# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 211617Orig1s000

# PRODUCT QUALITY REVIEW(S)

**Recommendation: Approval**

# NDA 211617
# Review 1

| | |
|---|---|
| Drug Name/Dosage Form | Nexlizet (bempedoic acid and ezetimibe) tablets |
| Strength | 180 mg/10mg |
| Route of Administration | Oral |
| Rx/OTC Dispensed | Rx |
| Applicant | Esperion Therapeutics Inc. |
| US agent, if applicable | - |

| SUBMISSION(S) REVIEWED | DOCUMENT DATE | DISCIPLINE(S) AFFECTED |
|---|---|---|
| Original and amendments (NDA 211616) | Original submission (2/26/2019). Amendments: 4/15/19, 4/30/19, 5/06/29, 5/17/19, 5/20/19, 5/23/19, 7/08/19, 8/28/19, 9/09/19, 9/10/19, 9/17/19, 10/04/19, 10/07/19, 10/18/19, and 10/24/19. | Quality modules 3, 1.14 and 1.11 |

**Quality Review Team**

| DISCIPLINE | REVIEWER | BRANCH/DIVISION |
|---|---|---|
| Drug Substance | Paresma Patel | Branch II/New Drug API |
| Drug Product | John Amartey | Branch VI/New Drug Products II |
| Process/Microbiology/ Facility | Christina Capacci-Daniel | Branch II/ Inspectional Assessment/OPF |
| Regulatory Business Process Manager | Leeza Rahimi | Branch I/Regulatory Business Process Management I |
| Biopharmaceutics | Kamrun Nahar | Division of Biopharmaceutics/ ONDP |
| Application Technical Lead | Muthukumar Ramaswamy | Branch VI/New Drug Products II |
| Environmental Analysis (EA) | James Laurenson | Environmental Assessment/ Office of New Drug Products |

# Quality Review Data Sheet

## 1. RELATED/SUPPORTING DOCUMENTS

### A. DMFs:

| DMF # | Type | Holder | Item Referenced | Status | Date Assessment Completed | Comments |
|---|---|---|---|---|---|---|
| (b) (4) | III | (b) (4) | | Active | 04/08/1998 | Current 10/15/2018 |
| | III | | | Active | 3/1/2004 | LOA dated 11/1/2018 |
| | III | | | Active | 05/23/2007 | LOA dated 10/11/18 |
| | III | | | Active | 03/06/2002 | LOA dated 1/22/2019 |
| | III | | | Active | 03/01/2013 | LOA dated 10/11/18 |
| | III | | | Active | 01/26/2006 | LOA dated 10/12/2018 |
| | III | | | Active | 08/30/2007 | LOA dated 1/21/2019 |
| | III | | | Active | 05/01/2008 | LOA 10/14/2018 |
| | III | | | Active | 07/14/2008 | LOA 10/11/18 |
| | II | | | Active | 12/21/2011 | LOA dated 10/1/2018 |
| | III | | | Active | 11/09/2012 | LOA 10/12/2018 |
| | III | | | Active | 11/09/2012 | LOA dated 10/12/2018 |

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

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| IND | 130707 | |
| NDA | 211616 | |

## 2. CONSULTS: None

| DISCIPLINE | STATUS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|---|
| | | | | |
| | | | | |

# Executive Summary

## I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (OPQ) for NDA 211617 is approval, which includes acceptable recommendation for the facilities listed in the application.

## II. Summary of Quality Assessments

### A. Product Overview

Nexlizet is a fixed dose combination of bempedoic acid, an adenosine triphosphate-citrate lyase (ACL) inhibitor and ezetimibe, a cholesterol absorption inhibitor. NEXLIZET (bempedoic acid and ezetimibe) 180/10 mg tablet is intended for use as an adjunct to diet [redacted] (b) (4)

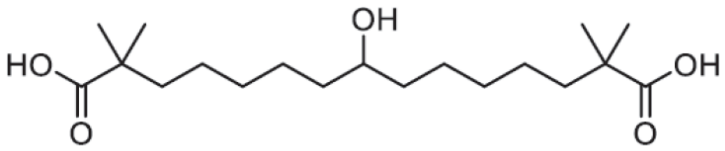
NEXLIZET tablets contain 180 mg of bempedoic acid and 10 mg of ezetimibe along with commonly used tableting excipients. The proposed tablets are blue oval shaped tablets debossed with "ESP" on one side and on the other side with 818. NEXLIZET tablets will be available as 30ct or 90ct in HDPE bottles with desiccant or as 7ct blister pack sample. Nexlizet tablets should to be stored in original packaging at temperature between 68ºF to 77ºF (20ºC to 25ºC) excursions permitted to 15℃ to 30℃ (59℉ to 86℉).

| | |
|---|---|
| **Proposed Indication(s) including Intended Patient Population** | *Refer to CTDL memo* |
| **Duration of Treatment** | *Refer to CTDL memo* |
| **Maximum Daily Dose** | *180 mg bempedoic acid/10mg ezetimibe* |
| **Alternative Methods of Administration** | *Not applicable* |

