.

31. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

The formulation used in the clinical Phase III studies is the same as the intended commercial formulation.

Applicant's Response: N/A

Reviewer's Assessment:N/A

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:
The Biopharmaceutics information is adequate.

Reviewer's Signature
Vidula Kolhatkar, Ph.D.
Branch II
Division of Biopharmaceutics/ONDP
03/21/2016

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Secondary Review Comments and Concurrence:

I have reviewed the Biopharmaceutics assessment and I concur.

Kelly M. Kitchens, Ph.D.
Acting Quality Assessment Lead
Division of Biopharmaceutics, Branch II
March 21, 2016

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ASSESSMENT OF MICROBIOLOGY

Product Quality Microbiology Assessment

The Agency's 11/24/2015 and 02/05/2016 information requests addressed in the body of the review as comments (in italics) were responded to on 12/22/2015 and 03/01/2016 respectively.

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

Description of drug product –

(section 3.2 P.1).

BF-200 ALA 10 % gel is a non-sterile gel formulation with (b) (4) nanoemulsion for topical administration containing 10 % of 5-aminolevulinic acid hydrochloride (equal to 7.8 % of the 5-aminolevulinic acid as free acid).

Drug product composition –

(section 3.2.P.1).

Ingredient	Function	Content per mL
5-Aminolevulinic acid hydrochloride	Active ingredient	100.0
Xanthan gum, Ph.Eur / USP-NF	(b) (4)	
Soybean phosphatidylcholine		
Polysorbate 80		
Medium chain Triglycerids, d Ph.Eur / USP-NF		
Isopropyl alcohol, Ph.Eur / USP-NF		
(b) (4)		
Propylene glycol, Ph.Eur / USP-NF		
Sodium benzoate, Ph.Eur / USP-NF		
Purified water, Ph.Eur / USP-NF		

Description of container closure system –

(section 3.2.P.1; section 3.2.P.7).

A (b) (4) aluminum tube is used as container closure system for BF-200 ALA gel. (b) (4) The top of the tube has an inner foil seal made of (b) (4) aluminum and a threaded screw head that fits the white high-density polyethylene (HDPE) screw cap. (b) (4)

The filled tubes are packed into cardboard boxes.

Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Antimicrobial Effectiveness Testing -

(section 3.2.P.2.5).

Antimicrobial effectiveness testing was performed according to USP <51>.

Results

Study/Report # not provided and date: not provided.

(b) (4) Sodium benzoate

The release and stability specifications for Sodium benzoate are the same: (b) (4)

The following lots were used to validate antimicrobial effectiveness test: 101E, 102E and 103E

(b) (4)

The compendial organisms were used for the studies at the following initial microbial loads:

Microorganism	Initial microbial load (b) (4)
Escherichia coli (ATCC 8739)	CFU/g
Pseudomonas aeruginosa (ATCC 9027)	CFU/g
Staphylococcus aureus (ATCC 6538)	CFU/g
Candida albicans (ATCC 10231)	CFU/g
Aspergillus niger (ATCC 16404)	CFU/g

(b) (4) effectiveness test was performed on the three lots of the drug product and contained the amounts of the (b) (4) specified above.

Batch #	Time	Microbial count (CFU/g) / log reduction in microbial count				
		E. coli	*P. aeruginosa*	*S. aureus*	*C. albicans*	*A. niger*
101E	14 days	(b) (4)				
	28 days					
102E	14 days					
	28 days					
103E	14 days					
	28 days					

Sufficient antimicrobial validation data, per USP<51>, was provided to support the minimum release and stability specification for Sodium benzoate (b) (4)

Acceptable

P.3 Manufacture

P.3.1 Manufacturers

(b) (4)

(b) (4)

Environmental monitoring including product bioburden -
The manufacturing of BF-200 ALA 10% gel complies with the requirements of the current version of the guidelines for good manufacturing practice (GMP). All batches of BF-200 ALA 10% gel are manufactured according to the validated manufacturing process (b) (4) The manufacturing environment was not described.

The following deficiency was issued in the 11/24/2015 microbiology information request:

Comment: Non-sterile aqueous drug products may potentially be contaminated with organisms in the Burkholderia cepacia complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional (b) (4) *systems. Thus, despite the presence of otherwise adequate* (b) (4) *systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see PDA J. Pharm. Sci. Tech. 2011; 65(5): 535-43.*

In order to control for the presence of BCC in the product please consider the following:

a. Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled

as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.

