CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211616Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 211616
Review 1

Drug Name/Dosage Form	Nexletol (bempedoic acid) tablets
Strength	180 mg
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 (2/21/2019). Amendments: 5/06/19 (Methods), 5/17/19 and 5/23/29 (Method validation), 6/07/19 (Labeling), 6/24/19 (Environmental Assessment), 7/08/19 (Process), 8/12/19 (Process), 8/28/19 (DS, DP, and Process), 9/09/19 (DS, Process and DP), 9/10/19 (DP-packaging), 9/26/19 (Biopharm), 10/04/19 (DS), and 10/24/19 (method validation).	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
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	-	Admin filing issue (5/16/2018)
	III			Active	4/13/2009	Current
	III			Active	1/14/2013	Current
	III			Active	9/24/2012	Current
	III			Active	12/7/1994	Updated 6/30/2008
	III			Active	10/12/2012	
	III			Active	06/28/2007	Current
	III			Active	05/23/2012	Current
	III			Active	04/08/1998	Current 10/152018
	III			Active	1/1/2007	Current per LOA
	III			Active	3/1/2004	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	106554, (b) (4)	
NDA	211617	

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 211616 is approval, which includes acceptable recommendation for the facilities listed in the application.

II. Summary of Quality Assessments

A. Product Overview

NEXLETOL (bempedoic acid) 180 mg tablet is an immediate release dosage form. NEXLETOL tablets are intended for use as an adjunct to diet (b) (4)

Bempedoic acid is a prodrug. It is activated to thioester with coenzyme A in the liver. The activated substance (Bempedoic acid-CoA) is an adenosine triphosphate-citrate lyase (ACL) inhibitor that lowers low-density lipoprotein cholesterol (LDL-C) by inhibition of cholesterol synthesis in the liver.

NEXLETOL (bempedoic acid) tablets contain180 mg of bempedoic acid and the following inactive ingredients: colloidal silicon dioxide, hydroxyl propyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are finished with a common film coating comprising partially hydrolyzed polyvinyl alcohol, polyethylene glycol, talc, and titanium dioxide.

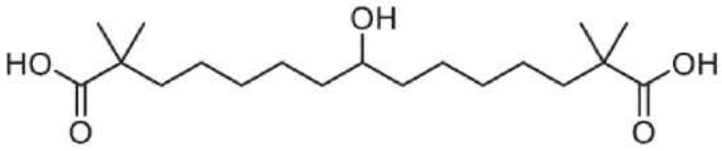
Nexletol tablets will be available as 180 mg tablets in 30ct or 90ct (b) (4) with desiccant or as 7ct blister pack samples. Nexletol tablets should to be stored at temperature between 68ºF to 77ºF (20ºC to 25ºC) excursions permitted to 15℃ to 30℃ (59℉ to 86℉).

Proposed Indication(s) including Intended Patient Population	*Refer to CTDL memo*
Duration of Treatment	*Refer to CTDL memo*
Maximum Daily Dose	*180 mg*
Alternative Methods of Administration	*Not applicable*

B. Quality Assessment Overview

Drug Substance

The chemical name for bempedoic acid is 8-hydroxy-2,2,14,14-tetramethyl-pentadecanedioic acid. Drug substance (DS) has the following structural formula:



Its molecular formula is C19H36O5, and its molecular weight is 344.5. It is a white to off-white crystalline powder. DS is freely soluble at pH >6 but insoluble at pH 5 and below. It exists in only one polymorphic form A. Polymorphic form A was used in non-clinical and clinical studies. Bempedoic acid is synthesized by (b) (4)

Dr. Paresma Patel reviewed the chemistry, manufacturing and control information for the drug substance. Her review concluded that the characterization data provided for the drug substance and impurities, proposed starting material specifications, control strategy for impurities, manufacturing process description, reference standard information, test method description and methods validation, stability data, and drug substance specifications are adequate to control the identity, purity, strength, and quality of the drug substance used for manufacturing the drug product. The proposed DS specifications are consistent with batches used in clinical, nonclinical, and registration stability studies.

Test methods used for assay and impurities were independently verified by FDA Division of Pharmaceutical Analysis (DPA) laboratories at St. Louis, MO. Drug substance reviewer granted a retest period of (b) (4) months for bempedoic acid drug substance when stored at (b) (4) Dr. Patel's recommendation for this application adequate based on drug substance section review. For additional details, please refer to Dr. Paresma Patel's CMC review dated 10/29/2019 in Panorama as well as DPA's method verification summary reports dated 7/17/19 in Panorama.

Drug Product

The proposed Nexletol 180 mg tablets are white to off-white oval shaped tablets debossed with "ESP" on one side and on the other side with 180. Nexletol tablets will be available in 30ct or 90ct bottle with desiccant or as 7ct PVC blister pack samples. The applicant is also proposing to provide a (b) (4)

Bempedoic acid exhibits low solubility below pH 6.0 (Similar to BCS Class II molecule) and high solubility above pH 6.0 similar to BCS Class II molecule (high solubility/high permeability). For Phase 1 and Phase 2 studies, bempedoic acid was formulated as capsules (b) (4) for oral absorption. During later stages of drug development (Phase 1, 2, and 3 clinical studies), the drug was formulated as 180 mg strength tablets with slight variations in excipient composition (Formulation 1, Formulation 2 and Formulation 2A). The formulation chosen for commercial use and in Phase 3 studies is

Formulation 2. Acceptability of the final product formulation was established based on clinical studies and available dissolution data.

Bempedoic acid (180mg) constitutes [redacted] of the total weight of the tablet formulation. In addition, the tablet formulation contains colloidal silicon dioxide [redacted], hydroxyl propyl cellulose [redacted] lactose monohydrate [redacted], magnesium stearate [redacted] microcrystalline cellulose [redacted], and sodium starch glycolate [redacted]. The tablets are coated with [redacted] film comprising of partially hydrolyzed polyvinyl alcohol, polyethylene glycol, talc, and titanium dioxide. All excipients present in the drug product are USP/NF grade. The components of coating agent conform to USP grade excipients.

Drug product related CMC information was reviewed by drug product reviewer. Nexletol tablet manufacturing process uses [redacted]

The composition of the product, the drug product manufacturing process, 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 half of the proposed commercial batch size [redacted] The manufacturing process flow information is aligned with the proposed master batch record. .