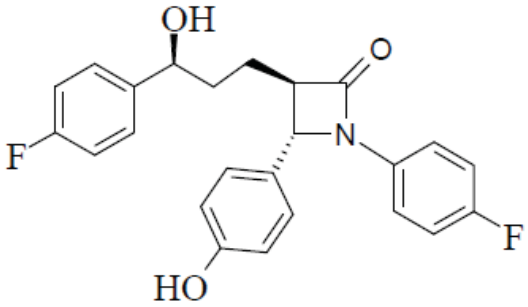
### B. Quality Assessment Overview

**Drug Substance**

Bempedoic acid is a new molecular entity. The chemical name for bempedoic acid is 8-hydroxy-2,2,14,14-tetramethyl-pentadecanedioic acid. Molecular formula is $C_{19}H_{36}O_5$. Molecular weight is 344.49 g/mol. Bempedoic acid has the following structural formula:




The chemical name of ezetimibe is as follows: (3R,4S)-1-(*p*-fluorophenyl)-3-[(3S)-3-(*p*-fluorophenyl)-3-hydroxypropyl]-4-(*p*-hydroxyphenyl)-2-azetidinone. Molecular Formula is $C_{24}H_{21}F_2NO_3$.Molecular weight is 409.43 g/mol. It has the following structural formula:




The applicant has cross-referenced the CMC information for bempedoic acid and ezetimibe to NDA 211616 and DMF (b) (4) respectively. Dr. Paresma Patel reviewed the chemistry, manufacturing and control information for bempedoic acid (NDA 211616) and ezetimibe (DMF (b) (4)) including drug substance (DS) and impurities characterization data, control strategy for impurities, manufacturing process description, reference standard information, test method description and methods validation, stability data, and drug substance specifications. Her review concluded that CMC information provided in DMF (b) (4) and NDA 211616 is adequate to control the identity, purity, strength, and quality of the drug substances used for manufacturing the proposed fixed dose combination product.

Test methods used for assay and impurities independently verified by FDA Division of Pharmaceutical Analysis (DPA) laboratories at St. Louis, MO. For additional details, please refer to the following CMC reviews in Panorama: DS review for NDA 211616 and 211617 dated 10/29/2019 and 10/30/19, DMF (b) (4) review dated 7/26/2019 and DPA's method verification summary reports dated 7/17/19 in Panorama under NDA 211617 and 211616.

**Drug Product**

The proposed Nexlizet 180mg/10mg tablets are blue oval shaped tablets debossed with "ESP" on one side and on the other side with 818. Nexlizet tablets will be available in 30ct or 90ct HDPE bottle supplied with desiccant or as 7ct (b) (4) blister pack samples.

(b) (4)

The Nexlizet tablet contains 180 mg of Bempedoic acid and 10 mg ezetimibe. In addition, it contains colloidal silicon dioxide (b) (4), hydroxyl propyl cellulose (b) (4) lactose monohydrate (b) (4), magnesium stearate (b) (4), microcrystalline cellulose (b) (4), povidone K30 (b) (4) sodium lauryl sulfate (b) (4), and sodium starch glycolate (b) (4) The tablets are coated with film comprising of partially hydrolyzed polyvinyl alcohol, FD&C Blue #2/ (b) (4) FD&C Blue #1/Brilliant Blue FCF Aluminum lake, talc, and titanium dioxide. All excipients present in the drug product are USP/NF grade. The components of coating agent used in drug product conform to USP grade excipients.

The drug product development is based on bempedoic acid monotherapy product (NDA 211616), excipient compatibility studies, and knowledge of the ezetimibe innovator product formulation. Drug product is manufactured by (b) (4)

Nexlizet tablet manufacturing process uses (b) (4)

The composition of the product, the process used for manufacturing the drug product batches and the packaging system used for the drug product in phase 3 clinical studies are the same as that proposed for commercial use. The registration batches are one third of the proposed commercial batch size (b) (4) kg, (b) (4) tablets).The manufacturing process flow information is aligned with the proposed master batch record. The batches used in clinical and stability studies are identified in the application.

The applicant's control strategy for producing acceptable quality drug product is based on process design, control of input materials (e.g., specifications for drug substance and excipients, and container closure components), in-process controls, and in-process tests, finished product specifications, (b) (4), and appropriate product packaging to ensure control of the quality of the finished product. Dr. Christina Capacci-Daniel reviewed the manufacturing process/control information and facility compliance information. OPF process review includes risk assessment for manufacturing process control and its relationship to drug product critical quality attributes. OPF review concluded that the process and facilities information provided in the NDA is adequate. Please refer to process/facilities review in Panorama dated 9/30/2019.

The applicant performed a risk assessment for elemental impurities per ICH Q3D and provided justification for not including routine elemental impurities testing in the product. In addition, Dr. Ramaswamy performed a risk assessment for the finished

product critical quality attributes and his assessment concluded that the final quality risk is low for the proposed product (Refer to Appendix I).