Response: The applicant has described a 'risk assessment' of BCC contamination by looking at the active pharmaceutical ingredient, all excipients including purified water, packaging components and equipment used in drug product manufacture.

(b) (4)

(b) (4) Based on all these, the applicant concluded that each step of the manufacturing process is low risk for contamination and in a very unlikely case of contaminated final product with BCC (or any other germ), the treatment of contaminated BF-200 ALA 10 % gel would not increase the risk of infection with BCC for patients and practitioners.

Acceptable

b. Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.

As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product (b) (4) *to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.*

For more information, we refer you to Envir. Microbiol. 2011; 13(1):1 – 12 and J. Appl. Microbiol. 1997; 83(3):322 – 6.

Response: Biofrontera has started investigations in order to establish and validate a test method for BCC. They expect, that first data will be available within the next months.

The following deficiency was issued in the 02/05/2016 microbiology information request:

Comment: It is acknowledged that the 'risk assessment' of Burkholderia cepacia complex (BCC) contamination was described for the active pharmaceutical ingredient, all excipients including purified water, packaging components and equipment used in drug product manufacture. However, BCC strains have a well-documented ability to ferment a wide variety of substrates including drug products containing some of the excipients in the subject drug product formulation and are known to proliferate in the presence of many traditional (b) (4) *systems. Thus, despite the presence of otherwise adequate* (b) (4) *systems, BCC strains can survive and even proliferate in product during storage. Please provide additional description of the controls to minimize bioburden in the facility and during the manufacturing process, cleaning and sanitization procedures for the manufacturing area, personnel gowning requirements and historical bioburden results for purified water.*

Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Please validate and discuss the test methods provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.

As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product without (b) (4) *to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.*

Response: In addition to other measures previously described, the following additional measures are described to reduce bioburden in the production area:

(b) (4)

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(b) (4)

After method validation, microbial testing for the absence of BCC was confirmed for the following product batches: 101E, 102E, 103E, 105H and 117H; all 5 batches of the drug product demonstrated the absence of BCC.

Acceptable

P.5 Control of Drug Product

P.5.1 Specification

(section 3.2.P.5.1).

The product release specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria (b) (4)	Exhibit Batch results		
			Lot #105H	Lot #106H	Lot #107H
Microbial limit	USP <61>, <62>				
TAMC			Conforms	Conforms	Conforms
TYMC			Conforms	Conforms	Conforms
Staphylococcus aureus			Conforms	Conforms	Conforms
Pseudomonas aeruginosa			Conforms	Conforms	Conforms

TAMC: total aerobic microbial count
TYMC: total yeast and mold count

The following deficiency was issued in the 11/24/2015 microbiology information request:

Comments: It is acknowledged that acceptable release microbial limit specification, test methods and acceptance criteria to demonstrate that the product is free from S. aureus and P. aeruginosa are provided. Please revise the microbial limit release specification to include test methods and acceptance criteria to demonstrate that the product is free of the objectionable microorganism B. cepacia.

Response: Biofrontera has started investigations in order to establish and validate a test method for BCC. They expect, that first data will be available within the next months. They commit to conduct the requested investigations within the next month(s). Once a method is established and first data is available, the answers to this deficiency will be provided.

The following deficiency was issued in the 02/05/2016 microbiology information request:

Comments: It is acknowledged that acceptable release microbial limit specification, test methods and acceptance criteria to demonstrate that the product is free from S. aureus and P. aeruginosa are provided. Please revise the microbial limit release specification to include test methods and acceptance criteria to demonstrate that the product is free of the objectionable microorganism B. cepacia.

Response: The following revised product release specifications are provided in sections 3.2.P.5.1 and section 3.2.P.5.4.

