CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761468Orig1s000

Trade Name:	Hepcludex injection
Generic or Proper Name:	Bulevirtide-gmod
Sponsor:	Gilead Sciences, Inc.
Approval Date:	May 22, 2026
Indication:	Hepcludex is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in adults without cirrhosis or with compensated cirrhosis.

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761468Orig1s000

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APPLICATION NUMBER:

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APPROVAL LETTER

U.S. FOOD & DRUG ADMINISTRATION

BLA 761468

BLA ACCELERATED APPROVAL

Gilead Sciences, Inc.
Attention: Amelia Spinrad, MS
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Amelia Spinrad:

Please refer to your biologics license application (BLA) dated and received on September 22, 2025, and your amendments, submitted under section 351(a) of the Public Health Service Act for Hepcludex (bulevirtide-gmod), for injection.

LICENSING

We have approved your BLA for Hepcludex (bulevirtide-gmod) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Hepcludex under your existing Department of Health and Human Services U.S. License No. 2258. Hepcludex is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in adults without cirrhosis or with compensated cirrhosis.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture bulevirtide-gmod drug substance at (b) (4). The final formulated product will be manufactured and filled at (b) (4), and labeled and packaged at Gilead Sciences, Inc., La Verne, CA (FEI: 3013189568). You may label your product with the proprietary name Hepcludex and market it in 8.5 mg of lyophilized powder in a single-dose vial.

DATING PERIOD

The dating period for Hepcludex shall be 24 months from the date of manufacture when stored at 25 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Hepcludex to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Hepcludex, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL AND LABELING

We have completed our review of this application, as amended. It is approved under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 601.41, effective on the date of this letter, for use as recommended in the enclosed agreed-upon approved labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the accelerated approval statutory provisions and regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert and Instructions for Use). Information on submitting SPL files using eLIST may be found in the draft guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* (October 2009).[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling 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*

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] When final, this guidance will represent FDA's current thinking on this topic. 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.

Specifications (February 2020, Revision 7). For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761468.** Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Hepcludex was not referred to an FDA advisory committee because outside expertise was not necessary as there were no controversial issues that would have benefited from advisory committee discussion.

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 601.41, you are required to conduct further adequate and well-controlled studies intended to verify and describe clinical benefit. You are required to conduct such studies with due diligence. If required postmarketing studies fail to verify clinical benefit or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated April 9, 2026. This requirement is listed below.

4982-1 Complete an observational study in adult patients with chronic hepatitis delta virus (HDV) infection to verify and describe the clinical benefit of bulevirtide-gmod induced reductions in HDV RNA levels and ALT normalization. The study should collect, analyze, and compare long-term data, with up to 5 years of follow-up, on liver-related clinical outcomes (i.e., development of cirrhosis, hepatic decompensation, liver transplantation, hepatocellular carcinoma, and liver-related death) in patients treated with bulevirtide-gmod versus a historical control group of adult patients with chronic HDV infection who received standard of care and were not treated with bulevirtide-gmod.

The timetable you submitted on April 9, 2026, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	Completed
Study Completion:	02/2033
Final Report Submission:	06/2034

Submit clinical protocols to your IND 125159 for this product. 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.

You must submit reports of the progress of each study required under section 506(c) (listed above) to this BLA 180 days after the date of approval of this BLA and

approximately every 180 days thereafter (see section 506B(a)(2) of the FDCA) (hereinafter "180-day reports").

You are required to submit two 180-day reports per year for each open study or clinical trial required under 506(c). The initial report will be a standalone submission, and the subsequent report will be combined with your application's annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 601.70. The standalone 180-day report will be due 180 days after the date of approval (with a 60-day grace period). Submit the subsequent 180-day report with your application's ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted[3].

Your 180-day reports must include the information listed in 21 CFR 601.70(b). FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics,* to submit your 180-day reports.[4]

180-day reports must be clearly designated "**BLA 761468 180-Day AA PMR Progress Report**."

FDA will consider the submission of your application's ASR under section 506B(a)(1) and 21 CFR 601.70, in addition to the submission of reports 180 days after the date of approval each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

Submit final reports to this BLA as a supplemental application. For administrative purposes, the cover page of all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

TROPICAL DISEASE PRIORITY REVIEW VOUCHER

Your request for a tropical disease priority review voucher for chronic hepatitis delta virus infection is denied. This application is not eligible for a tropical disease priority review voucher because, at the time of approval, hepatitis delta virus infection has not been designated as a tropical disease under section 524(a)(3) of the FD&C Act. See section 524(a)(4)(A)(i) of the FD&C Act. See also, "Notice of Decision Not To Designate Hepatitis Delta Virus Diseases as an Addition to the Current List of Tropical Diseases in the Federal Food, Drug, and Cosmetic Act" 91 FR 30312 *et seq.* (May 22, 2026).

[3] You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.
[4] FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

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(s) 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.

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

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]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

[5] https://www.fda.gov/media/128163/download

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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.

If you have any questions, contact Talia Lindheimer, Regulatory Project Manager, at (301) 960-3449 or talia.lindheimer@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Wendy Carter, DO
Acting Office Director
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - 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/

WENDY W CARTER
05/22/2026 11:32:51 AM