CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215498Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

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

Date: **July 5, 2021**
From: **Hitesh Shroff, Ph.D.**
Application Technical Lead, Branch IV
Division of New Drug Products II
Office of New Drug Products

To: **CMC Review #1 of NDA 215498**

Subject: Final Recommendation for NDA 215498

At the time when the CMC Review #1 was completed on May 3, 2021, it had noted the following pending issues:

- The label/labeling issues were not resolved.

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

On June 30, 2021, the applicant submitted revised labeling. The CMC sections of the labeling were reviewed and found to be acceptable (**Attachment -1)**.

In the amendment dated June 21, 2021 the CMC information regarding the manufacture of Process Performance Qualification (PPQ) batches of drug product was provided. (see **Manufacturing Integrated Assessment**)

Recommendation:
This NDA is now recommended for Approval from the OPQ perspective.

Application Technical Lead's Assessment and Signature

The NDA is recommended for Approval from the quality perspective.

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch IV
Division of New Drug Products II
July 5, 2021

Memorandum

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

Date: **June 30, 2021**

From: **Zhengfang Ge, Ph.D.**
ONDP/Division II/Branch IV

Through: **Wendy Wilson, Ph.D.**
Director, ONDP/Division II

To: **Labeling Review of NDA 215498: BYLVAY (odevixibat) capsules and BYLVAY (odevixibat) oral pellets**

Subject: **Final Recommendation for Labeling/Labels**

The CMC related deficiencies identified in the previous labeling review have been adequately addressed in the revised labeling. The revised container/carton labels provided in the **Attachment** are satisfactory.

Recommendation:

This NDA is **now** recommended for **Approval** from the labeling perspective.

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Zhengfang Ge

Digitally signed by Zhengfang Ge
Date: 7/01/2021 01:43:09PM
GUID: 508da7210002a030e76df4f60ccd142a

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 7/01/2021 01:43:34PM
GUID: 50816dbc000085595ca3284bbca465a8

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	NDA 215498
Drug Product Name	Odevixibat
Strengths	200, 400, 600 and 1200 mcg.
Dosage Form	Capsules
Administration Route	Oral
Indication	Treatment of pruritus in patients with progressive familial intrahepatic cholestasis (PFIC).
Applicant Name	Albireo AB

Note: This is 505 (b) (1) application.

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

(b) (4)

Sachinkumar Patel

Digitally signed by Sachinkumar Patel
Date: 6/22/2021 01:05:37PM
GUID: 5473743d0009397d357495553e649536

Yubing Tang

Digitally signed by Yubing Tang
Date: 6/22/2021 02:34:44PM
GUID: 508da7210002a024fb160a84a176e3c7

RECOMMENDATION

☐ Approval
☒ Not Ready for Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215498
Assessment 1

Drug Product Name	Odevixibat Capsules and Odevixibat Oral Pellets
Dosage Forms	Capsules and Oral Pellets
Strength	Capsules: 400 mcg and 1200 mcg Oral Pellets: 200 mcg and 600 mcg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Albireo AB, Göteborg, Sweden
US agent, if applicable	Albireo Pharma, Inc.; Boston, USA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	Nov 20, 2020	OPQ
Amendment	Dec 18, 2020	OPMA
Amendment	Jan 22, 2021	ONDP
Amendment	Mar 12, 2021	OPMA
Amendment	Mar 26, 2021	OPMA
Amendment	Apr 7, 2021	OPMA
Amendment	Apr 9, 2021	OPMA
Amendment	Apr 15, 2021	OPMA
Amendment	Apr 19, 2021	OPMA

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Gaetan Ladouceur	Donna Christner
Drug Product	Zhengfang Ge	Wendy Wilson
Manufacturing/ Microbiology	Sachinkumar Patel	Jean Tang
Biopharmaceutics	Jia Yin	Tapash Ghosh
Regulatory Business Process Manager	Oumou Barry	
Application Technical Lead	Hitesh Shroff	
Laboratory (OTR)	N/A	N/A
Environmental	Zhengfang Ge	Wendy Wilson

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	N/A	LOA: Mar 4, 2020
	IV			Active	N/A	LOA: Feb 26, 2020

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

Document	Application Number	Description
IND	130591	Indication: Treatment of (b) (4). Submission Date: May 12, 2016 Refer to all information in this IND.

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed Bylvay (odevixibat) capsules and Bylvay (odevixibat) oral pellets.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has made a final overall "**Approval**" recommendation for the facilities involved in this application.

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

The label/labeling has *not* been finalized as of this review.

Therefore, from the OPQ perspective, this NDA is ***not*** deemed ready for approval in its present form per CFR 314.125(b)(6) until the label/labeling is finalized.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Bylvay is an ileal bile acid transporter (IBAT) inhibitor. It is supplied as 400 mcg and 1200 mcg capsules as well as 200 mcg and 600 mcg oral pellets. Patients who cannot swallow capsules may open the capsules and mix the contents with soft food such as banana, yoghurt, apple sauce, etc.

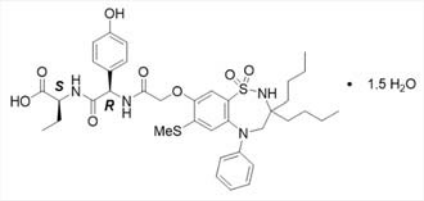
Bylvay is an NME because it has never been approved or lawfully marketed in US. Bylvay has an FDA Orphan designation for the proposed indication.