Test	Test Method	Acceptance Criteria	Exhibit Batch results		
			Lot #101E	Lot #102E	Lot #103E
Microbial limit	USP <61>, <62>	(b) (4)			
TAMC			Conforms	Conforms	Conforms
TYMC			Conforms	Conforms	Conforms
Staphylococcus aureus			Conforms	Conforms	Conforms
Pseudomonas aeruginosa			Conforms	Conforms	Conforms
B. cepacia			Conforms	Conforms	Conforms
			Lot #105H	**Lot #106H**	**Lot #107H**
Microbial limit	USP <61>, <62>				
TAMC			Conforms	Conforms	Conforms
TYMC			Conforms	Conforms	Conforms
Staphylococcus aureus			Conforms	Conforms	Conforms
Pseudomonas aeruginosa			Conforms	Conforms	Conforms
B. cepacia complex (BCC)			Conforms	Not tested	Not tested

TAMC: total aerobic microbial count

Acceptable

P.8 Stability

P.8.1 Stability Summary and Conclusion

(section 3.2.P.8.1).

Products manufactured with drug substance obtained from two sources were placed on stability for after 48 h under the following storage conditions:

Long-term storage (normal use/storage): 2 – 8 °C

Accelerated condition: 25 ± 2 °C/60 % ± 5 % RH

Additional condition: 30 ± 2 °C/65 % ± 5 % RH

Additional condition: 40 ± 2 °C/75 % ± 5 % RH

Proposed Expiry: (b) (4) months

All results were within the specifications.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

Stability data provided for at least three manufactured batches.

Acceptable

P.8.3 Stability Data

Batch numbers #101E, 102E and 103E all passed (b) (4) effectiveness testing at the 12 month time point. They also met specifications at the 12 month time point for TAMC, TYMC, absence of *S. aureus* and absence of *P. aeruginosa*. However, the product was not tested for the absence of *B. cepacia.*

The following deficiency was issued in the 11/24/2015 microbiology information request:

Comments: It is acknowledged that acceptable stability data were provided for TAMC, TYMC, absence of S. aureus and absence of P. aeruginosa. Please revise the stability program to include testing to confirm the absence of B. cepacia.

Response: The applicant has started investigations in order to establish and validate a test method for BCC. They expect, that first data will be available within the next months. They commit to conduct the requested investigations within the next month(s). Once a method is established and first data is available, the answers to this deficiency will be provided.

The following deficiency was issued in the 02/05/2016 microbiology information request:

Comments: It is acknowledged that acceptable stability data were provided for TAMC, TYMC, absence of S. aureus and absence of P. aeruginosa. Please revise the stability program to include testing to confirm the absence of B. cepacia.

Response: Absence of BCC was demonstrated for ICH stability batches 101-103E stored at 2 – 8 °C for 26 months and for on-going stability batches #105H and #117H. Microbial testing of BCC will be implemented for stability testing. Section 3.2.P.8.1 was updated to reflect the change which is reproduced below.

Test	USA		EU	
Microbial Contamination** TAMC TYMC *S. aureus* *P. aeruginosa* *B. cepacia complex (BCC)*	USP <61>,<62>*,**	(b) (4)	Ph.Eur. 2.6.12*,** Ph.Eur. 2.6.13*,**	(b) (4)

Acceptable

A APPENDICES

A.2 Adventitious Agents Safety Evaluation – (section 3.2.A.2).

No excipients of human or animal origin are contained in the drug product or are used during the manufacture of the drug product. Respective statements are presented for the following:

- Ameluz
- (b) (4)
- Isopropyl alcohol
- Polysorbate 80
- Propylene glycol
- Sodium benzoate
- (b) (4)
- Soybean phosphatidylcholine
- Triglycerides, medium-chain
- Xanthan gum

Therefore, BSE/TSE risk does not exist.

Acceptable

R REGIONAL INFORMATION

R.1 Executed Batch Record

(section 3.2.R).

Executed batch records for lot #118C were included in the submission.

Acceptable

R.2 Comparability Protocol – No CP was included in the application.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

(section 1.14.3).

The drug product is supplied in an aluminum tube, with a screw cap. Each tube contains 2 g gel, (b) (4)

(b) (4)

Store in a refrigerator, 2 – 8 °C (36 – 46 °F). Excursions permitted to 15 – 30 °C (59 – 86 °F).

After opening, (b) (4) can be stored for up to 12 weeks in a refrigerator at 2 – 8 °C (36 – 46 F) (b) (4) the tube is tightly closed.

Acceptable

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:
Microbiology is complete and adequate. There are no outstanding issues. NDA is recommended on basis of sterility assurance.