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, [redacted] 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. For additional information, please refer to process/facilities review dated 9/30/2019 in Panorama.

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 by RPHPLC/UV, assay, uniformity of dosage units, impurities (HPLC-[redacted], microbial

purity, [redacted], and dissolution. The quality attributes considered for inclusion in the drug product specification are in alignment with the attributes recommended for oral dosage forms under USP <2> Oral drug products –product quality tests. Please refer to Dr. Amartey's drug product review dated 11/21/19 for additional information.

A dissolution test is proposed for measuring the quality of Nexletol tablets (Apparatus II, paddles; 50 rpm with 900ml 50 mM phosphate buffer pH [redacted]. The proposed dissolution acceptance criteria is based on dissolution data available for clinical batches and extrapolated dissolution information for 9-18 months old stability batches. Dr. Nahar reviewed the dissolution method and the proposed dissolution acceptance criteria. Dr. Nahar's recommendation for this NDA is adequate. Please refer to biopharma review dated 11/13/19 in Panorama.

The applicant submitted environmental assessment for bempedoic acid. Dr. Laurenson reviewed the environment assessment. His 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. Please refer to 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 18 months of long-term storage stability data (25°C/60% RH) for 3 primary stability batches. The applicant also provided up to 24 months of long-term stability and 6 months of accelerated stability for 6 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 (30ct or 90ct or [redacted] with desiccant) with respect to assay, appearance, impurities dissolution, [redacted] and microbial quality.

[redacted]

A shelf-life of 30 months is granted 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 11/21/19 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 211616 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 Uniformity	Formulation, process (tablet weight), container/ stability/ Method	M		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	An-interim dissolution specification of Q=(b) (4)% at 20 min is proposed.

FDA/CDER/OPQ/OTR
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis MO 63110
P: 314.539.2135

METHOD VERIFICATION REPORT SUMMARY

Date: July 17, 2019

To: Paresma Patel, Drug Substance Reviewer
Muthukumar Ramaswamy, Drug Product Reviewer
Leeza Rahimi, RBPM

Through: Connie Ruzicka, Ph.D., Lab Chief, Branch II, CDER/OPQ/OTR/DPA

From: Dongping Dai, Chemist, Ph. D., OGROP/ORA/ORS/OMPTSLO
Bruce Harris, Chemist, Ph. D., OGROP/ORA/ORS/OMPTSLO
Cynthia Sommers, MVP Coordinator, CDER/OPQ/OTR/DPA
Michael Hadwiger, Chemist, CDER/OPQ/OTR/DPA

Subject: Method Verification for NDA 19-211-616: Bempedoic Acid Drug Substance and Bempedoic Acid Tablets (180 mg)

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

1. Assay of drug product by HPLC [(b) (4)] tablets, NDA 211616, using UV detector)
   Method: Pharm Finished Product Analytical Method
   ETC-1002 180mg [(b) (4)]
   (SANDM-001299 Ver:. 5.0)

2. Determination of Identity and Assay of Bempedoic Acid by HPLC-UV
   Method: Identification and Assay of [(b) (4)] Bempedoic Acid [(b) (4)] [redacted] (Number: S1698, Date: 11/20/2018)

A paper review of the following methods were conducted and the methods are considered acceptable for quality control and regulatory purposes:

1. Degradation products of bempedoic in [(b) (4)] tablets, NDA 211616 using [(b) (4)] detector. (see FY19-153-DPA-S).
2. Determination of Chemical Purity of Bempedoic Acid by HPLC-[(b) (4)] (see FY19-152-DPA-S)

Original analyst worksheets can be viewed using this ECMS link:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f8831f6695

Summary of Analysis

Drug Substance

Method Reference: Identification and Assay of [redacted] (Number: S1698, Date: 11/20/2018)

Identification

The sample peak retention time [redacted] matches that of the corresponding peak [redacted] in the standard solution. (RT differs ≤ [redacted]%) **Pass**

Assay Specification: [redacted]% [redacted]% Bempedoic Acid [redacted]

Assay Preparation 1: 99.8%

Assay Preparation 2: 99.7%

Average Assay: **99.8% Pass**

Drug Products: Bempedoic Acid Tablets 180 mg

Method Reference: Pharm Finished Product Analytical Meth (SANDM-001299 Ver:. 5.0)

Identification

The sample peak retention time [redacted] matches that of the corresponding peak [redacted] in the standard solution. (RT differs ≤ [redacted]%) **Pass**

Assay Specification: [redacted]% [redacted]% of Label Amount Bempedoic Acid

Assay Preparation 1: 100.2%

Assay Preparation 2: 100.2%

Average Assay: **100.2% Pass**

Related Substances (HPLC-UV)

Specification: NMT [redacted]% for Individual Related Substance,
NMT [redacted]% for Total Related Substances

Individual Related Substance: RRT [redacted] = [redacted]% **Pass**

Total Related Substances: [redacted]%

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Testing and Research
Division of Pharmaceutical Analysis

OTR-Short Form Report

Date: 2019-07-17

From: Michael E. Hadwiger, Ph.D. OTR/DPA

Through: Connie Ruzicka, PhD., Lab Chief, Branch II, CDER/OPQ/OTR/DPA

To: Paresma Patel, Drug Substance Reviewer
Muthukumar Ramaswamy, Drug Product Reviewer
Leeza Rahimi, RBPM

Subject: Evaluation of 3.2.P.5.2.5 *Related Substances (HPLC-* (b) (4)

Background: A regulatory high-performance liquid chromatography method using a (b) (4) (3.2.P.5.2.5) was submitted by Esperion Therapeutics, Inc. as part of NDA 211616 for FDA review. The method is for the determination of related substances in Bempedoic Acid tablets. Direct evaluation of methods using (b) (4)

Conclusions: The HPLC (b) (4) regulatory method (3.2.P.5.2.5) for Bempedoic Acid tablets is suitable for quality assurance testing with comments in the results section.

Results and Discussion:

Overall, the HPLC (b) (4) method is well-described except for the method's assumption that (b) (4) While this deficiency exists, data provided in the accuracy section of the validation report indicate that any differences in analyte response do not adversely affect the recovery to an unacceptable degree.