Proposed Indication(s) including Intended Patient Population	BYLVAY is an ileal bile acid transporter (IBAT) inhibitor indicated for the treatment of pruritus in pediatric patients, 3 months to 17 years of age, with progressive familial intrahepatic cholestasis (PFIC).
Duration of Treatment	As needed
Maximum Daily Dose	(b) (4) mcg (weight-based daily dosage 40 mcg/kg /day)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance in Bylvay is odevixibat sesquihydrate. It is a white to off-white solid. It is a chiral molecule with two chiral centers and produced in (b) (4). It is insoluble in low pH but its solubility increases at pH above 5. Its chemical name is (2S)-2-[(2R)-2-(2-{[3,3-dibutyl-7-(methylsulfanyl)-1,1-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-1λ6,2,5-benzothiadiazepin-8-yl]oxy}acetamido)-2-(4-hydroxyphenyl)acetamido] butanoic acid sesquihydrate. Its chemical structure, molecular formula and molecular weight are shown below.



Molecular formula: $C_{37}H_{48}N_4O_8S_2$
Molecular Weight: 768.0 g/mol

Odevixibat sesquihydrate is manufactured, tested and packaged in accordance with Good Manufacturing Practices (cGMP) at (b) (4) The applicant has provided sufficient information for the starting materials including synthesis, specification and batch data. The detailed CMC information regarding the raw materials, intermediates, drug substance manufacturing process, critical steps and in-process controls is deemed adequate.

The chemical structure of odevixibat sesquihydrate is unambiguously confirmed by many modern analytical methods such as proton (^{1}H) and carbon (^{13}C) NMR spectroscopy; Infrared (IR) spectroscopy, mass spectroscopy, (b) (4)

The identity, purity and quality of the drug substance, odevixibat sesquihydrate, is assured by its specification for appearance, identity by FTIR and HPLC; purity by HPLC assay, organic impurities by HPLC, residual solvents by GC-HS, water content per USP <921> and elemental impurities per USP <233>.

No potential genotoxic impurities were identified by in-silico assessment using DEREK and Leadscope in accordance with ICH M7. The non-clinical reviewer assessed the QSAR report and concluded that the drug substance impurities can be classified as non-genotoxic.

The non-compendial analytical methods were validated per ICH Q2R1. Satisfactory batch analyses of multiple batches from (b) (4) kg of the drug substance including non-clinical, clinical, validation and stability batches confirmed that the drug substance manufacturing process is robust.

Based on long-term and accelerated stability testing per ICH Q1A(R2) of registration and supporting batches of drug substance a retest period of (b) (4) months

is granted when stored at controlled room temperature in (b) (4)

The drug substance reviewer, Dr. Gaetan Ladouceur, concluded that the applicant has submitted adequate CMC information regarding the regulatory starting materials, raw materials, intermediates, manufacturing process and the drug substance specification for identity, purity and quality of the drug substance, Odevixibat sesquihydrate. (see the **Drug Substance** review).

Drug Product: Adequate

Bylvay is indicated for the treatment of pruritus in patients with progressive familial intrahepatic cholestasis. Bylvay is supplied in two dosage forms, oral pellets and capsules. 200 µg and 600 µg oral pellets are filled in size 0 capsules. 400 mg and 1200 mg capsules are supplied as size 3 capsules. Both dosage forms contain the following ingredients: drug substance odevixibat sesquihydrate, hypromellose as (b) (4) and microcrystalline cellulose as (b) (4) Four different strengths of capsules are different color capsules and imprinted with unique codes for easy identification.

Bylvay is supplied in white high-density polyethylene (HDPE) bottle closed with a temper evident, child resistant white (b) (4) grooved screw cap. Each bottle contains 30 size 0 or size 3 capsules.

The identity, strength, purity and quality of the drug products are controlled by their specifications. The release and stability specifications include the following tests: description by visual inspection, identity by UPLC and UPLC-DAD, strength by UPLC, purity via assessment of the degradation products by UPLC and microbial enumeration and specified organism per USP <61> and USP <62>; quality by uniformity of dosage form per USP <905> and dissolution per USP <711>. The in-house developed, non-compendial analytical methods were validated per ICH Q2(R1). The specifications for oral pellets and capsules were reviewed by the drug product reviewer and concluded to be adequate.

The compatibility study results support that the capsule contents can be mixed with soft food such as apple sauce, carrots (puree), baby food, vanilla yoghurt, rice pudding, chocolate pudding and banana puree prior to administration without significant degradation in quality for patients who are unable to swallow whole capsules as well as the pediatric patients. (b) (4)

On the basis of the satisfactory long-term and accelerated stability data a 24-month expiration dating period from the date of the (b) (4) is

granted when the drug products are stored at 20 to 25ºC (68 to 77ºF) with excursions permitted to 15 to 30ºC (59 to 86ºF). (See the Drug Product review by Dr. Zhengfang Ge).

Labeling: Inadequate

The label/labeling has not been finalized as of this review. (see labeling Deficiencies)

Manufacturing: Adequate

Bylvay oral pellets and capsules are manufactured and tested by (b) (4)

Bylvay oral pellets, 200 µg and Bylvay capsules, 400 µg contain (b) (4) Bylvay oral pellets, 600 µg and Bylvay capsules, 1200 µg contain (b) (4)

(b) (4)

The applicant provided a flow diagram and a detailed drug product manufacturing process description with all incoming materials, unit operations, in-process controls, process parameters and equipment used.

The proposed drug product manufacturing facility, drug substance testing facility, microbial testing facility for drug substance and drug product, primary and secondary packaging facilities are approved. The proposed drug substance manufacturing facility required pre-approval inspection via 704(a) (4) and it is recommended for approval.
The OPMA reviewer, Dr. Sachinkumar Patel, concluded that the applicant has submitted adequate CMC information regarding Bylvay oral pellets and Bylvay

capsules manufacturing process. (see **Manufacturing Integrated Assessment** review)

Biopharmaceutics: Adequate

The drug substance, odevixibat sesquihydrate, is designated as BCS Class IV compound due to its low aqueous solubility and poor permeability.

