

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

215498Orig1s000

Trade Name: BYLVAY

Generic or Proper Name: odevixibat

Sponsor: Albireo Pharma, Inc.

Approval Date: July 20, 2021

Indication: For the treatment of pruritus in patients 3 months of age and older, with progressive familial intrahepatic cholestasis (PFIC).

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CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	
Officer/Employee List	X
Integrated Review(s)	X
Product Quality Review(s)	X
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	X
Proprietary Name Review(s)	X
Administrative/Correspondence Document(s)	X

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RESEARCH**

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 215498

NDA APPROVAL

Albireo AB
c/o Albireo Pharma, Inc.
Attention: Martha J. Carter
Chief Regulatory Officer
10 Post Office Square, Suite 1000
Boston, MA 02109

Dear Ms. Carter:

Please refer to your new drug application (NDA) dated and received November 20, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BYLVAY (odevixibat) Capsules and Oral Pellets.

This NDA provides for the use of BYLVAY (odevixibat) Capsules and Oral Pellets for the treatment of pruritus in patients 3 months of age and older, with progressive familial intrahepatic cholestasis (PFIC).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling with minor editorial revisions reflected in the enclosed labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Instructions for Use) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible via publicly available labeling repositories.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling and carton and container labeling submitted on June 18, and June 30, 2021, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 215498.**” Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for BYLVAY (odevixibat) Capsules and Oral Pellets shall be 24 months from the date (b) (4) (b) (4) when stored at 20°C to 25°C (68°F to 77°F).

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV NDA 215498. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, “Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher.”
- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred,

the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.

- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
 - o the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
 - o the estimated demand in the U.S. for the product, and
 - o the actual amount of product distributed in the U.S.
- You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease Priority Review Voucher Program web page.³

ADVISORY COMMITTEE

Your application for BYLVAY was not referred to an FDA advisory committee meeting because the clinical trial design was acceptable, the benefit-risk profile of the drug was found acceptable for the intended population, and outside expertise was not necessary, as there were no controversial issues that would have benefitted from an advisory committee meeting.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

³ <https://www.fda.gov/industry/developing-products-rare-diseases-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs>

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of adverse maternal and fetal outcomes in females of child-bearing potential who are prescribed BYLVAY.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

- 4109-1 Conduct a worldwide descriptive study that collects prospective and retrospective data in females of child-bearing potential who are prescribed BYLVAY (odevixibat) during pregnancy and/or lactation to assess risk of maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The study will collect information for a minimum of 10 years.

The timetable you submitted on July 6, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2021
Final Protocol Submission:	05/2022
Interim Report Submissions:	04/2023
	04/2024
	04/2025
	04/2026
	04/2027
	04/2028
	04/2029
	04/2030
	04/2031
	04/2032
Study Completion:	05/2032
Final Report Submission:	01/2033

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.⁴

Submit clinical protocol(s) to your **IND 130591** with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 4109-2 Conduct a prospective, long-term, observational study of patients aged 3 months or older with progressive familial intrahepatic cholestasis (PFIC) in order to assess the long-term safety of treatment with BYLVAY (odevixibat) over a 72-week treatment period.

The timetable you submitted on July 9, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 08/2021

⁴ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019).

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Final Protocol Submission: 12/2021
Interim Report Submission: 12/2022
Study Completion: 12/2023
Final Report Submission: 06/2024

- 4109-3 Conduct a 5-year registry-based study to collect data on the course of liver disease in patients chronically treated with BYLVAY (odevixibat). Report yearly on the incidence of biliary diversion surgery, liver transplantation, and all-cause mortality in patients chronically treated with BYLVAY. Compare the incidence of these safety outcomes to a control group that did not receive BYLVAY.

The timetable you submitted on July 9, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 01/2022
Final Protocol Submission: 05/2022
Interim Report Submission: 08/2023
08/2024
08/2025
08/2026
Study Completion: 08/2027
Final Report Submission: 12/2027

- 4109-4 Conduct an in-vitro compatibility study with the drug product and each of the following liquids: water, juice, breast milk, infant formulas (most commonly used formulas in this population) to assess for degradation of the drug product in these vehicles. The compatibility study should test for description, assay, and degradation products.

The timetable you submitted on July 6, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/2021
Study Completion: 12/2021
Final Report Submission: 04/2022

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4109-5 Optimize your dissolution method for quality control to address the following:

- Provide additional justification

(b) (4)

(b) (4)

The timetable you submitted on June 30, 2021, states that you will conduct this study according to the following schedule:

Final Report Submission: First annual report

Submit clinical protocols to your **IND 130591** for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.⁵

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.⁶ Information and Instructions for completing the form can be found at FDA.gov.⁷

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

⁵ For the most recent version of a guidance, check the FDA guidance web page at

<https://www.fda.gov/media/128163/download>.

⁶ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁷ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

If you have any questions, contact Ayanna Augustus Bryant, PhD, RAC, Chief, Project Management Staff, at ayanna.augustus@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - o Prescribing Information
 - o Instructions for Use
- Carton and Container Labeling

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/

JULIE G BEITZ
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