While the method validation raw data were not available for review, validation of analytical method parameters required by ICH Q2 (R1) for a quantitative impurity assay were presented in summary and all necessary elements were present (Table 1). To support specificity, example chromatograms illustrating separation efficiency were provided. The method's calculations are

correct and stability data indicate little, if any change, in accelerated storage conditions.

Finally, the system suitability criteria mandated in the method (captured in the bullets below) assure confidence in the final reported values by insuring adequate sensitivity (s/n ratio from injected standard), column performance, (plate count (N), peak shape (tailing factor)), and chromatographic resolution.

- (b) (4)
- impurities. This proves that impurities can be detected and resolved in an adequate manner.
- System suitability criteria are used to assure column performance (measured as plate count (N) and tailing factor).

Table 1: Analytical method parameters required by ICH Q2 (R1) for a quantitative impurity method.

ICH Q2 (R1) Element	Reported	Specification	Pass/Fail
Specificity	Yes	No interference from placebo components, example chromatograms provided	Pass
Linearity	Yes	R^2 NLT (b) (4)	R = (b) (4) Pass
Accuracy	Yes	Recovery is (b) (4)% at (b) (4)% Recovery is (b) (4)% at higher %	Recovery was (b) (4)% at all conc. Pass
Precision (Repeatability)	Yes	%RSD NMT (b) (4)% at (b) (4)% %RSD NMT (b) (4)% at higher conc.	(b) (4)%: %RSD= (b) (4)% Higher conc: %RSD= (b) (4)%, (b) (4)% Pass
Precision (Intermediate)	Yes	%RSD NMT (b) (4)%	Pass
Range	Yes	(b) (4)%	Pass
DL	Yes	s/n >= (b) (4)	Pass
QL	Yes	s/n >= (b) (4)	Pass
Robustness	Yes	System Suitability Specs	Sys. Suit. not affected by column (b) (4)
Solution Stability	Yes	No	Stable for up to (b) (4) days at ambient

References

1. (b) (4)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Testing and Research
Division of Pharmaceutical Analysis

OTR-Short Form Report

Date: 2019-07-17

From: Michael E. Hadwiger, Ph.D. OTR/DPA

Through: Connie Ruzicka, PhD., Lab Chief, Branch II, CDER/OPQ/OTR/DPA

To: Paresma Patel, Drug Substance Reviewer
Muthukumar Ramaswamy, Drug Product Reviewer
Leeza Rahimi, RBPM

Subject: Evaluation of (b) (4) Chemical Purity (Impurities) (b) (4)

Background: A regulatory high-performance liquid chromatography method using a (b) (4) (HPLC- (b) (4) was submitted by Esperion Therapeutics, Inc. as part of NDA 211616 for review by the FDA. The method is for the determination of chemical purity of Bempedoic Acid drug substance. Direct evaluation of methods using (b) (4)

Conclusions: The (b) (4) HPLC (b) (4) regulatory method for Bempedoic Acid is well-described and suitable for quality assurance testing.

Results and Discussion:

While the method validation raw data are not available for review, the system suitability solutions prepared for the method assure confidence in the final reported values by insuring adequate sensitivity (s/n ratio from injected standard). The calculations are correct. Validation of analytical method parameters required by ICH Q2 (R1) for a quantitative impurity assay were presented in summary and all necessary elements were present (Table 1). To support specificity, example chromatograms illustrating separation efficiency were provided. Finally, data presented in the long-term stability studies indicate that (b) (4) is stable and that the increase of impurities due to storage is minimal.

Table 1: Analytical method parameters required by ICH Q2 (R1) for a quantitative impurity method.

Required ICH Q2 (R1) Element	Reported	Specification	Pass/Fail
Specificity	Yes	R NLT (b) (4)	Pass
Linearity	Yes	R NLT (b) (4) CI of y-int includes origin (b) (4)	Pass
Accuracy	Yes	(b) (4)%	Pass
Precision (Repeatability)	Yes	%RSD NMT (b) (4)%	Pass
Precision (Intermediate)	Yes	%RSD NMT %%	Pass
Range	Yes	(b) (4) µg/mL	Pass [1]
DL	Yes	LOD (or DL) NMT (b) (4)%	Pass
QL	Yes	LOQ (or QL) NMT %%	Pass
Robustness	Yes	s/n nor resolution affected	Pass
Solution Stability	Yes	Soln's stable for (b) (4)days	Reported

[1] Range determined from linearity data alone versus linearity, accuracy and precision sections.

Office of Pharmaceutical Quality

New Drug Application (NDA 211616)

Integrated Quality Assessment Template

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	Active		Admin filing issue (5/16/2018)
	III			Active	4/13/2009	Current
	III			Active	1/14/2013	Current
	III			Active	9/24/2012	Current
	III			Active	12/7/1994	Updated 6/30/2008
	III			Active	10/12/2012	
	III			Active	06/28/2007	Current
	III			Active	05/23/2012	Current
	III			Active	04/08/1998	Current 10/152018
	III			Active	1/1/2007	Current per LOA
	III			Active	3/1/2004	

Note: Adequate information is provided in the DMFs for this NDA application.

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NA		

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH-ODE				
CDRH-OC	NA			
Clinical	NA			
Other	NA			

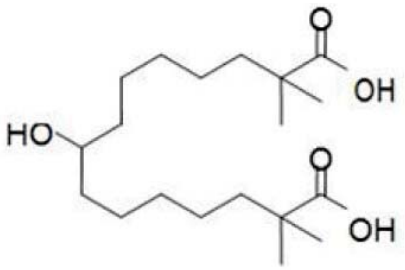
NDA 211616 LABELING REVIEW

Section 3 Dosage Form and Strengths

Tablets (180 mg): White to off-white, oval, film coated, debossed with “180” on one side and “ESP” on the other side.

Section 11 Description

[redacted] (b) (4) an adenosine triphosphate-citrate lyase (ACL) inhibitor. 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 [redacted] (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 is insoluble in water and aqueous solutions below pH 5. The structural formula [redacted] (b) (4)



[redacted] (b) (4)

180 mg of bempedoic acid and the inactive ingredients: colloidal silicon dioxide, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The film-coating [redacted] (b) (4) comprises of partially hydrolyzed polyvinyl alcohol, polyethylene glycol, talc and titanium dioxide.