The finished product specification was finalized by the drug product and biopharmaceutics reviewers. The drug product is tested for visual appearance, identity, assay, uniformity of dosage units, impurities, (b) (4) and dissolution. FDC drug product batches will be tested at release and stability for microbiological purity. Please refer to Dr. Amartey's drug product review dated 12/9/19 for additional information.

A dissolution test is proposed for the quality control of Nexlizet tablets. Dr. Nahar reviewed the dissolution method and the proposed dissolution acceptance criteria for the fixed dose combination product. Per FDA's recommendation, the applicant has agreed to use a dissolution specification of Q = (b) (4)% in 30 minutes for both bempedoic acid (final specification) and ezetimibe (interim dissolution specification). The applicant has also agreed to collect ezetimibe dissolution data at the (b) (4) time points for the first 20 consecutively manufactured commercial batches of FDC tablets on both release and stability programs (b) (4) Dr. Nahar's recommendation for this NDA is adequate. Please refer to biopharma review dated 10/28/19 in Panorama.

The applicant submitted environmental assessment (EA) for bempedoic acid and a claim for categorical exclusion from environmental assessment for ezetimibe. Dr. Laurenson reviewed the environmental assessment for bempedoic acid and the categorical exclusion claim for ezetimibe. His EA review concluded that the proposed action for bempedoic acid does not significantly affect the environment and thus finding of no significant impact (FONSI) is recommended. His review also concluded categorical exclusion from an EA for ezetimibe is acceptable. Please refer to Dr. Laurenson's environmental assessment review dated 10/16/19 in panorama for additional information.

*Expiration Date & Storage Conditions:* The application contains 6 month accelerated stability (40°C/75% RH) and 12 months of long-term storage stability data (25°C/60% RH) for 3 primary stability batches. The applicant also provided 12-18 months of long-term stability and 6 months of accelerated stability for 3 supporting stability batches. Stability information was reviewed by drug product reviewer. His review concluded that the product is stable when stored in the proposed commercial packaging (in 30ct or 90ct (b) (4) with desiccant (b) (4) A shelf-life of 24 months is granted for drug product, when stored at 68 -77°F ((20°-25°C) in original packaging. Excursions permitted to 59°-86°F (15°-30°C) [see USP Controlled Room Temperature]. Please refer to drug product review dated 12/9/19 in Panorama for additional information.

*Container and Carton Label Review:* Drug product reviewer completed review of container and carton label. Dosage form, strength, established name, NDC #, Lot #/expiry, and storage conditions are adequately described in the carton and container label, which meets relevant regulatory requirements for labeling. Refer to drug product review for a copy of the label.

## OVERALL ASSESSMENT AND SIGNATURES:

OPQ CMC review concludes that there are no outstanding deficiencies related to drug substance, drug product, process, facilities, biopharmaceutics, environmental analysis, container and carton label. *OPQ overall recommendation for NDA 211617 is approval.*

***Muthukumar Ramaswamy, Ph.D. 12/9/2019***

***Application Technical Lead Name and Date:***

# Attachment I: Final Risk Assessments

| *From Initial Risk Identification* | | | *Review Assessment* | | |
|---|---|---|---|---|---|
| ***Attribute/ CQA*** | ***Factors that can impact the CQA*** | ***Initial Risk Ranking*** | ***Risk Mitigation Approach*** | ***Final Risk Ranking*** | ***Lifecycle Considerations/ Comments*** |
| Drug content (potency) | Formulation, process (tablet weight), container/ stability/Method | M | (b) (4) | Acceptable | None |
| Dose content uniformity | Formulation, process (tablet weight), container/ stability/ Method | L | | Acceptable | |
| Particle Size Distribution of API | Formulation, process | M | | Acceptable | none |
| Impurities | Formulation, stability, Process, Container closure | L | | Acceptable | none |
| Appearance | Formulation, process, Container closure, stability | L | | Acceptable | none |
| Microbial load | Container closure (b) (4) | L | | Acceptable | none |
| In vitro dissolution | Formulation, process, incoming materials | M | | Acceptable | A dissolution specification of Q (b) (4)% at 30 min is proposed. (b) (4) |

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# NDA 211617 LABELING REVIEW

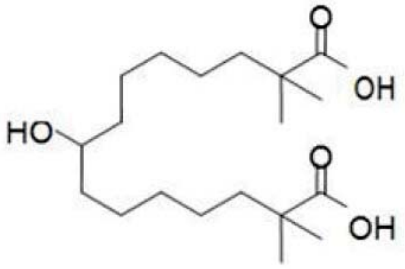
## Section 3 Dosage Form and Strengths

Tablets (b) (4) 180 mg/ 10 mg): blue, oval, (b) (4) debossed with “818” on one side and “ESP” on the other side.