Eric Adeeku, Ph.D., Mirobiologist. Eric K. Adeeku -A Digitally signed by Eric K. Adeeku -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Eric K. Adeeku -A, 0.9.2342.19200300.100.1.1=1300417839 Date: 2016.03.30 09:41:06 -04'00'

Secondary Review Comments and Concurrence:
I concur.

Jesse Wells, Ph.D., Microbiologist. Jesse Wells -S Digitally signed by Jesse Wells -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jesse Wells -S, 0.9.2342.19200300.100.1.1=0012236983 Date: 2016.03.30 10:34:53 -04'00'

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

32. Is the applicant's claim for categorical exclusion acceptable?

    Yes

33. Is the applicant's Environmental Assessment adequate for approval of the application?

    NA

Applicant's Response:

Reviewer's Assessment: Satisfactory

The sponsor has submitted a claim of categorical exclusion under 21 CFR 25.31(c) and (b). The active ingredient of Amelux is 5-aminolevulinic acid (5-ALA) which on a mass basis represents approximately (b) (4)% of the annual amount of 5-ALA in human urine naturally released into waste water. The exclusion at 21 CFR 25.31(c) is for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. Based on the information about the occurrence and distribution of 5-ALA, the cited categorical exclusion is appropriate for the submitted application. A

statement of no extraordinary circumstances has been submitted. The EA reviewer has no information to indicate the presence of "extraordinary circumstances". A secondary claim under 21 CFR 25.31(b) is also acceptable based on the minimal production of drug product (b) (4)

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:
The claim of categorical exclusion is acceptable.

Raanan A. Bloom, Ph.D.
ONDP/EA Team
January 7, 2016

Raanan A. Bloom -S

Digitally signed by Raanan A. Bloom -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300062595, cn=Raanan A. Bloom -S
Date: 2016.03.30 16:00:29 -04'00'

Secondary Review Comments and Concurrence:
Concur.

Scott Furness, Deputy Director, ONDP
January 7, 2016

Michael S. Furness -S

Digitally signed by Michael S. Furness -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300153233, cn=Michael S. Furness -S
Date: 2016.03.31 12:33:53 -04'00'

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Carton and Container Labels

Immediate container labels

2 g Gel Tube Label

(b) (4)

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The drug name is presented correctly. **Not Satisfactory**
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Displayed as 10% **Satisfactory**
Net contents (21 CFR 201.51(a))	Net content not properly displayed. **Not Satisfactory**
"Rx only" displayed prominently on the main panel	The statement is not displayed. **Not Satisfactory**
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	Exact NDC number is not displayed. **Not Satisfactory**
Lot number and expiration date (21 CFR 201.17)	Displayed properly **Satisfactory**
Storage conditions	Storage condition is not displayed. However, it is acceptable due to the small size of the label. It is on the carton label. **Satisfactory**
Bar code (21CFR 201.25)	Barcode is not displayed. However, it is acceptable due to the small size of the label. It is on the carton label. **Satisfactory**
Name of manufacturer/distributor	Not consistent with PI. **Not Satisfactory**
List of Ingredients	Ingredients are not listed. However, it is acceptable due to the small size of the label. . It is on the carton label. **Satisfactory**

Evaluation: Not adequate. The 2 g gel tube labels should be revised to include the following information:

- The drug product title should be revised as follows to avoid medical error:

(b) (4)

Carton labels

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size, prominence) (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	The established name is not correctly described. **Not Satisfactory**
Dosage strength (21CFR 201.10(d)(1), 21CFR 201.100(b)(4))	Displayed as 10 % **Satisfactory**
Net quantity of dosage form (21 CFR 201.51(a))	Net content not properly displayed. **Not Satisfactory**
"Rx only" displayed prominently on the main panel (21 CFR 201.100 (b)(1))	The statement is displayed on the carton. **Satisfactory**
Expiration date and lot number (21 CFR 201.17 and 21 CFR 201.18)	Lot and Exp are displayed. **Satisfactory**
Storage conditions	Storage condition is not described adequately.. **Not Satisfactory**
Bar code (21CFR 201.25)	Barcode location is displayed. **Satisfactory**
NDC number (21 CFR 201.2, 21 CFR 207.35(b)(3)(i))	NDC number is not displayed correctly **Not Satisfactory**
Manufacturer/distributor's name 21CFR201.1(a)	Not consistent with PI. **Not Satisfactory**
The list of inactive ingredients, 21CFR 201.10(a), if not oral dosage form; and quantitative ingredient information, if parenteral injection. 21CFR 201.100(b)(5)(iii)	Ingredients are listed properly. **Not Satisfactory**
Statement of being sterile (if applicable)	N/A
"See package insert for dosage information"	This statement is correctly displayed as (b) (4)