Section 16: How Supplied/ Storage and Handling

[redacted] (b) (4)

(b) (4)

Storage and handling:

(b) (4)

(b) (4)

Danae Christodoulou

Digitally signed by Danae Christodoulou
Date: 11/21/2019 08:57:53AM
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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) and EEC (b) (4) are considered worst case, and the lowest effect concentration among the assays and all endpoints, (b) (4) 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

BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA 211616-ORIG-1

Drug Product Name / Strength: Bempedoic acid film coated tablet, 180 mg

Route of Administration: Oral

Applicant Name: Esperion Therapeutics, Inc.

FDA Received date: 6/20/2019

Review Summary: ADEQUATE

The proposed drug product, bempedoic acid immediate release film coated tablet 180 mg is indicated as an adjunct to diet in combination with (b) (4) The product formulation is an immediate release film coated tablet.

Solubility: The Applicant claimed bempedoic acid is a BCS class 2 compound. Solubility of the bempedoic acid (BA) is pH dependent and solubility increases with increased pH. Aqueous solubility profile of BA is exhibiting low solubility across pH range of 1 to 6.8.

Formulation used in clinical study: Initial phase I and phase 2 studies used a capsule formulation (2.5 mg to 40 mg). Subsequent clinical studies used three tablet formulations, i.e. Formulation 1: 60 and 180 mg tablets, Formulation 2A: 180 mg and Formulation 2: 180 mg (i.e. Tablet formulation 1, 2A and 2 is used in phase 3 studies). Formulation 2 is the to-be-marketed formulation and was used in 73% patients in phase 3 clinical studies. Additionally, a post hoc PK/PD analysis, POPPK and PK/PD models demonstrated that formulation changes during development did not have an impact on the known exposure-response relationship between bempedoic acid PK and LDL-C lowering (please refer to clinical pharmacology review for additional details).

Table 1: Bempedoic acid formulation used in clinical studies

Formulation	Strength	Clinical Study
capsule	4x40 mg +20 mg= 180 mg	Phase 1 and 2
Tablet Formulation 1	60 mgx3, 180 mg	Phase 2 and 3
Tablet, Formulation 2A (BE criteria with Formulation 1)	180 mg	2 phase 1 & 1 phase 3 study
Formulation 2 (similar to formulation 2A), to be marketed formulation	180 mg	73% phase 3 study

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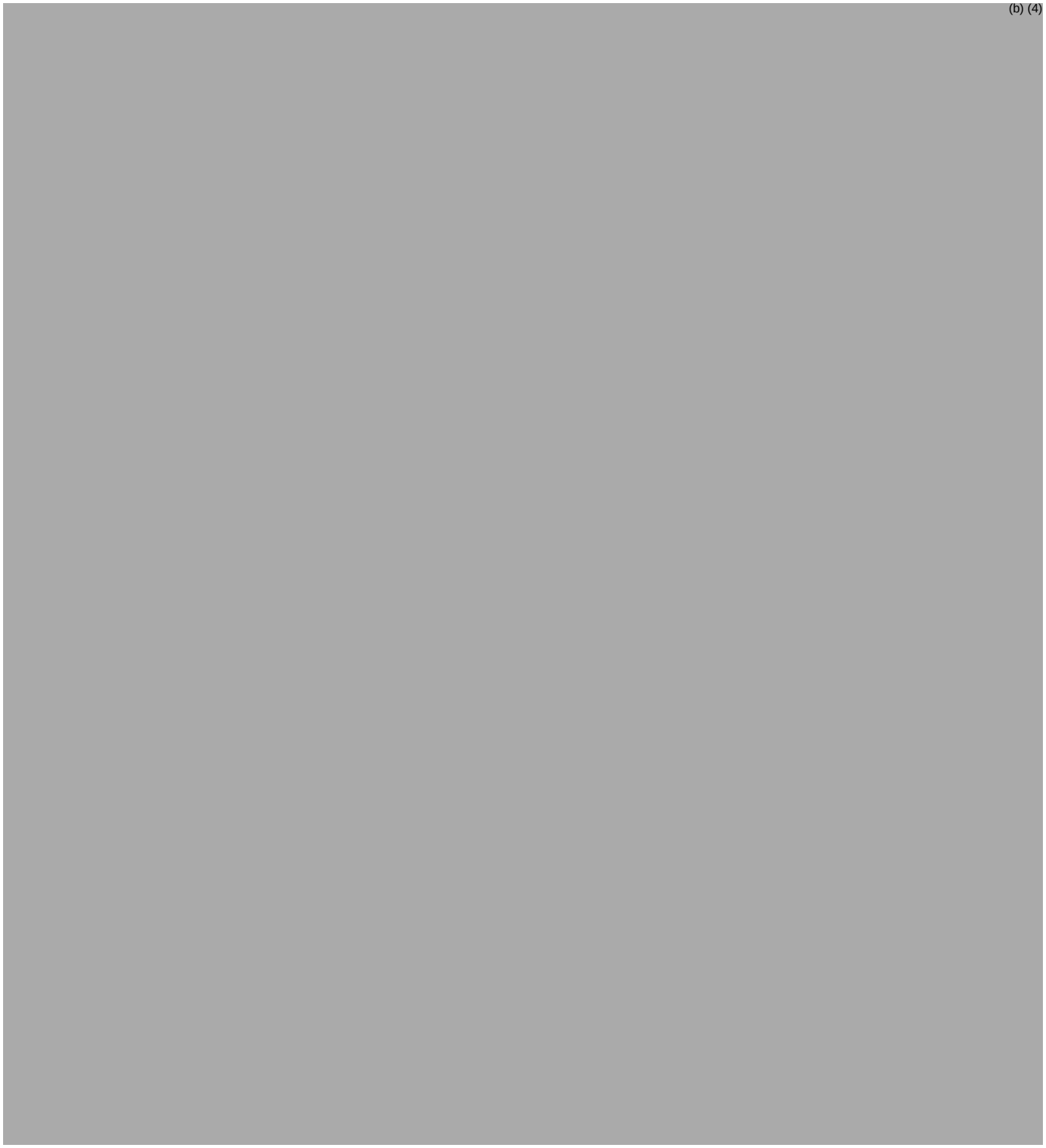


Composition of proposed drug product:

The Applicant developed an immediate release film coated tablet of bempedoic acid. Table 1 below shows the Bempedoic acid tablet formulation.