The Applicant conducted a relative bioavailability study (A4250-004) on the highest strength 1200 µg capsules to assess the food effect (high fat meal and sprinkle on applesauce). In addition, all four strengths were studied in a Phase 3 efficacy and safety clinical study (A4250-005). A biowaiver request was not submitted.

The dissolution method, dissolution method development, dissolution data and dissolution acceptance criteria; bridging between the pivotal clinical batch and the commercial batch formulations were reviewed. This NDA is recommended from the biopharmaceutics perspective. However, the dissolution method and dissolution specification are approved on the interim basis. The final determination of the dissolution method and dissolution specification will be made when additional data in response to the Post Marketing Commitment is submitted in the first annual report. (see **Post Marketing Commitment** and **Biopharmaceutics Review**)

Microbiology: Adequate

Bylvay capsules and oral pallets are non-sterile drug products. Both drug products specifications include microbial enumeration test for total aerobic microbial count and total combined yeast/molds count per USP <61> and test for specified micro-organisms Escherichia Coli per USP <62>. The acceptance criteria will adhere to USP <1111> for non-sterile products. Microbial limits testing will be performed at release and stability. The stability data of the registration batches, post-approval stability protocol and microbiological purity specifications were reviewed by Dr. Sachinkumar Patel and deemed acceptable. (See the **Manufacturing Integrated Assessment** review).

Environmental Assessment: Adequate

The applicant has submitted a claim of categorical exclusion under 21CFR 25.31(b) based on low production and use of the API. The sponsor estimates (b) (4) kg/year odevixibat is produced for direct use. This level corresponds to an expected introduction concentration (EIC) of odevixibat into the aquatic environment of (b) (4) The sponsor also states that there are no extraordinary circumstances. This level of production and use is considered by the EA Team as de minimus and qualifies the application for a categorical exclusion under 21 CFR 25.31(b). A supporting Environmental Risk Assessment Report prepared for the European Medicines Agency is provided. Based on the

low use level and statement of no extraordinary circumstances, the claim of categorical exclusion is accepted. (see the **Drug Product** Review).

Comparability Study: Adequate

The applicant submitted a post-approval comparability protocol (b) (4) [redacted]. The CMC information provided in the comparability protocol was reviewed and deemed adequate by the manufacturing process reviewer. the supplement reporting category is determined to be CBE-30. (see the **Manufacturing Integrated Assessment** Review)

Post-marketing Commitments (PMC):

Biopharmaceutics Comments for PMC

We acknowledge that you have submitted a complete dissolution method development report. However, there are deficiencies in your selection of dissolution method. Therefore, we are approving your dissolution method on an interim basis. We will make final decision on the dissolution method and acceptance criterion once you submit document addressing the following deficiencies in your first annual report. Consider this as a Post Marketing Commitment (PMC).

1. We acknowledge that you have provided data to support the selection of (b) (4) [redacted]

(b) (4) [redacted]

(b) (4)

Lifecycle Management Considerations:

(b) (4)

C. Risk Assessment

Product Attribute / CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation Approach	Risk Evaluation	LifeCycle consideration/ Comments
Assay and content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	(b) (4)	The drug product is expected to be safe for oral administration during the entire shelf life from product quality perspective. Low to None	None
Related Substances Impurities / Degradants	•Raw materials •Process parameters • Container/closure system	L		Low to None	None

			(b) (4)		
Drug Substance	(b) (4)	L		Low to None	(b) (4)

D. List of Deficiencies

Labeling Deficiencies

The following changes have been implemented in the PI:
For Prescribing Information:

1. Change the dosage form from [redacted] (b) (4) to "capsules", [redacted] (b) (4) to "oral pellets" wherever they appear
2. Change the Product Title Line to the following:
   BYLVAY (odevixibat) capsules, for oral use
   BYLVAY (odevixibat) oral pellets

Section 11 Description

3. Make the following Change for the ingredients:

   The capsule shells for the [redacted] (b) (4) contain hypromellose, titanium dioxide and yellow iron oxide and red iron oxide.

   The capsule shells for the oral pellets contain hypromellose, titanium dioxide and yellow iron oxide

   The imprinting ink contains [redacted] (b) (4) ferrosoferric oxide/black iron oxide, [redacted] (b) (4) shellac glaze [redacted] (b) (4)

The following deficiencies in the carton/container labels need to be conveyed to the applicant

1. Change [redacted] (b) (4) to "capsules" and [redacted] (b) (4) to "oral pellets" wherever they appear

2. Move the net quantity to another place. The net quantity should not be placed in the middle of the name and dosage form. The order of the proprietary name, established name, dosage form and strength should be:

Bylvay (odevixibat) oral pellets
200 mcg

Bylvay (odevixibat) oral pellets
600 mcg

Bylvay (odevixibat) capsules
400 mcg

Bylvay (odevixibat) capsules
1200 mcg

3. Delete (b) (4) from the carton labels

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch IV
Division of New Drug Products II
May 3, 2021

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The Prescribing Information is deemed not ADEQUATE as proposed until it is revised satisfactorily to meet the regulatory requirements (See the **List of Deficiencies** at the end of this review).

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	**BYLVAY**	**Adequate**
Established name(s)	(b) (4)	**Not Adequate** Established name should be change to the following after consulting OPQ labeling committee: Regular capsules: odevixibat capsules

		(b) (4): odevixibat oral pellets Product Title Line: BYLVAY (odevixibat) capsules, for oral use BYLVAY (odevixibat) oral pellets
Route(s) of administration	oral	**Adequate**
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4): 400 mcg, 1200 mcg (3) (b) (4): 200 mcg, 600 mcg (3)	**Not Adequate** change to: capsules, for oral use: 400 mcg, 1200 mcg oral pellets: 200 mcg, 600 mcg
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

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(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Instructions for taking 1) "oral pellets" with soft foods are provided, 2) (b) (4) not chew or crush the capsules	**Not Adequate** • Change (b) (4) to "oral pellets"

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

400 mcg: (b) (4) capsule with medium orange opaque cap and white opaque body; imprinted "A400" (black ink).
1200 mcg: (b) (4) capsule with medium orange opaque cap and body; imprinted "A1200" (black ink).