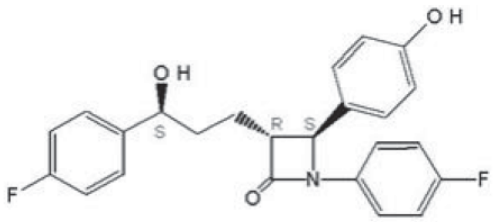
## Section 11 Description

NEXLIZET tablets contain bempedoic acid, an adenosine triphosphate-citrate lyase (ACL) inhibitor, and ezetimibe a (b) (4)

The chemical name is 8-hydroxy-2,2,14,14-tetramethyl-pentadecanedioic acid. The molecular formula is $C_{19}H_{36}O_5$, and its molecular weight is 344.4 (b) (4) Bempedoic acid is a white to off-white crystalline powder that is highly soluble in ethanol, isopropanol and pH 8 phosphate buffer, and (b) (4) insoluble in water and aqueous solutions below pH 5. The structural formula (b) (4)




The chemical name for ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorphenyl)-3(S)-hydroxypropyl]-4 (S)-(4-hydroxyphenyl)-2-azetidinone. The molecular formula is $C_{24}H_{21}F_2NO_3$ and the molecular weight is 409.4 (b) (4). The structural formula (b) (4)



(b) (4) inactive ingredients: colloidal silicon dioxide, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone K30, sodium lauryl sulfate, and sodium starch glycolate. The film-coating (b) (4) comprising FD&C Blue#1/Brilliant Blue FCF Aluminum Lake, FD&C Blue #2 Indigo Carmine Aluminum Lake, glyceryl monocaprylocaprate, partially hydrolyzed polyvinyl alcohol, sodium lauryl sulfate, talc, and titanium dioxide.

**Section 16: How Supplied/ Storage and Handling**

(b) (4)

**Storage and handling:**

(b) (4)

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# CHAPTER III: ENVIRONMENTAL

IQA NDA Assessment Guide Reference

## R REGIONAL INFORMATION

The applicant submitted an environmental assessment (EA) for bempedoic acid (NDAs 211616 and 211617) and a claim for a categorical exclusion from an EA for ezetimibe (NDA 211617). FDA concludes that the EA contains sufficient information to enable FDA to determine whether the proposed action for may significantly affect the quality of the human environment, per 21 CFR 25.15(a). FDA also concludes that the proposed action for bempedoic acid does not significantly affect the environment, and thus a finding of no significant impact (FONSI) is recommended. The categorical exclusion cited for ezetimibe is 21 CFR 25.31(a), which is for substances that would not increase in use following approval of the application. The required statement of no extraordinary circumstances has been submitted, per 21 CFR 25.15(d). Based on a review of the supporting data provided for this claim, a categorical exclusion from an EA for ezetimibe is acceptable.

### Environmental

(b) (4)

Bempodoic Acid

(b) (4)


(b) (4)

the applicant agreed with assuming that the conjugates could be active due to the potential for bacterially mediated transformation back to the parent compound. Thus, unmetabolized bempedoic acid was used for the purposes of environmental fate and effects testing and risk analysis. The applicant also provided data indicating that bempedoic acid is highly soluble within typical environmental pH ranges, is not volatile, has low bioaccumulation potential, can be classified as having a medium level of mobility in soils and sludges, and can be characterized as readily biodegradable. Environmental concentrations were estimated using a simplifying assumption that all bempedoic acid used by patients, along with metabolites, will enter publicly owned treatment works (POTW) and will be discharged to the environment in POTW effluent without any degradation. The EIC for bempedoic acid was estimated as (b) (4) µg/L POTW effluent. Based on a 10-fold dilution

factor, the expected environmental concentration (EEC) was calculated as (b) (4) µg/L in surface water. Due to solubility, biodegradability, and limited binding to soils and sludges, the EA did not include an assessment of terrestrial effect concentrations.

Toxicity data for bempedoic acid in aquatic systems were obtained from an activated sludge respiration inhibition test, an algal growth inhibition test, an invertebrate reproduction test, and a fish early life stage toxicity test. No adverse effects on wastewater treatment processes were expected due to the projected usage of bempedoic acid drug product. The toxicity margins of safety for freshwater green algae calculated on the basis of bempedoic acid concentration in effluent and surface water were both >1000. Therefore, the applicant noted that no significant impact of bempedoic acid on algae is expected due to the projected usage of the bempedoic acid drug product. The applicant also stated that no significant impacts of bempedoic acid on aquatic invertebrates or on fish are expected due to the projected usage of the bempedoic acid drug product.

In summary, the applicant stated that bempedoic acid is highly soluble in water at environmentally relevant pH levels, exhibits low sorption to soils and sludges, and is readily biodegradable and not bioaccumulative. Based on these findings, the only potentially significant route of environmental exposure is expected to be aquatic. Furthermore, applicant concluded that the aquatic effects of bempedoic acid due to patient use of bempedoic acid drug product at the predicted rate of production, determined through laboratory toxicity testing, would not be significant. Conservative estimates of the EIC and EEC of bempedoic acid are below the environmental effect levels, even though these calculations do not account for the likely substantial environmental biodegradation of bempedoic acid. Particularly, the conservative estimate of bempedoic acid concentration in surface water (b) (4) µg/L) is more than (b) (4) times lower than the lowest environmental effect level (b) (4) mg/L) determined among algae, aquatic invertebrates, and fish. In conclusion, bempedoic acid drug product is unlikely to represent a risk to the aquatic environment.

This EA is reviewed below under Assessment.