Table 6: Composition of the bempedoic acid tablet formulation 2, to-be-marketed formulation

Components	Quality Standard	Function	% w/w[1]	Amount (mg/tablet)
Core Tablet:				
Bempedoic acid	In-house (see Section 3.2.S.4.1)	Active Pharmaceutical Ingredient	(b) (4)	180.0
Microcrystalline cellulose (PH 101)	NF, Ph. Eur.	(b) (4)		
Lactose monohydrate	NF, Ph. Eur.			
Hydroxypropylcellulose	NF, Ph. Eur.			
Colloidal silicon dioxide	NF, Ph. Eur.			
Sodium starch glycolate	NF, Ph. Eur.			
Magnesium stearate	NF, Ph. Eur.			
(b) (4)				
Core Tablet Weight				
Film-Coating (b) (4)				
(b) (4)		(b) (4)		
Polyvinyl Alcohol, partially hydrolyzed	*USP, FCC, Ph Eur, JPE*			
Titanium Dioxide	*USP, FCC, Ph Eur, JP*			
(b) (4) *PEG*	*USP, FCC, Ph Eur, JECFA, JP*			
Talc	*USP, FCC, Ph Eur, JP, JECFA*			
(b) (4)				
Total Tablet Weight				

FCC = Food Chemicals Codex; JECFA = Joint Evaluation Committee on Food Additive; JP = Japanese Pharmacopoeia; JPE = Japanese pharmaceutical excipient; NA = Not applicable; NF = National Formulary; PEG = polyethylene glycol; Ph. Eur. = European Pharmacopoeia; q.s. = quantum sufficit; USP = United States Pharmacopeia.

1 (b) (4)
2
3
4

Bridging study (BA BE studies):

In an IND meeting dated 3/2/2017, the applicant provided the Agency the rational for changing their formulation 1 to formulation 2 and provided a comparative dissolution data. In that meeting package the applicant asked the agency whether their dissolution data are sufficient to demonstrate the equivalence among the two formulations and no further bioequivalence is not required to submit the NDA.

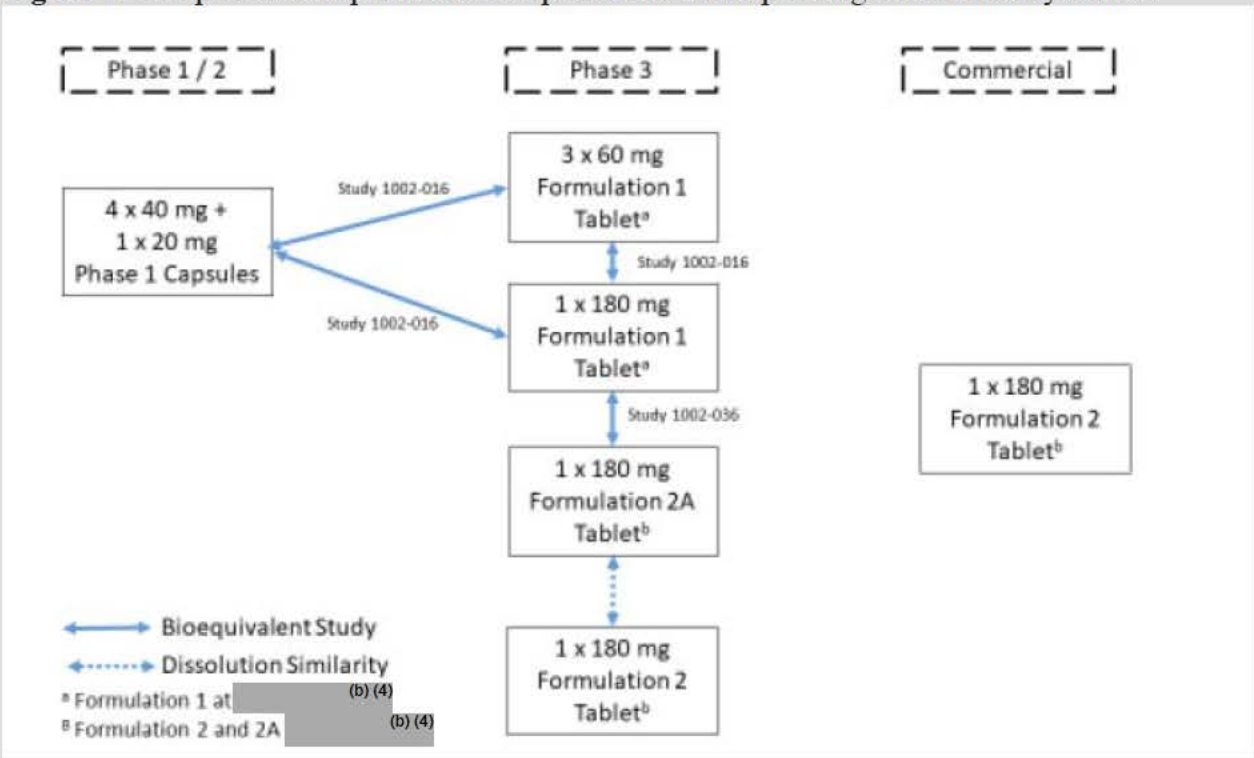
In response, FDA stated that **the proposed change in the scaled-up formulation is considered a level 3 composition change per the SUPAC-IR Guidance. Therefore, a bioequivalence study is needed to bridge the formulations. The applicant was also advised to submit comparative dissolution data of the two formulations.**

Multiple BA studies were performed during the development of bempedoic acid tablets to link the changes between the dosage forms, dosage strengths and formulations. Two BA studies were performed to bridge the formulation development across the dosage forms (capsules to tablets) and demonstrated the lack of impact due to Q1 and Q2 variations in excipients (capsule vs tablet and

tablet vs Formulation 2A). Clinical study 1002-16 demonstrated that bempedoic acid exposure was bioequivalent when given as a single 180 mg tablet (Formulation 1) or as multiple capsules (4x 40 mg + 1x 20 mg). The same study also demonstrated bioequivalence between single 180 mg tablet with 3x60 mg tablets of bempedoic acid. Study 1002-36 demonstrated that Formulation 1 and 2A are BE by comparing the bioavailability (BA) of these formulations. Comparative dissolution data was also provided for Formulation 1, 2A to 2.