(b) (4)

200 mcg: (b) (4) capsule with ivory opaque cap and white opaque body; imprinted "A200" (black ink).
600 mcg: (b) (4) capsule with ivory opaque cap and body; imprinted "A600" (black ink).

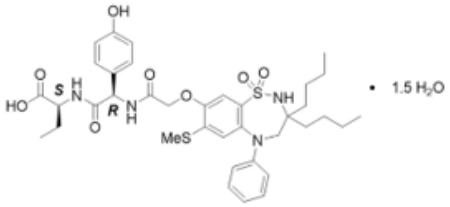
(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	(b) (4)	**Not Adequate** **Change (b) (4) to "oral pellets"** **Change (b) (4) to "capsules"**
Strength(s) in metric system	capsules: 400 mcg, 1200 mcg oral pellets: 200 mcg, 600 mcg	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	capsule size, color and imprinting are provided for each dose strength	**Adequate**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 (DESCRIPTION)

11 DESCRIPTION

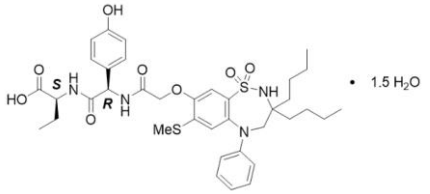
The active ingredient in BYLVAY [(b) (4)] an ileal bile acid transporter (IBAT) inhibitor, is (2S)-2-[(2R)-2-(2-{[3,3-dibutyl-7-(methylsulfanyl)-1,1-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-1λ6,2,5-benzothiadiazepin-8-yl]oxy}acetamido)-2-(4-hydroxyphenyl)acetamido]butanoic acid, which is formulated as the sesquihydrate having the following chemical structure:



The [(b) (4)] formula is $C_{37}H_{48}N_4O_8S_2$ x 1.5 H_2O, with a molecular weight of 768.0 g/mol (anhydrous 740.9 g/mol). Odevixibat sesquihydrate is a white to off-white solid. Its solubility in aqueous solutions is pH-dependent and increases with increased pH.

BYLVAY is available for oral administration as [(b) (4)] containing odevixibat sesquihydrate equivalent to 200 mcg or 600 mcg of odevixibat, and as [(b) (4)] containing odevixibat sesquihydrate equivalent to 400 mcg or 1200 mcg of odevixibat, and the following excipients: microcrystalline cellulose and hypromellose. [(b) (4)] The imprinting ink contains [(b) (4)] black iron oxides and [(b) (4)]

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	BYLVAY (b) (4)	**Not Adequate** Change to: BYLVAY (odevixibat) capsules and BYLVAY (odevixibat) oral pellets
Dosage form(s) and route(s) of administration	(b) (4)	**Not Adequate** Change to capsules and oral pellets
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	BYLVAY is available for oral administration as (b) (4) containing odevixibat sesquihydrate equivalent to 200 mcg or 600 mcg of odevixibat, and as (b) (4) containing odevixibat sesquihydrate equivalent to 400 mcg or 1200 mcg of odevixibat	**Adequate** The active ingredient is an odevixibat sesquihydrate, not a salt. The equivalence statement of odevixibat sesquihydrate to odevixibat is adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	microcrystalline cellulose and hypromellose. (b) (4) The imprinting ink contains (b) (4), black iron oxides and (b) (4)	**Not Adequate** The capsule shells for the (b) (4) (b) (4) contain hypromellose, titanium dioxide and yellow iron oxide and red iron oxide. The capsule shells for the oral pellets contain hypromellose, titanium dioxide and yellow iron oxide The imprinting ink contains (b) (4) ferrosoferric oxide/black iron oxide, (b) (4) shellac glaze (b) (4)
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	

Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	ileal bile acid transporter (IBAT) inhibitor	**Adequate**
Chemical name, structural formula, molecular weight	Name: (2S)-2-[(2R)-2-(2-{[3,3-dibutyl-7-(methylsulfanyl)-1,1-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-1λ6,2,5-benzothiadiazepin-8-yl]oxy}acetamido)-2-(4-hydroxyphenyl)acetamido]butanoic acid formula $C_{37}H_{48}N_4O_8S_2$ x 1.5 H_2O molecular weight 768.0 g/mol (740.9 g/mol anhydrous) 	**Adequate**
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Odevixibat sesquihydrate is a white to off-white solid. Its solubility in aqueous solutions is pH-dependent and increases with increased pH	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

200 mcg (b) (4)**:**

Supplied as Size 0 capsules with ivory opaque cap and white opaque body; imprinted "A200" (black ink). Supplied in:

Bottles of 30 with child-resistant closure (NDC 74528-020-01)

600 mcg (b) (4)**:**

Supplied as Size 0 capsule with ivory opaque cap and body; imprinted "A600" (black ink). Supplied in:

Bottles of 30 with child-resistant closure (NDC 74528-060-01)

(b) (4)

400 mcg (b) (4)**:**

Supplied as Size 3 capsules with medium orange opaque cap and white opaque body; imprinted "A400" (black ink). Supplied in:

Bottles of 30 with child-resistant closure (NDC 74528-040-01)

1200 mcg (b) (4)**:**

Supplied as Size 3 capsules with medium orange opaque cap and body; imprinted "A1200" (black ink). Supplied in:

Bottles of 30 with child-resistant closure (NDC 74528-120-01)

Storage and Handling:

Store at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted between 15ºC and 30ºC (between 59ºF and 86ºF) [See USP Controlled Room Temperature].