(21 CFR 201.55)	(b) (4) **Satisfactory**
"Keep out of reach of children" (Required for OTC but Optional for Rx drugs)	Displayed **Satisfactory**
Route of Administration (21 CFR 201.100(b)	Described as "for tropical use only" **Satisfactory**

Evaluation: Not adequate. The 2 g gel container labels should be revised to include the following information:

- The drug product title should be as shown below:

  Ameluz (aminolevulinic acid hydrochloride) gel, 10%
- Display net content as "NET WT 2 g" (b) (4)
- Display correct NDC number
- To be consistent with the PI replace (b) (4) with Distributed by:"
- Display the storage conditions as shown below:

  Store at 2°C-8°C (36°F-46°F), excursions are permitted to 15°C-30°C (59°F-86°F)
- The list of ingredients should be revised as shown below:

Each gram of gel contains 100 mg of the active ingredient aminolevulinic acid hydrochloride 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

- **Labeling Review**

The following is a summary of the labeling review.

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AMELUZ® safely and effectively. See full prescribing information for AMELUZ®.

AMELUZ® (aminolevulinic acid HCl) Gel, 10%, for topical use

----------DOSAGE FORMS AND STRENGTHS----------

(b) (4) Gel: 10% (3).

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name Dosage form, route of administration Controlled drug substance symbol (if applicable)	AMELZU (aminolevulinic acid HCl) gel, 10%, for topical use N/A	The drug product title is not described correctly. No abbreviation in the DP title if there is enough room **Not Satisfactory** Dosage form is and route of administration are displayed correctly. **Satisfactory**
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	(b) (4) Gel: 10%	The dosage form is not described correctly. The strength is described correctly. **Not Satisfactory**
Whether the drug product is scored (If the product is not scored, do not say "not scored.")	N/A	N/A **Satisfactory**

Evaluation: Not adequate. This section should be revised as follows:

- The drug product title should be as shown below without abbreviation:

Ameluz (aminolevulinic acid hydrochloride) gel, 10%, for topical use

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

3. **DOSAGE FORMS AND STRENGTHS**

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	gel	Dosage form is described correctly. **Satisfactory**
Strengths: in metric system	10%	The strength is described correctly. **Satisfactory**
Description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	(b) (4)	The gel is not described properly. **Not Satisfactory**

Evaluation: Adequate. This section should be revised as follows:

- Revise the dosage form description as shown below:

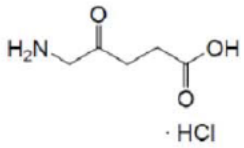
  Each gram of (b) (4) *Ameluz Gel, 10% contains 100 mg of aminolevulinic acid hydrochloride.*

#11: Description (21CFR 201.57(c)(12))

11. DESCRIPTION

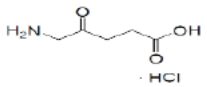
(b) (4)

ALA (b) (4) is a white to off-white crystalline solid. It is readily soluble in water, methanol and dimethylformamide. (b) (4) chemical name (b) (4) is 5-amino-4-oxo-pentanoic acid hydrochloride (MW= 167.59). The structural formula is represented below:



The inactive ingredients (b) (4) xanthan gum, soybean phosphatidylcholine, polysorbate 80, triglycerides medium-chain, isopropyl alcohol, (b) (4) (b) (4) propylene glycol, sodium benzoate (b) (4) purified water.