Ezetimibe

The claim for a categorical exclusion for ezetimibe was submitted per 21 CFR 25.31(a), which is for substances that would not increase in use following approval of the application. The required statement of no extraordinary circumstances also had been submitted, per 21 CFR 25.15(d). The applicant noted that ezetimibe in the product tablets will be used at the same dose, similar

indication, and in the same intended patient population as that already approved for ezetimibe tablets, and thus the marketing approval of the FDC tablets is not expected to increase the use of ezetimibe. This claim is reviewed below under Assessment.

**Assessment:** ***Adequate***

Bempodoic Acid

The main goals of this review of the EA, per 21 CFR 25.15(a) and (b), are to determine (1) whether the EA contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment and (2) if so, whether the proposed action will significantly affect the environment.

The EA method, results, and conclusions were reviewed. FDA agrees that the EIC (b) (4) µg/L) and EEC ( (b) (4) µg/L) are considered worst case, and the lowest effect concentration among the assays and all endpoints, (b) (4) mg/L, result in a margin of exposure (MoE) of over (b) (4) when compared to the EIC. This EIC is considered worst-case because the calculation of the EIC did not take into consideration (1) metabolism, (2) degradation during wastewater treatment, or (3) dilution, degradation, or removal in surface water.

Given the concern about whether bempodoic acid is relevant to FDA's 2016 Q&A guidance on estrogenic, androgenic, or thyroid effects, FDA conducted an additional assessment, using the fish plasma model (FPM; Nallani et al., 2016). Using the therapeutic $C_{max}$ of 21 µg/mL, a logD of 0.8 at pH 7, and a maximum expected environmental concentration (MEEC) of (b) (4), FDA calculated a MoE of about (b) (4) which is larger than the minimum MoE of 1,000 recommended by Nallani et al.

Therefore, FDA concludes that EA and the additional analysis conducted by FDA provide sufficient information to enable a determination of whether the proposed action may significantly affect the quality of the human environment. The available data appear to be accurate and objective. Therefore, the EA is adequate for approval. Based on a review of the information provided in the EA, and on the scientific validity of the conclusions of the EA, no significant adverse environmental impacts are expected from the approval of this NDA.

Based on the information available to date, a FONSI is recommended for this portion of the application.

Ezetimibe

Based on a review of the supporting data provided for this claim, per 21 CFR 25.31(a), including the required statement of no extraordinary circumstances has been submitted, per 21 CFR 25.15(d), a categorical exclusion from an EA for ezetimibe is acceptable.

References

Celiz, M. D., Tso, J. and Aga, D. S. 2009. Pharmaceutical metabolites in the environment: Analytical challenges and ecological risks. Environmental Toxicology and Chemistry, 28: 2473–2484. doi:10.1897/09-173.1

Nallani, G., Venables, B., Constantine, L., & Huggett, D. 2016. Comparison of Measured and Predicted Bioconcentration Estimates of Pharmaceuticals in Fish Plasma and Prediction of Chronic Risk. Bulletin of environmental contamination and toxicology, 96(5), 580-584.

USFDA. 2016. Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity. Center for Drug Evaluation and Research. https://www.fda.gov/downloads/Drugs/Guidances/UCM444658.pdf

*Primary Environmental Assessor Name and Date:* James Laurenson, October 14, 2019

*Secondary Assessor Name and Date (and Secondary Summary, as needed):* M. Scott Furness, October 16, 2019

James Laurenson

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Michael Furness

Digitally signed by Michael Furness
Date: 10/14/2019 09:18:50PM
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## BIOPHARMACEUTICS

**Product Background:**

**NDA/ANDA:** NDA 211617-ORIG-1

**Drug Product Name / Strength:** Bempedoic acid and ezetimibe as a Fixed-Dose Combination film coated tablet, 180 mg and 10 mg

**Route of Administration:** Oral

**Applicant Name:** Esperion Therapeutics, Inc.

**FDA Received date:** 2/25/2019

***Review Summary:*** **Adequate**

The proposed drug product, bempedoic acid and ezetimibe as a Fixed-Dose Combination film coated tablet, 180 mg and 10 mg, immediate release film coated tablet is indicated as an adjunct to diet in combination with (b) (4) The drug product is an immediate release film coated tablet.

**Solubility:** The Applicant claimed that both bempedoic acid and Ezetimibe are BCS class 2 compounds. Solubility of the bempedoic acid (BA) is pH dependent and solubility increases with increased pH. Aqueous solubility profile of BA was demonstrated across pH range of (b) (4). Ezetimibe exhibited low solubility across physiological pH range. Ezetimibe is soluble at low pH of 1.20 and insoluble at pH above 4.01 and practically insoluble in water (b) (4)

**Formulation used in clinical study:** The (b) (4) FDC product is the to-be-marketed product. All FDC studies used the to-be-marketed formulation. The two FDC formulations (b) (4) were used in study 1002FDC-034.