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	(b) (4)	**Not Adequate:** Change to: - Oral pellets - Capsules
Strength(s) in metric system	Oral pellets: 200 mcg, 600 mcg Capsules: 400 mcg, 1200 mcg	**Adequate**
Available units (e.g., bottles of 100 tablets)	Bottle of 30	**Adequate**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	capsule size, color and imprinting are provided for each dose strength NDC space holder is provided	**Adequate**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)		**Adequate**
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30ºC (59°F to 86ºF) [see USP Controlled Room Temperature].	**Adequate**
Latex: If product does not contain latex and manufacturing	N/A	

of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."		
Include information about child-resistant packaging	child resistant closure	**Adequate**

1.2.5 Other Sections of Labeling

N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Albireo Pharma, Inc. 10 Post Office Square Boston, MA 02109	**Adequate**

2.0 PATIENT LABELING

The following CMC information provided in the Patient Consoling Information is adequate

17 PATIENT COUNSELING INFORMATION

(b) (4)

3.0 CARTON AND CONTAINER LABELING

3.1 Bottle Label

Displayed below are 200 mcg (oral pellets) and 400 mg (capsules). The 600 mcg and 1200 mcg only differ in the strengths respectively

(b) (4)

3.2 Carton Labeling

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Bylvay (odevixibat) 30 (b) (4) 200 mcg (or 600 mcg) Bylvay (odevixibat) 30 (b) (4) 400 mcg (or 1200 mcg)	**Not Adequate** - Change dosage form (b) (4) to "capsules" - Change dosage form (b) (4) to oral pellets - The orders of the proprietary name, established name, dosage form and strength should be: Bylvay (odevixibat) oral pellets 200 mcg (or 600 mcg) Bylvay (odevixibat) capsules 400 mcg (or 1200 mcg) - The net quantity should not be placed in the middle of the name and dosage form
Dosage strength	200 mcg, 400 mcg, 600 mcg, 1200 mcg	**Adequate**
Route of administration	oral	**Adequate**
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	30	**Adequate**
"Rx only" displayed on the principal display	Provided	**Adequate**
NDC number	Provided	**Adequate**
Lot number and expiration date	Provided	**Adequate**

Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F). (b) (4) (b) (4)	**Not Adequate** - Delete (b) (4) (b) (4)
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Provided	**Adequate**

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for, and distributed by, Albireo Pharma, Inc. Boston, MA 02109 © 2021 Albireo Pharma, Inc.	**Adequate**
Medication Guide (if applicable)	(b) (4)	**Adequate**
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	Each (b) (4) contains 400mcg (or 1200 mcg) of odevixibat	**Adequate**

Assessment of Carton and Container Labeling: *Inadequate*

1. The net quantity should not be placed in the middle of the name and dosage form. The order of the proprietary name, established name, dosage form and strength should be:

   Bylvay (odevixibat) oral pellets
   200 mcg (or 600 mcg)

   Bylvay (odevixibat) capsules
   400 mcg (or 1200 mcg)

2. Delete (b) (4) (b) (4) (b) (4)

ITEMS FOR ADDITIONAL ASSESSMENT

List of Deficiencies

The following changes have been implemented in the PI

For Prescribing Information:

1. Change the dosage form from [redacted] (b) (4) to "capsules", [redacted] (b) (4) to "oral pellets" wherever they appear
2. Change the Product Title Line to the following:

   BYLVAY (odevixibat) capsules, for oral use
   BYLVAY (odevixibat) oral pellets

   Section 11 Description

3. Make the following Change for the ingredients:

   The capsule shells for the [redacted] (b) (4) contain hypromellose, titanium dioxide and yellow iron oxide and red iron oxide.

   The capsule shells for the oral pellets contain hypromellose, titanium dioxide and yellow iron oxide

   The imprinting ink contains [redacted] (b) (4), ferrosoferric oxide/black iron oxide, [redacted] (b) (4), shellac glaze [redacted] (b) (4).

The following deficiencies in the carton/container labels need to be conveyed to the applicant

1. Change (b) (4) to "capsules" and (b) (4) to "oral pellets" wherever they appear
2. Move the net quantity to another place. The net quantity should not be placed in the middle of the name and dosage form. The order of the proprietary name, established name, dosage form and strength should be:

Bylvay (odevixibat) oral pellets
200 mcg

Bylvay (odevixibat) oral pellets
600 mcg

Bylvay (odevixibat) capsules
400 mcg

Bylvay (odevixibat) capsules
1200 mcg

3. Delete (b) (4) (b) (4) (b) (4)

Overall Assessment and Recommendation:

The NDA is not ready for approval in its present form per CFR 314.125(b)(6) until the outstanding labeling issues listed in the **List of Deficiencies** are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Zhengfang Ge, Ph. D.
Reviewer, BRANCH IV/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Wendy Wilson, Ph. D.
Director/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Zhengfang Ge

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Wendy Wilson- Lee

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BIOPHARMACEUTICS

NDA: NDA 215498 (associated IND 130591)
Submission Type: 505(b)(1)
Drug Product Name / Strength: Odevixibat Capsule/400 µg and 1200 µg (b) (4), 200 µg and 600 µg (b) (4)
Dosage Form: Immediate-release (IR) Capsule
Route of Administration: Oral
Applicant: Albireo AB
Indication: pruritis in patients with progressive familial intrahepatic cholestasis (PFIC)
Submission Date: 11/20/2020
Primary Reviewer: Jia Yin, Ph.D.
Secondary Reviewer: Tapash Ghosh, Ph.D.

Background: The Applicant seeks approval for Odevixibat Capsule under 505(b)(1) pathway for the treatment of prutitus in patients with progressive familial intrahepatic cholestasis (PFIC). Odevixibat is considered as a new molecular entity (NME) and this NDA is granted priority review status.