Item	Information Provided in NDA	Reviewer's Assessment

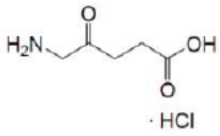
Proprietary name and established name	AMELUZ (b) (4)	The proprietary name and the established name are not correctly displayed. **Not Satisfactory**
Dosage form and route of administration	Gel	Dosage form and route of administration are not displayed correctly. **Not Satisfactory**
Active moiety expression of strength with equivalence statement for salt (if applicable)	Not present	The equivalency statement is not present. **Not Satisfactory**
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	xanthan gum, soybean phosphatidylcholine, polysorbate 80, triglycerides medium-chain, isopropyl alcohol, (b) (4) propylene glycol, sodium benzoate (b) (4), purified water.	The inactive ingredients are not listed correctly. **Not Satisfactory**
Statement of being sterile (if applicable)	Not applicable	**Not applicable**
Pharmacological/ therapeutic class	Not provided	The Pharmacological/ therapeutic class not provided **Not Satisfactory**
Chemical name, structural formula, molecular weight	Chemical Name: 5-amino-4-oxo-pentanoic acid hydrochloride Molecular formula: Not provided Molecular weight: 167.59 molecular structure is: 	The molecular weight of API is not provided. **Not Satisfactory**
If radioactive, statement of important nuclear characteristics.	N/A	Not applicable

Other important chemical or physical properties (such as pKa, solubility, or pH)	(b) (4)	he DP and DS escribed not properly. **ot Satisfactory**
	ALA (b) (4) is a white to off-white crystalline solid. It is readily soluble in water, methanol and dimethylformamide.	

Evaluation: No adequate. This section should be revised as follows:

Ameluz (aminolevulinic acid hydrochloride) Gel, 10%, a porphyrin precursor, is a non-sterile white to yellowish topical gel.

The active ingredient, aminolevulinic acid hydrochloride is a white to off-white solid. It is readily soluble in water, methanol and dimethylformamide. Its chemical name is 5-amino-4-oxo-pentanoic acid with molecular weight 167.59, molecular formula $C_5H_9NO_3HCl$. Its structural formula is:



Each gram of Ameluz Gel contains 100 mg of aminolevulinic acid hydrochloride (equivalent to 78 mg of aminolevulinic acid) 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

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16. HOW SUPPLIED/STORAGE AND HANDLING

AMELUZ® is supplied in an aluminium tube, with a screw cap. Each tube contains 2 g gel. (b) (4)

(b) (4)

Store AMELUZ® in a refrigerator, 2° – 8°C (36° - 46°F). Excursions permitted to 15° – 30°C (59° -86°F).

After opening, AMELUZ® can be stored for up to 12 weeks in a refrigerator at 2° – 8°C (36° - 46°F) (b) (4) the tube is tightly closed.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Not displayed	The strength is not described. **Not Satisfactory**
Available units (e.g., bottles of 100 tablets)	2g tube	This information should be revised **Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Dosage form and NDC number provided	This information is provided. **Satisfactory**
Special handling (e.g., protect from light, do not freeze)	N/A	N/A **Satisfactory**
Storage conditions	Store AMELUZ® in a refrigerator, 2° – 8°C (36˚ - 46˚F). Excursions permitted to 15° – 30°C (59° -86°F). After opening, AMELUZ® can be stored for up to 12 weeks in a refrigerator at 2° – 8°C (36˚ - 46˚F) (b) (4) the tube is tightly closed.	Information provided correctly. **Satisfactory**

Evaluation: Not adequate. Section 16. How Supplied and Handling section should be revised as follows:

Ameluz (aminolevulinic acid hydrochloride) Gel, 10% is supplied in an aluminum tube, with a white high density polyethylene (HDPE) screw cap. Each tube contains 2 g of gel.

NDC XXXX-XXXX-XX *2 g tube*

- Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Distributed by: Bifrontera Inc., (b) (4)	Information is correctly rovided. **Satisfactory**

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

The applicant has provided preliminary labels and package insert, and they have not been finalized as of this review. The comments for revision should be resovled during the labeling discussions with the applicant.