**Bempedoic acid and Ezetimibe fixed dose combination Formulation development:** Esperion Therapeutics, Inc., the applicant submitted the NDA 211617 for the fixed dose combination (FDC) drug product bempedoic acid 180 mg and Ezetimibe 10 mg (nexlizet) immediate release tablets. The Applicant developed two types of formulations with (b) (4)

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**Discriminatory ability of the dissolution method:**

**Bempedoic acid:** The discriminatory ability of the bempedoic acid dissolution method was evaluated for both monotherapy (i.e. bempedoic acid 180 mg tablet) and FDC tablet. Please refer to the Biopharmaceutics review of NDA 211616 for the discriminatory ability of the discriminatory ability of the bempedoic acid dissolution method for monotherapy drug product. The discriminatory ability of the bempedoic acid in FDC product was evaluated by varying tablet hardness and in dissolution media with different pH, (b) (4)

**Table 4: In process parameters for various feasibility batches of** (b) (4)

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(b) (4)

**Reviewer's assessment:**
The in vitro dissolution method development considered physicochemical properties of the drug substance, drug product formulation aspects and dissolution release method parameters. The following parameters were evaluated in the method development: drug substance solubility, pH range, agitation rates, media volume and sink conditions. The discriminatory ability was demonstrated by changing formulation variables, and process variables. The dissolution method to determine bempedoic acid and ezetimibe is adequate.

The final dissolution methods used-

| Drug | Apparatus | Media and temperature | Media volume (mL) | Speed (rpm) |
|---|---|---|---|---|
| Bempedoic acid | USP Apparatus II | 0.05M Potassium phosphate buffer, pH 6.6 | 900 | 50 |
| Ezetimibe | USP Apparatus II | 0.05M Sodium acetate buffer pH 4.5 with 0.45% SLS | 900 | 50 |

**Dissolution method Validation:**
The validation report for dissolution analytical method is adequate.

**Dissolution acceptance criteria:**

**Table 10:** Fixed dose combination (bempedoic acid 180 mg and ezetimibe 10 mg) Tablets batch 17165a/17165H2, bempedoic acid dissolution, pH 6.6

| Method | Vessel | 5 min | 10 min | 15 min | 20 min | 30 min | 45 min | 60 min | 75 min |
|---|---|---|---|---|---|---|---|---|---|
| Apparatus 2, 0.05M Potassium Phosphate Buffer pH 6.6, 900 mL 50 rpm | 1 | (b) (4) | | | | | | | |
| | 2 | | | | | | | | |
| | 3 | | | | | | | | |
| | 4 | | | | | | | | |
| | 5 | | | | | | | | |
| | 6 | | | | | | | | |
| | 7 | | | | | | | | |
| | 8 | | | | | | | | |
| | 9 | | | | | | | | |
| | 10 | | | | | | | | |
| | 11 | | | | | | | | |
| | 12 | | | | | | | | |
| **Average** | | **25** | **52** | **68** | **76** | **86** | **92** | **95** | **99** |
| %RSD | | 19.1 | 6.6 | 3.6 | 2.2 | 1.1 | 0.9 | 1.2 | 1.2 |

min = minute; rpm = revolutions per minute; RSD = relative standard deviation.
[a] Date of Manufacture: (b) (4); retested (b) (4), results (b) (4).

**Table 11:** Fixed Dose Combination (bempedoic acid 180 mg + ezetimibe 10 mg) Tablets Batch 17165a / 17165H2 – ezetimibe Dissolution, 900 mL

| Method | Vessel | 5 min | 10 min | 15 min | 20 min | 30 min | 45 min | 60 min | 75 min |
|---|---|---|---|---|---|---|---|---|---|
| Apparatus 2, 0.45% SLS in 0.05M Acetate buffer pH 4.5 900 mL 50 rpm | 1 | (b) (4) | | | | | | | |
| | 2 | | | | | | | | |
| | 3 | | | | | | | | |
| | 4 | | | | | | | | |
| | 5 | | | | | | | | |
| | 6 | | | | | | | | |
| | 7 | | | | | | | | |
| | 8 | | | | | | | | |
| | 9 | | | | | | | | |
| | 10 | | | | | | | | |
| | 11 | | | | | | | | |
| | 12 | | | | | | | | |
| **Average** | | **35** | **76** | **84** | **87** | **90** | **92** | **92** | **95** |
| %RSD | | 23.1 | 4.0 | 3.4 | 3.3 | 3.6 | 3.6 | 4.0 | 3.6 |

min = minute; rpm = revolutions per minute; RSD = relative standard deviation; SLS = sodium lauryl sulfate.
[a] Date of Manufacture: (b) (4); retested January (b) (4), results (b) (4).

Based on the in vitro dissolution data of the clinical batches of the to be marketed products in QC method, it is observed that more than (b) (4)% of bempedoic acid and ezetimibe were released from the tablet in 30 minutes (b) (4) There is not much variability observed in the data. Therefore, the proposed dissolution acceptance criteria of Q= (b) (4)% in 30 minutes is permissive. Hence, the reviewer recommended the following acceptance criteria based on the data: "Bempedoic acid: Q= (b) (4)% dissolved in 30 minutes; Ezetimibe: Q= (b) (4)% dissolved in (b) (4) minutes". An IR was sent to the applicant asking to revise the dissolution acceptance criteria and revise the NDA accordingly. Please refer to the Appendix 2 for detailed information of the IR. The applicant has accepted the specification for bempedoic acid, but counter-proposed Q= (b) (4)% in 30 minutes for ezetimibe.