Odevixibat capsule is an immediate-release (IR) capsule with four strengths: 200 µg, 400 µg, 600 µg, 1200 µg. The four strengths are developed for two different uses: 200 µg and 600 µg are intended for oral administration after opening the capsule shell and sprinkling the content onto a food vehicle (b) (4) while 400 µg and 1200 µg are intended for direct oral administration (b) (4) The recommended dose is (b) (4) µg/kg once daily in the morning with a meal. (b) (4)

The Applicant conducted a relative bioavailability study (A4250-004) on the highest strength 1200 µg oral capsule with the final formulation to determine the food effect (high fat meal and sprinkle on applesauce). In addition, all four strengths were studied in a Phase 3 efficacy and safety clinical study A4250-005. No biowaiver request was submitted.

REVIEW SUMMARY
The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting **1)** formulation bridging between the pivotal clinical batch and the commercial batch, and **2)** the proposed dissolution method and acceptance criterion. The key review findings are summarized as follows:

Formulation Bridging: Adequate

As the formulation used in Phase 3 clinical studies (Formulation C) is the proposed commercial formulation, no in vivo formulation bridging study is needed.

Dissolution Method: Interim Approval

Based on provided data, the selection of dissolution medium (10 mM citrate buffer pH 6), medium volume (500 mL), surfactant, and apparatus (USP apparatus II, paddle) is reasonable. However, insufficient justification is provided (b) (4) and the lack of discriminating ability of the proposed dissolution method. In addition, no data were provided (b) (4). As there is a medical demand for this product to be on the market, we will approve this dissolution method for interim use. More studies are needed to improve the dissolution method for quality control, which will be conveyed to the Applicant in the post-market commitment (PMC).

Dissolution Acceptance Criterion: Acceptable

Based on the provided dissolution data of primary stability batches and clinical batches, the proposed dissolution acceptance criteria of Q = (b) (4)% in 20 min for odevixibat oral pellets (200 µg and 600 µg) and Q = (b) (4)% in 30 min for odevixibat capsule (400 µg and 1200 µg) are acceptable.

RECOMMENDATION:

Based on the review of the current information, from a Biopharmaceutics perspective, NDA 215498 for Odevixibat Immediate Release Capsule is recommended for Approval with an interim dissolution method with deficiencies to be addressed in a Post Marketing Commitment (PMC) as described below:

Biopharmaceutics Comments for PMC

We acknowledge that you have submitted a complete dissolution method development report. However, there are deficiencies in your selection of dissolution method. Therefore, we are approving your dissolution method on an interim basis. We will make final decision on the dissolution method and acceptance criterion once you submit document addressing the following deficiencies in your first annual report. Consider this as a Post Marketing Commitment (PMC):

1. We acknowledge that you have provided data (b) (4)

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BIOPHARMACEUTICS ASSESSMENT

List Submissions Being Reviewed

Received Date	Submission
11/20/2020	Original submission

BCS Designation

Reviewer's Assessment:

Based on provided solubility data, odevixibat sesquihydrate has pH-dependent solubility. The highest strength 1200 µg (highest daily single dose 7200 µg) is insoluble in 250 mL or less aqueous medium at pH 5 and below. Per BCS criterion, odevixibat sesquihydrate has low solubility. In addition, the drug substance is designed to have very low oral permeability with minimal systemic exposure and is intended to act locally in the terminal ileum. Low solubility and low permeability support BCS IV designation of the drug substance, odevixibat sesquihydrate.

Drug Substance:

Odevixibat exists in (b) (4) Odevixibat sesquihydrate (b) (4) is the confirmed as the form of drug substance for the proposed drug product. (b) (4)

According to the Applicant, the (b) (4) remains unchanged during drug product manufacturing and upon storage.

Solubility:

Odevixibat sesquihydrate exhibits pH-dependent solubility (**Table 1**). The highest strength (1200 µg) is not soluble in 250 mL or less aqueous medium at pH 5 and below. Per BCS criterion, the drug substance, odevixibat sesquihydrate has low solubility.

Table 1 Aqueous Solubility of Odevixibat sesquihydrate at 37°C

TARGET PH	INITIAL PH	FINAL PH	SOLUBILITY AFTER 24 HOURS (µg/mL)	SOLUBILITY AFTER 72 HOURS (µg/mL)
1	1.01	1.04	Not detected	Not detected
2	2.03	2.05	Not detected	Not detected
3	3.03	3.06	Not detected	Not detected
4	3.99	4.02	Not detected	Not detected
5	4.98	5.00	0.28	0.23
6	5.99	5.94	6.83	6.88
7	7.01	6.75	10.30	9.27
8	8.03	7.37	8.72	9.25

[a]All buffer solutions were prepared as directed in the USP <34> under solutions/buffer solutions at 50 mM concentration.

Permeability:
According to the Applicant, the drug substance has been designed to have very low oral permeability with minimal systemic exposure and is intended to act locally in the terminal ileum.

Formulation Bridging

Reviewer's Assessment: ***Adequate***
As the Formulation C used in Phase 3 studies is the proposed commercial formulation, no in vivo formulation bridging study is needed.