Hitesh Shroff, Ph.D.
Branch V
Division of New Drug Products II

Hitesh N. Shroff -A
Digitally signed by Hitesh N. Shroff -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -A
Date: 2016.03.29 15:48:51 -04'00'

Secondary Review Comments and Concurrence:

I concur with Dr. Shroff's recommendation on labeling and labels.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V/DNDP II/ONDP

Moojhong Rhee -S
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Date: 2016.03.29 16:09:33 -04'00'

II. List of Deficiencies To Be Communicated

A. Regarding Label/labeling

Immediate container labels:

The 2 g gel tube labels should be revised to include the following information:

(b) (4)

Carton labels:

The 2 g gel container labels should be revised to include the following information:

- The drug product title should be as shown below:

  Ameluz (aminolevulinic acid hydrochloride) gel, 10%

- Display net content as "NET WT 2 g" (b) (4)
- Display correct NDC number
- To be consistent with the PI replace (b) (4) with Distributed by:"
- Display the storage conditions as shown below:

  Store at 2°C-8°C (36°F-46°F), excursions are permitted to 15°C-30°C (59°F-86°F)

- The list of ingredients should be revised as shown below:

Each gram of gel contains 100 mg of the active ingredient aminolevulinic acid hydrochloride (equivalent to 78 mg of aminolevulinic acid) 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

PI

"Highlights" Section

This section should be revised as follows:

- The drug product title should be revised as shown below without abbreviation:

  Ameluz (aminolevulinic acid hydrochloride) gel, 10%, for topical use

"Dosage Forms and Strength" Section

This section should be revised as follows:

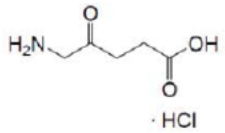
- *Each gram of* (b) (4) *Ameluz Gel, 10% contains 100 mg of aminolevulinic acid hydrochloride.*

#11 Description

This section should be revised as follows:

Ameluz (aminolevulinic acid hydrochloride) Gel, 10%, a porphyrin precursor, is a non-sterile white to yellowish topical gel.

The active ingredient, aminolevulinic acid hydrochloride is a white to off-white solid. It is readily soluble in water, methanol and dimethylformamide. Its chemical name is 5-amino-4-oxo-pentanoic acid with molecular weight 167.59, molecular formula $C_5H_9NO_3HCl$. Its structural formula is:



Each gram of Ameluz Gel contains 100 mg of aminolevulinic acid hydrochloride (equivalent to 78 mg of aminolevulinic acid) 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

#16 How supplied/storage and handling

This section should be revised as follows:

Ameluz (aminolevulinic acid hydrochloride) Gel, 10% is supplied in an aluminum tube, with a white high density polyethylene (HDPE) screw cap. Each tube contains 2 g of gel.

NDC XXXX-XXXX-XX *2 g tube*

B. Regarding Facility Inspections

- The Office of Process and Facility has not made a final "Approval" recommendation.