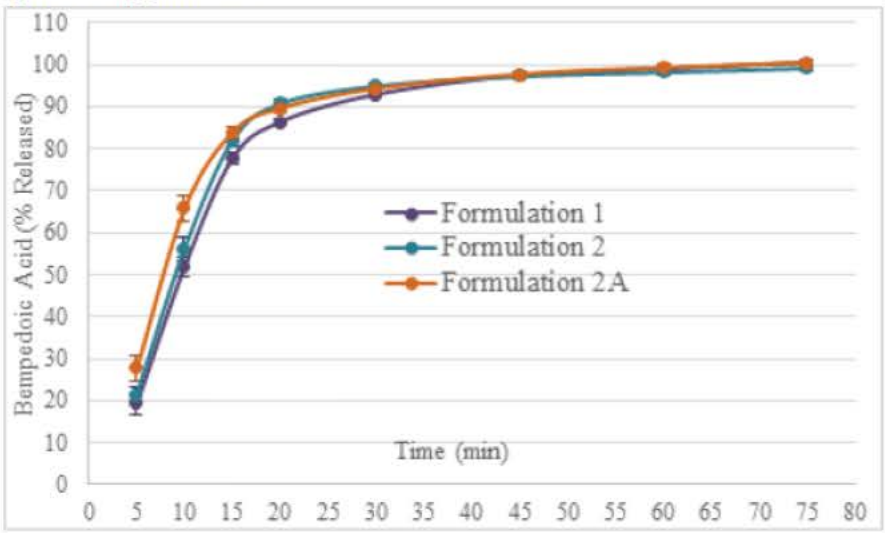
Dissolution of three formulations 1, 2A and 2:

Figure 1: Bempedoic acid product development and corresponding bioavailability studies



The change in the formulation and process was assessed by dissolution study among formulation 1, 2A and 2.

Figure 2: Dissolution profile comparison of formulation 1, 2A and 2 in 900 mL buffered media, pH 6.6, 50 rpm and apparatus 2



In vitro dissolution study:

The Applicant developed a discriminatory and quality control dissolution method. The establishment of dissolution method included all these considerations-

- Drug substance solubility data
- Dissolution media evaluation across the pH range
- Media volume and sink conditions
- Hydrodynamic agitation rate
- Discriminatory work involving tablets manufactured with different process and formulation attributes were evaluated.

The selected dissolution method is as follows- 0.05M Potassium phosphate (pH 6.6), USP apparatus II, 50 rpm in 900 mL media. Adequate solubility and sink conditions were ensured under these conditions.

(b) (4)

[redacted]

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(b) (4)

Discriminatory ability evaluation:

The discriminatory ability of the dissolution method was evaluated during product development stage to evaluate formulation and process variability using USP apparatus II, 900 mL of either 0.05M potassium phosphate (at pH 6.6 (b) (4) at 50 rpm.

Discriminatory ability of the dissolution method was evaluated to understand the different formulation attributes during drug development process, ex, (b) (4) Dissolution method has been used to support process parameter evaluation, e.g. (b) (4).

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Figure 10: Dissolution profiles from bempedoic acid tablets comparing table [redacted] (b) (4)

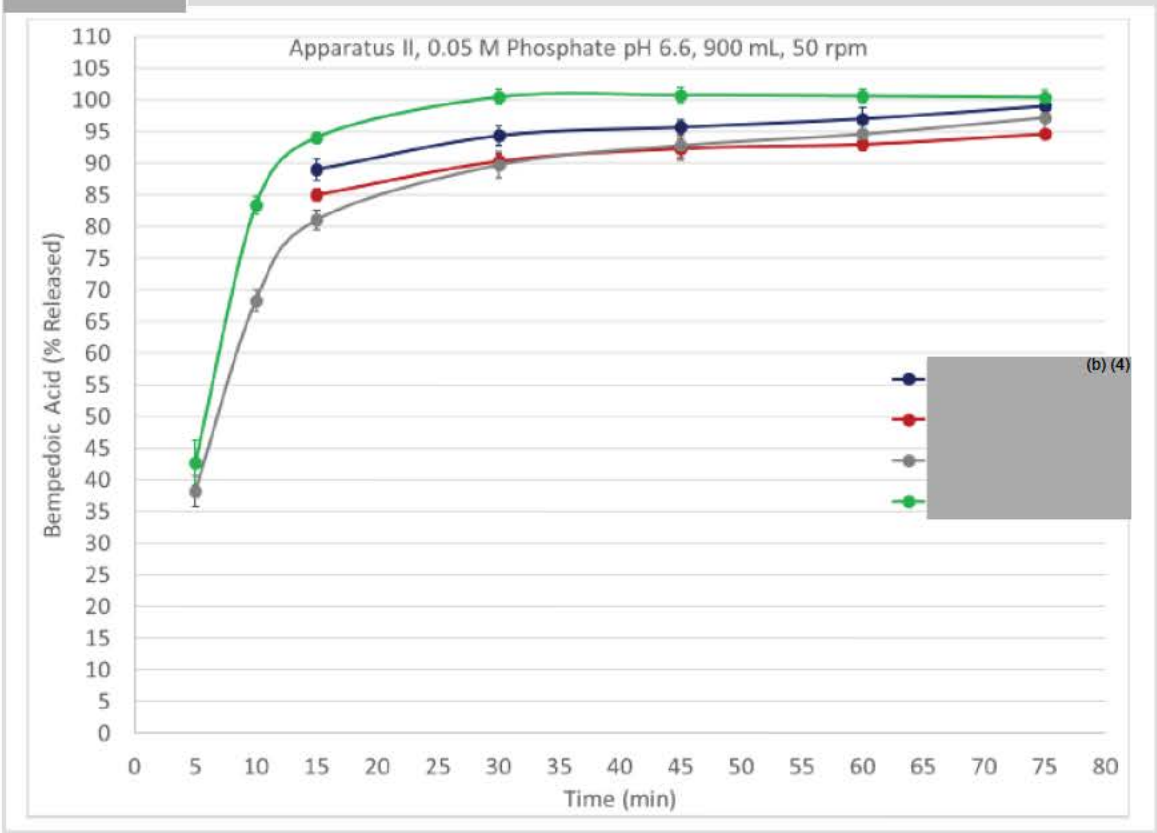

Figure 11: Dissolution release profiles of bempedoic acid tablets from lab scale formulation and process variants