The proposed drug product is capsule [redacted] (b) (4) Formulation C [redacted] (b) (4) is used in pivotal Phase 3 clinical studies and is the proposed commercial formulation (**Table 2**). As shown in **Table 3**, the composition of the odevixibat pellets [redacted] (b) (4) is identical between Formulation C and the proposed commercial formulation. [redacted] (b) (4) [redacted] (b) (4)

Table 2 Formulations used in clinical studies

	Formulation Designation		
	A	**B**	**C**
Material use	A4250-001 (Phase 1)	A4250-003 (Phase 2)	A4250-004 (Phase 1) A4250-005 (Phase 3) A4250-008 (Phase 3) A4250-013 (Phase 1) Primary and supportive stability
Site(s) of manufacture	[redacted] (b) (4)		[redacted] (b) (4)
Formulation description			Oral and sprinkle capsules
Odevixibat pellet strength			[redacted] (b) (4)
Odevixibat capsule strength			200, 400, 600, 1200 µg

Table 3 Composition of odevixibat pellets in Formulation C (used in Phase 3 clinical studies) and proposed commercial formulation

Component	Phase 3				Intended Commercial (M3.2.P.3.2)			
	%w/w	g/batch	%w/w	g/batch	%w/w	g/batch	%w/w	g/batch
(b) (4)								
(b) (4) pellets								
Odevixibat								
Hypromellose								
(b) (4)								
Odevixibat pellets								
(b) (4)								

Table 4 Composition of Formulation C (commercial formulation)

Component	Drug Product Strength							
	200 µg		400 µg		600 µg		1200 µg	
	mg	% w/w	mg	% w/w	mg	% w/w	mg	% w/w
Odevixibat	0.200	(b) (4)	0.400	(b) (4)	0.600	(b) (4)	1.200	(b) (4)
(b) (4) pellets								
Hypromellose								
(b) (4)								
(b) (4) capsule	Size 0		Size 3		Size 0		Size 3	
(b) (4)								

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

Dissolution Method: ***Interim Approval***

Based on provided data, the selection of dissolution medium (10 mM citrate buffer pH 6), medium volume (500 mL), surfactant, and apparatus (USP apparatus II, paddle) is reasonable. However, insufficient justification is provided (b) (4) and the lack of discriminating ability of the proposed dissolution method. In addition, no data were provided (b) (4) As there is a medical demand for this product to be on the market, we will approve this dissolution method for interim use. More studies are needed to improve the dissolution method for quality control, which will be conveyed to the Applicant in the post-market commitment (PMC).

Dissolution Acceptance Criterion: ***Acceptable***

Based on the provided dissolution data of primary stability batches and clinical batches, the proposed dissolution acceptance criteria of Q = (b) (4)% in 20 min for odevixibat oral pellets (200 µg and 600 µg) and Q = (b) (4)% in 30 min for odevixibat capsule (400 µg and 1200 µg) are acceptable.

Proposed Dissolution Method

Table 5 Proposed dissolution method

METHOD PARAMETER	METHOD CONDITION
Apparatus	USP Apparatus 2 (paddles)
Dissolution medium	10 mM citrate buffer pH 6.0 (b) (4)
Rotation speed	(b) (4)
Dissolution bath temperature	37.0°C ± 0.5°C
Dissolution vessel volume	500 mL
Number of vessels	6
Sample size	400 mg and 1200 mg (b) (4) 6 single capsules, (b) (4) 1 capsule per vessel
	200 mg and 600 mg (b) (4) 6 single capsules; 1 capsule content per vessel

Proposed Dissolution Acceptance Criterion

For 200 µg and 600 µg (b) (4): Q = (b) (4)% in 20 minutes

For 400 µg and 1200 µg (b) (4): Q = (b) (4)% in 30 minutes

Dissolution Method Development

(b) (4)

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(b) (4)

Reviewer's Assessment

Based on provided data, the proposed dissolution method is not discriminating. The

(b) (4)

The Applicant's justification for the necessity of discriminating ability of the proposed QC dissolution method is reasonable but insufficient. More data are needed to justify the lack of discriminating ability of the dissolution method.

Justification for Dissolution Acceptance Criterion

The dissolution acceptance criterion was selected based on the mean dissolution profile data of the primary stability batches (under long-term stability condition, 3 batches for each strength) and the clinical batches (3 batches for each strength). For stability batches, the dissolution data of both bulk and packaged samples were provided. And for each stability batch, the dissolution data at initial, 3 months, 6 months, 9 months, and 12 months were provided. The average dissolution data for each strength (including stability batches and clinical batches) were used to determine the dissolution acceptance criterion for that strength (**Figure 12 – 15**).

According to the Applicant, based on the assessment of this entire data set, a single-point dissolution specification of Q = (b) (4)% of label claim at 20 minutes is considered appropriate,

both for release and stability testing of odevixibat (b) (4) Similarly, a single-point dissolution specification of Q = (b) (4)% of label claim at 30 minutes is considered appropriate, both for release and stability testing of odevixibat (b) (4) The proposed time points for (b) (4) (20 minutes) and (b) (4) (30 minutes) correspond to the time point where the plateau of dissolution starts.

Figure 12 Mean dissolution profile of odevixibat (b) (4) 200 µg from primary stability and clinical batches

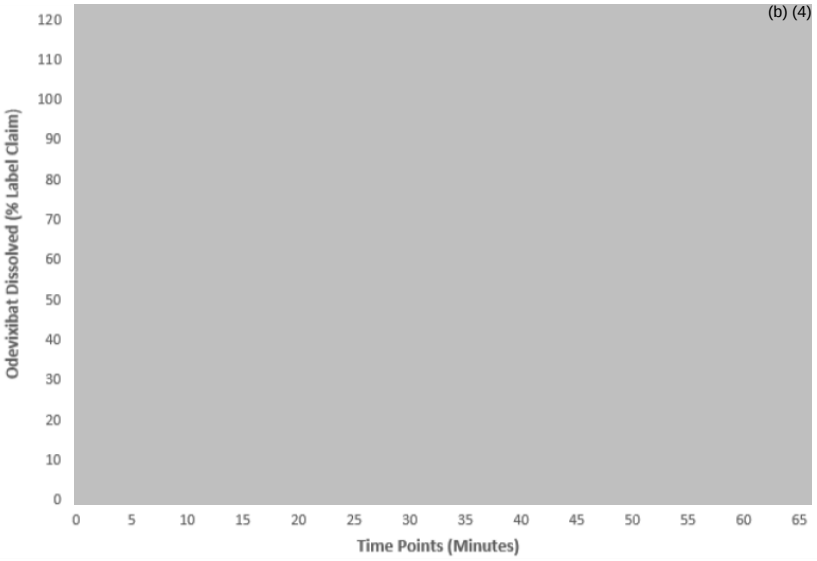


Figure 13 Mean dissolution profile of odevixibat (b) (4) 600 µg from primary stability and clinical batches