The following acceptance criteria are found to be acceptable:

- Bempedoic acid Dissolution - NLT (b) (4)% (Q) of the labeled amount of bempedoic acid is dissolved in 30 minutes (Final specification).
- Ezetimibe Dissolution - NLT (b) (4)% (Q) of the labeled amount of ezetimibe is dissolved in 30 minutes (Interim specification).

In addition, for Ezetimibe, the applicant agreed to collect dissolution data at (b) (4) time points for the first 20 consecutively manufactured commercial batches of FDC tablets on both release and stability programs (b) (4) Until the dissolution acceptance criterion for the Ezetimibe is finalized, the applicant should include the following term "Interim dissolution acceptance criterion" in the relevant sections of the application including drug product specification table for the Ezetimibe and follow up with the agency to finalize the dissolution acceptance criterion as per the commitment.

**List Submissions being reviewed (table):** Dissolution method and acceptance criterion, bridging among formulations.

**Highlight Key Outstanding Issues from Last Cycle: None.**

**Conclusion:**

The NDA 211617 is adequate for approval from biopharmaceutics perspective.

Approved dissolution methods and dissolution acceptance criteria of the FDC tablet:

| Drug | Apparatus | Media, volume | rpm | Dissolution acceptance criteria |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| Bempedoic acid | USP apparatus II | 0.05 Potassium phosphate buffer pH 6.6, 900 mL | 50 | Q = (b) (4)% in 30 minutes |
| Ezetimibe | USP apparatus II | 0.05M Sodium acetate buffer pH 4.5 with 0.45% SLS, 900 mL | 50 | Q = (b) (4)% in 30 minutes (Interim specification, (b) (4) |

***Signature Block***

***Primary Biopharmaceutics Reviewer Name:***

Kamrun Nahar, PhD. 10/23/2019

***Secondary Biopharmaceutics Reviewer Name:***

Haritha Mandula, PhD. 10/23/2019

# Appendix 1

Application 211617 - Sequence 0010 - Cover Letter 04/30/2019 - Response to Information Request: Chemistry, Manufacturing, and Controls Information
Application 211617 - Sequence 0022 - Response to Request for Chemistry, Manufacturing, and Controls Information 08/28/2019
Application 211617 - Sequence 0027 - Response to Request for Chemistry, Manufacturing, and Controls Information 10/07/2019

***List of Deficiencies:***

***Information request***
**Information request 1:**

"*Reference is made to your NDAs 211616 and 211617. We could not locate the individual dissolution test data of the formulations used in the clinical studies. Please provide the location of that data. If not already submitted, please submit the data by 4/30/2019."*

**Information request 2:**

1. We acknowledge that you have provided discriminating ability of the dissolution method comparing your proposed method target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations). However, you did not provide discriminatory ability of the developed dissolution method demonstrating the differences in the relevant critical process parameters (for example, drug substance particle size distribution (PSD) among the formulations for both mono (bempedoic acid tablet) and fixed dose combination (bempedoic acid + ezetimibe tablet) drug products. Therefore, we recommend that you demonstrate a meaningful discriminatory ability of your dissolution method for the most relevant critical process parameters by varying the range (e.g., ± 10-20% change to the specified values or ranges for these variables) of the developed formulations. In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.
2. You've provided us the comparative dissolution profiles for the bempedoic acid tablet product, i.e. formulations 1, 2A and 2 of bempedoic acid tablets. However, no individual dissolution data were provided. Therefore, please provide us the complete dissolution profile of the individual tablet of all three formulation of the bempedoic acid tablet data in QC dissolution method.
3. In the response to the IR dated 04/30/2019, you've provided us the dissolution data of the bempedoic acid tablets for both FDC products and mono drug product in the dissolution media with pH (b) (4). The final dissolution method was chosen with pH 6.6. Hence, please provide us the full profile of the dissolution data (N=12 tablets /batch) for both mono and FDC products (corresponding to ezetimibe and bempedoic acid release) at different time points in the QC method. Alternatively, demonstrate that this difference in pH will not alter the release of your proposed drug product.
4. You did not mention the type of dissolution vessel and dissolution media temperature you've used to conduct the dissolution studies. Please confirm the type of dissolution media temperature and dissolution vessel type.
5. Please update the stability information.

***Applicant's response for the IR 2:***

**Applicant's response for the IR 2: comment# 1:**
Application 211617 - Sequence 0022 - Response to Request for Chemistry, Manufacturing, and Controls Information 08/28/2019

**Summary of applicant's response for the IR 2: comment# 1:**
The applicant evaluated discriminatory ability of the FDC tablets by varying formulation variabilities (b) (4)

Initially, particle size distribution (PSD) was considered as a critical process parameter. Study 1002-016 showed that despite having differences in PSD of bempedoic acid capsule (d90 (b) (4) µm) and formulation 1 tablet (d90 (b) (4) µm), PK parameters of these formulations are similar. Hence, the potential impact of different PSD on dissolution does not appear to pose any clinically meaningful effect.