C, Regarding CDRH Consults for BF-RhodoLED lamp

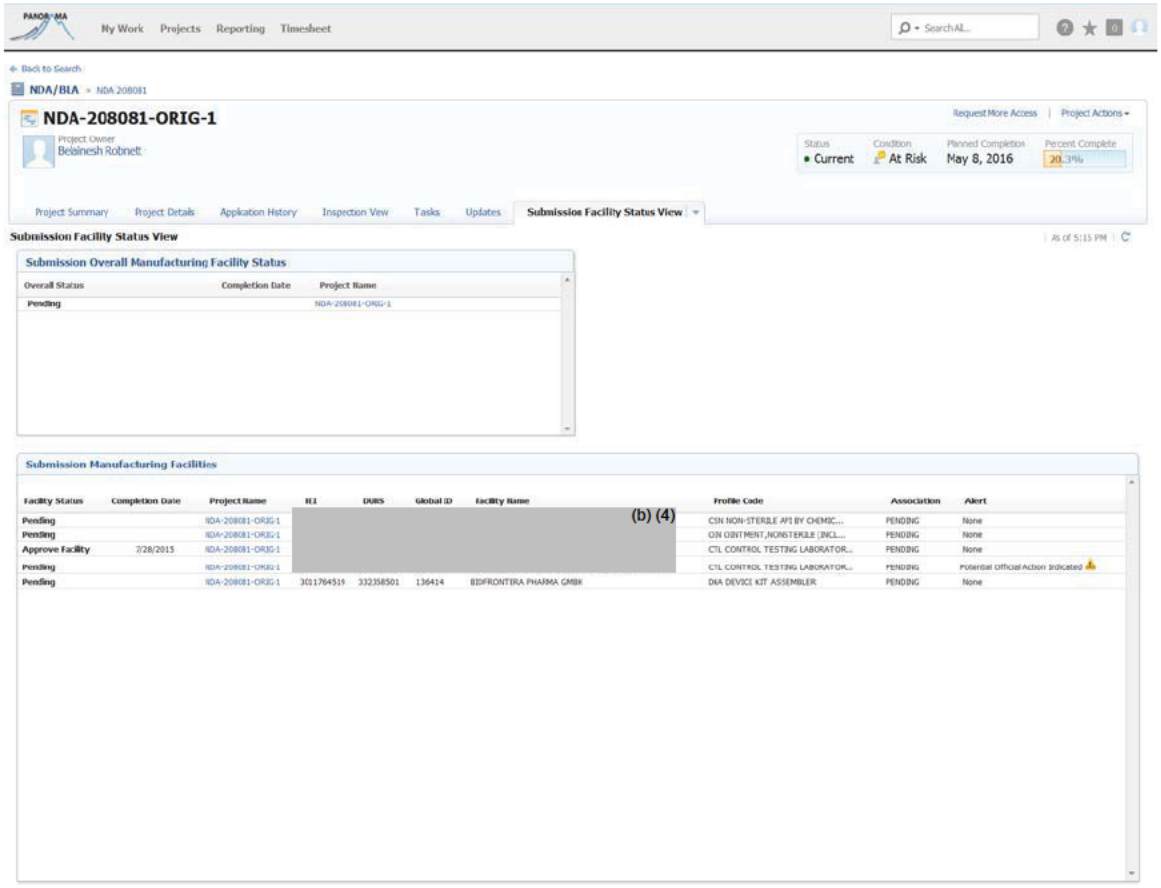
- The Office of Compliance as well as the Office of Device Evaluation in CDRH have not made final recommendations.

III. Attachments

A. Facilities

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
(b) (4)		**CSN:** API manufacturing, (b) (4) (b) (4)	High No Inspection History	Last Inspection (b) (4) OAI to VAI	Pending
		OIN: DP manufacturing, (b) (4) (b) (4) **packaging & labeling**	High No Inspection History	Last Inspection (b) (4) VAI	Pending
		CTL (b) (4) **testing of finished product**	LOW	Last Inspection (b) (4) NAI	Acceptable
		CTL: (b) (4) **analysis of the finished product**	High No Inspection History	Last Inspection (b) (4) OAI Under Review	Pending
Biofrontera Pharma GmbH, Germany	3011764519	**DKA: Device manufacturing – Red light lamp**	High No Inspection History	Inspection Scheduled on May 2-6, 2016	Pending

Overall Recommendation: The Office of Process and Facilities has not made a final overall manufacturing inspection "Approval" recommendation in Panorama for the facilities involved in this application.



B) Lifecycle Knowledge Mangaement:

a) Drug Product

Risk Assessment:

Risk Assessment for aminolevulinic acid hydrochloride gel, 10%

Product Attribute/CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation Approach	Risk Evaluation	Life-Cycle Consideration/ Comments
Assay (aminolevulinic acid)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	It is determined by an in-house validated HPLC method at release.	Low to None	None
Impurities	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	The DS impurities are fully characterized and controlled in DS specification. The impurities are also controlled by DP specification. The impurities are assessed by an in-house validated HPLC-MS method.	Low to None	None
(b) (4) (b) (4) **(sodium benzoate)**	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	The (b) (4) concentration is confirmed to meet the specification by an in-house validated HPLC method at release.	Low to None	None
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	High	(b) (4) s in the DP formulation to minimize microbial contamination. (b) (4) (b) (4) concentration is determined by a validated HPLC method in DP at release and stability. Microbial limit tests are in the DP specification.	Low to None	None
pH	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Moderate	The pH of the DP is controlled at various stages in the DP manufacturing as IPC and it is also controlled by DP specification.	Low to None	None
Viscosity (cps)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Moderate	The pH of the DP is controlled during the DP manufacturing as IPC and it is also controlled by DP specification.	Low to None	None
Particle Size of API in DP	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Moderate	The particle size of the API in the drug product is controlled during the DP manufacturing as IPC. It is also controlled by DP specification. It determined by an in-house validated method.	Lot to None	None