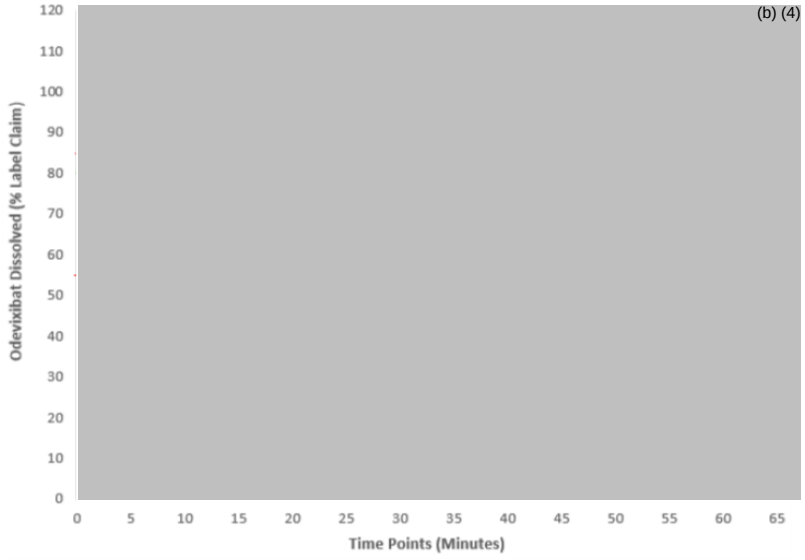


Figure 14 Mean dissolution profile of odevixibat (b) (4) 400 µg from primary stability and clinical batches

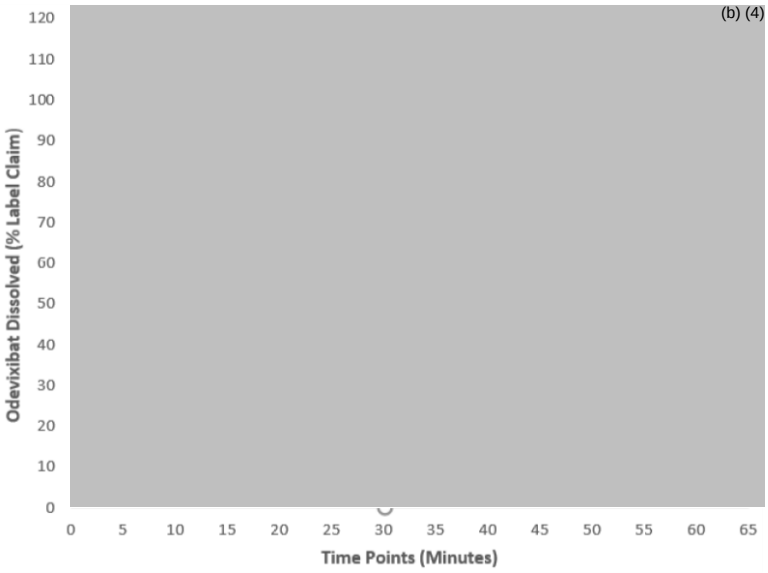
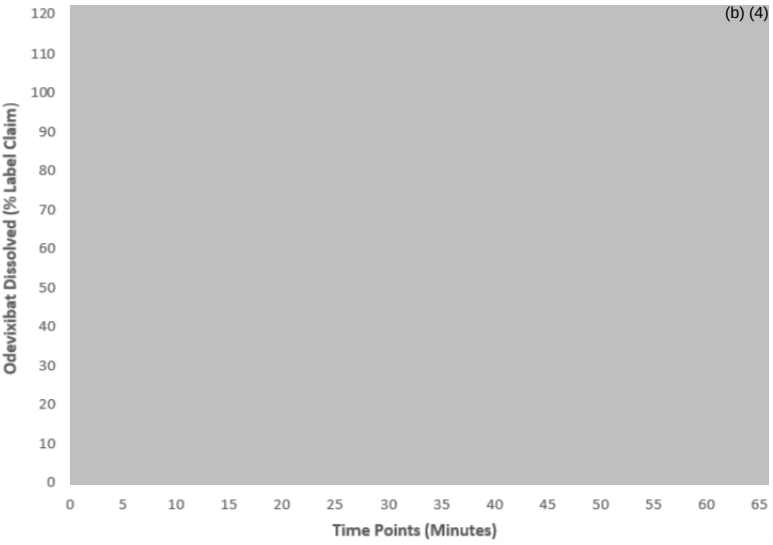


Figure 15 Mean dissolution profile of odevixibat (b) (4) 1200 µg from primary stability and clinical batches



Reviewer's Assessment

Based on the provided data, the dissolution acceptance criterion (Q = (b) (4)% in 30 min) for odevixibat (b) (4) (400 µg and 1200 µg) is acceptable. The dissolution acceptance criterion (Q = (b) (4)% in 20 min) for odevixibat (b) (4) (200 µg and 600 µg) can be (b) (4) However, for an immediate release drug product, (b) (4) is not expected to have significant clinical impact. Overall, the proposed dissolution acceptance criteria are acceptable.

Tapash Ghosh

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Jia Yin

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Sachinkumar Patel

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Yubing Tang

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