In the FDC tablets, bempedoic acid in FDC tablet showed discriminatory ability due to differences in hardness.

In the FDC tablets, ezetimibe in FDC tablet showed discriminatory ability due to variation in (b) (4) the applicant considered that discriminatory ability of the dissolution is not necessary from PSD perspective.

**The reviewer's assessment:**

Applicant's justification, the response is deemed adequate.

**Applicant's response for the IR 2: comment# 2:**Application 211617 - Sequence 0022 - Response to Request for Chemistry, Manufacturing, and Controls Information 08/28/2019

**The reviewer's assessment:**

Applicant's response is deemed adequate.

**Applicant's response for the IR 2: comment# 3:**

Application 211617 - Sequence 0022 - Response to Request for Chemistry, Manufacturing, and Controls Information 08/28/2019

**Reviewer's assessment:**

The applicant provided dissolution data of one lot of fixed dose combination (FDC) product using the QC method. The applicant did not provide dissolution data of two more lots of FDC product due to unavailability of the samples. The applicant's response is adequate.

***You did not mention the type of dissolution vessel and dissolution media temperature you've used to conduct the dissolution studies. Please confirm the type of dissolution media temperature and dissolution vessel type.***

**Applicant's response for the IR 2: comment# 4:**

Application 211617 - Sequence 0022 - Response to Request for Chemistry, Manufacturing, and Controls Information 08/28/2019

**Reviewer's assessment:**

The applicant's response is adequate.

**Applicant's response for the IR 2: comment# 5:**Application 211617 - Sequence 0022 - Response to Request for Chemistry, Manufacturing, and Controls Information 08/28/2019

**Reviewer's assessment:**

Please refer to the drug substance and drug product review to see the adequacy of the response.

**Information request 3:**

(b) (4)

We recommend the following dissolution acceptance criterion:

Bempedoic acid: Q= (b) (4)% dissolved in 30 minutes
Ezetimibe: Q= (b) (4)% dissolved in (b) (4) minutes

We request that you acknowledge your acceptance of the recommended acceptance criterion and update your drug product release and stability specifications accordingly. In addition, please be advised that all proposed exhibit batches are expected to meet the revised dissolution specification in your stability program through your proposed expiry period.

**Applicant's response:**

Application 211617 - Sequence 0027 - Response to Request for Chemistry, Manufacturing, and Controls Information 10/07/2019

**Reviewer's assessment:**

1. The Applicant agrees to implement the recommended acceptance criterion for bempedoic acid in the FDC tablet. Therefore, their response for the bempedoic acid is adequate.
2. The applicant's counter proposed an interim dissolution acceptance for the ezetimibe, i.e. Q= (b) (4)% in 30 minutes for the first 20 consecutively manufactured commercial batches of FDC tablets on both the release and stability programs is acceptable.

On October 16, 2019, the applicant was sent an IR to confirm the dissolution acceptance criteria through an email communication. The information request is given below-

**Information request 4:**

With reference to your NDA information amendment dated 10/7/19 related to dissolution acceptance criteria for bempedoic acid and Ezetimibe fixed dose combination (FDC) tablet product, we agree to the following acceptance criteria:

- Bempedoic acid Dissolution - NLT (b) (4)% (Q) of the labeled amount of bempedoic acid is dissolved in 30 minutes (Final specification).
- Ezetimibe Dissolution - NLT (b) (4)% (Q) of the labeled amount of ezetimibe is dissolved in 30 minutes (Interim specification).

You have agreed to collect dissolution data at (b) (4) time points for the first 20 consecutively manufactured commercial batches of FDC tablets on both release and stability programs (b) (4) Until you finalize the dissolution acceptance criterion for the Ezetimibe, please include the following term "Interim dissolution acceptance criterion" in the relevant section in your application including drug product specification table for the Ezetimibe and follow up with the agency to finalize the dissolution acceptance criterion as per your commitment.

**Applicant's response:**

Application 211617 - Sequence 0029 - Response to Request for Chemistry, Manufacturing, and Controls Information 10/18/2019

**Reveiwer's assessment:**

The applicant accepted the Agency's proposal of accepting the dissolution acceptance criterion of ezetimibe as "interim dissolution acceptance criterion and collection of 20 batches ezetimibe dissolution data at (b) (4)

(b) (4). Therefore, the applicant's response is adequate. Hence, the application NDA 211617 is **adequate** for approval from Biopharmaceutics perspective.

Kamrun Nahar

Digitally signed by Kamrun Nahar
Date: 10/28/2019 09:12:59AM
GUID: 57b38236009c032e2a84627cd295a5cd

Haritha Mandula

Digitally signed by Haritha Mandula
Date: 10/28/2019 09:46:24AM
GUID: 508da6fb000282df41459408f32a1ce0

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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MUTHUKUMAR RAMASWAMY
12/09/2019 05:50:29 PM