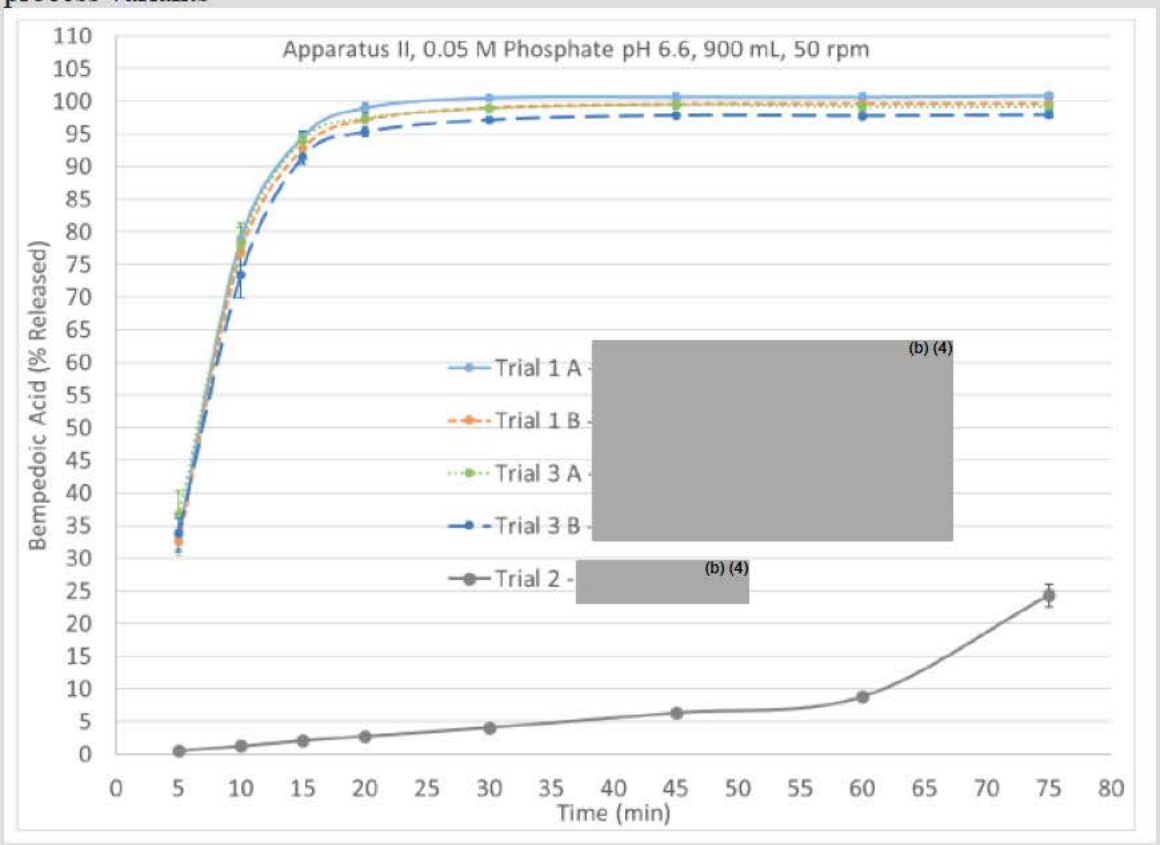

Figure 12: Dissolution release profiles of bempedoic acid tablets from [redacted] (b) (4) variants

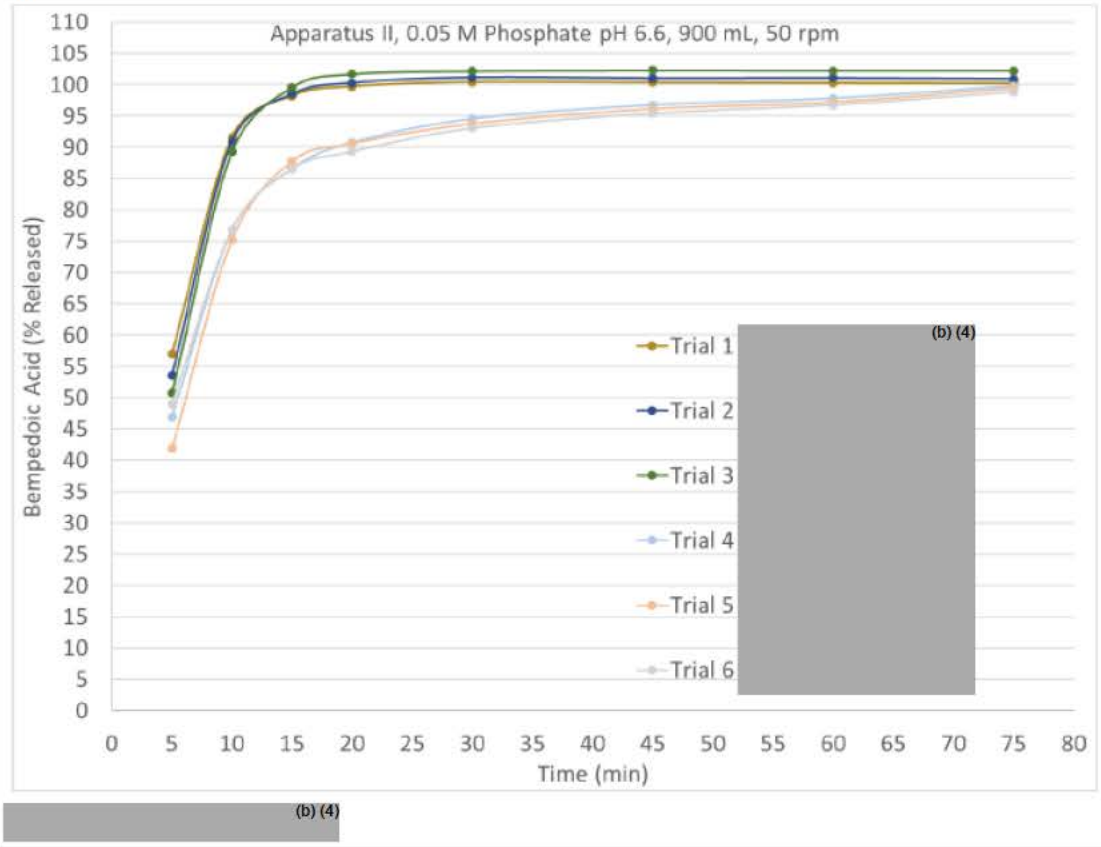

Table 8: Processing differences of bempedoic acid 180 mg tablets used for discriminatory work

Sample Description	[redacted] (b) (4)	f2 Similarity Factor (pH 6.6)	f2 Similarity Factor [redacted] (b) (4)
Run 1		47.1	
Run 2			

Figure 13: Dissolution release profiles of bempedoic acid tablets with different (b) (4)

Conclusion:
The dissolution method was developed considering drug substance solubility, pH range, agitation rates, media volume and sink conditions. The discriminatory ability was demonstrated by changing formulation variables, i.e. (b) (4)
process variables, i.e. (b) (4)

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

1. 0001 (1) 02/21/2019 ORIG-1/ Multiple Categories/Subcategories (NDA#211616)
2. 0010 (10) 04/30/2019 ORIG-1/Quality/Response To Information Request (NDA# 211617)
3. 0025 (25) 08/28/2019 ORIG-1/Quality/Response To Information Request (NDA#211616)
4. 0030 (30) 09/26/2019 ORIG-1/Quality/Response To Information Request (NDA#211616)

Highlight Key Outstanding Issues from Last Cycle: None.

Dissolution:
Please see below. method development report including the justification for the proposed dissolution parameters, discriminating ability of the dissolution method, dissolution method validation, and dissolution data.

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Assay and Identification Analytical Method Validation: Assay and Identification Analytical Method was validated in terms of specificity, linearity, accuracy, precision, range, solution stability and (b) (4) comparability were determined.

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

Dissolution acceptance criteria:
The applicant provided in vitro dissolution data of the two batches of to-be-marketed formulation 2, i.e. batch number YGHG (used in study# 1002-046 and 1002-047) and WPTP (used in study# 1002-040 and 1002-040) in QC method. Dissolution data are given below-

Table 12: Individual Dissolution Release Data for Formulation 2 (bempedoic acid tablets, 180 mg, Lot YGHG)

Batch	**Formulation 2: Packaged Lot # YGHG (Bulk Lot # YGHG)**							
Manufacture	**Manufactured at (b) (4) 15 April 2017**							
Analysis	**Dissolution Analysis Date Jan 2019 – QC method pH 6.6**							
Dissolution Results								
Vessel	**Time (minutes)**							
	5	**10**	**15**	**20**	**30**	**45**	**60**	**75**
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Minimum								
Maximum								
Mean	21	56	82	91	95	97	98	99

Standard Deviation	1.7	2.8	1.7	1.0	0.6	0.8	0.6	0.7
%RSD	7.7	5.0	2.1	1.1	0.7	0.9	0.6	0.7

QC = Quality Control.; RSD = Relative standard deviation.

[a] (b) (4)

Table 13: Individual Dissolution Release Data for Formulation 2 (bempedoic acid tablets, 180 mg, Lot WVCC)

Batch	**Formulation 2: Packaged Lot # WVCC (Bulk Lot # WPTP)**							
Manufacture	**Manufactured at (b) (4)[a] 03 Jul 2016**							
Analysis	**Dissolution Analysis Date Jan 2019 – QC method pH 6.6**							
Dissolution Results								
Vessel	**Time (minutes)**							
	5	**10**	**15**	**20**	**30**	**45**	**60**	**75**
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Minimum								
Maximum								
Mean	19	52	78	86	93	97	99	100
Standard Deviation	2.5	2.4	1.4	0.6	0.8	0.8	0.7	0.7
%RSD	12.9	4.6	1.8	0.7	0.9	0.8	0.7	0.7

QC = Quality Control.; RSD = Relative standard deviation.

[a] (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)% drug was released from the tablet in 20 minutes and there is not much variability is observed in the data. Therefore, the proposed dissolution acceptance criteria of Q=(b) (4)% in (b) (4)minutes is permissive. Hence, the reviewer recommended the dissolution acceptance criteria as "Q= (b) (4)% in 20 minutes based on the data". An IR was sent to the applicant asking to revise the dissolution acceptance criteria and revise the NDA accordingly. The applicant accepted the Agency's recommended dissolution acceptance criterion. Therefore, applicant's response is adequate. Please refer to the Appendix 2 for detail information of the IR and applicant's response.

Reviewer's Assessment:

Adequate, the NDA 211616 is acceptable for approval.

Approved dissolution method and acceptance criterion:

Apparatus	Media and temperature	Media volume (mL)	Speed (rpm)	Acceptance Criterion
USP Apparatus II	0.05M Potassium phosphate buffer, pH 6.6	900 mL	50	Q = (b) (4)% in 20 minu

Signature Block

Primary Biopharmaceutics Reviewer Name:

Kamrun Nahar, PhD.

Secondary Biopharmaceutics Reviewer Name:

Haritha Mandula, Ph.D.

Appendix 1

Application 211617 - Sequence 0010 - Cover Letter 04/30/2019 - Response to Information Request: Chemistry, Manufacturing, and Controls Information
Application 211616 - Sequence 0025 - Response to Request for Chemistry, Manufacturing, and Controls Information 08/28/2019
Application 211616 - Sequence 0025 - Response to Request for Chemistry, Manufacturing, and Controls Information 08/28/2019

Appendix 2

Information request:

Information request 1:

(b) (4)

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Post-Approval Stability Protocol and Commitment

The applicant commits to continue the ongoing long-term registration stability studies for batches of bempedoic acid tablets, 180 mg in bottles and blister presentations throughout the shelf-life, and in accordance with ICH Q1A(R2). The tests protocol, analytical procedures and specifications are discussed in the application.

Assessment: ADEQUATE

R REGIONAL INFORMATION

Environmental Assessment:

(b) (4)

[redacted]

Assessment: ADEQUATE

Methods Validation or Verification Package

The Agency requested method validation from the Division of Pharmaceutical Analysis (DPA- St. Louis). The methods have been verified by DPA and reported in panorama. The applicant provided additional validation data (eCTD seq# 0033 of 10/24/2019).

Assessment: *Adequate*

R.3 Comparability Protocol

(b) (4)

[redacted]

Haritha Mandula

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Okponanabofa Eradiri

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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.

/s/

MUTHUKUMAR RAMASWAMY
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