



NDA 221276

NDA APPROVAL

GlaxoSmithKline LLC
Attention: Stephanie I. Kim, Pharm.D.
Director, Global Regulatory Affairs
2929 Walnut Street, Suite 1700
Philadelphia, PA 19104

Dear Dr. Kim:

Please refer to your new drug application (NDA) received February 26, 2026, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Hibsago (bepirovirsen), injection.

This NDA provides for the use of Hibsago (bepirovirsen), injection, in combination with nucleos(t)ide analog reverse transcriptase inhibitor (NrtI) therapy for treatment of chronic hepatitis B virus (HBV) infection in adult patients without cirrhosis:

- who have been on NrtI therapy for at least 6 months and have suppressed HBV deoxyribonucleic acid (DNA), and
- who have HBV surface antigen (HBsAg) levels less than or equal to 3,000 IU/mL as determined by an FDA-authorized test.

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 listed below and reflected in the enclosed labeling.

In Section 5.2, the text was revised to remove

(b) (4)

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, Instructions for Use, and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL

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

files using eLIST may be found in guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.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 guidance for industry *SPL Standard for Content of Labeling Technical Qs & As*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 221276.**” 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 Hibsago (bepirovirsen) injection shall be 36 months from the date of manufacture when stored at 36°F to 46°F (2°C to 8°C).

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Stephanie Fuda
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2340
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

ADVISORY COMMITTEE

Your application for Hibsago was not referred to an FDA advisory committee because the safety profile is acceptable for a finite duration therapy for chronic hepatitis B and the clinical trial design is acceptable.

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>.

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.

We are waiving the pediatric study requirement for less than 2 years of age because necessary studies are impossible or highly impracticable. This is because the number of patients in this age group is too small.

We are deferring submission of your pediatric studies for ages 2 to less than 18 years of age for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FD&C Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FD&C Act. These required studies are listed below.

- 5075-1 Conduct a study to evaluate the safety, tolerability, pharmacokinetics, and treatment response of bepirovirsen in pediatric participants 12 years to less than 18 years of age with chronic hepatitis B virus (HBV) infection (without cirrhosis), HBV surface antigen (HBsAg) levels $\leq 3,000$ IU/mL, and receiving nucleos(t)ide reverse transcriptase inhibitor treatment.

Final Protocol Submission: 08/2027
Study Completion: 11/2034
Final Report Submission: 05/2035

- 5075-2 Conduct a study to evaluate the safety, tolerability, pharmacokinetics, and treatment response of bepirovirsen in pediatric participants 6 years to less than 12 years of age with chronic hepatitis B virus (HBV) infection (without cirrhosis), HBV surface antigen (HBsAg) levels $\leq 3,000$ IU/mL, and receiving nucleos(t)ide reverse transcriptase inhibitor treatment.

Final Protocol Submission: 08/2027
Study Completion: 11/2034
Final Report Submission: 05/2035

- 5075-3 Conduct a study to evaluate the safety, tolerability, pharmacokinetics, and treatment response of bepirovirsen in pediatric participants 2 years to less than 6 years of age with chronic hepatitis B virus (HBV) infection (without

cirrhosis), HBV surface antigen (HBsAg) levels $\leq 3,000$ IU/mL, and receiving nucleos(t)ide reverse transcriptase inhibitor treatment.

Final Protocol Submission:	11/2035
Study Completion:	08/2047
Final Report Submission:	11/2047

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

Submit the protocol(s) to your IND 122685, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FD&C Act 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 FD&C Act will not be sufficient to identify an unexpected serious risk of loss of virologic suppression after Week 96 (48 weeks after cessation of all anti-HBV treatment) which could lead to severe acute exacerbations of HBV infection.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FD&C Act will not be sufficient to assess this serious risk. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

- 5075-4 Complete the ongoing B-Sure long-term follow-up study to evaluate the durability of treatment response in participants who participated in a previous bepirovirsen study and completed the parent study. Submit the datasets with the final study report.

The timetable you submitted on October 1, 2026, states that you will conduct this study according to the following schedule:

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

Study Completion:	03/2029
Interim Report Submission:	02/2028
Final Report Submission:	12/2029

- 5075-5 Conduct long-term follow-up analysis of B-Well 1 and 2 participants with HBV DNA < LLOQ at Week 96, regardless of HBsAg status, to characterize durability of HBV DNA suppression, HBsAg trajectory post-NrtI cessation, and rates of delayed HBsAg re-suppression or late HBV DNA relapse. Submit the datasets with the final study report.

The timetable you submitted on October 1, 2026, states that you will conduct this study according to the following schedule:

Interim Report Submission:	02/2028
Final Report Submission:	12/2029

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.³

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of serious risk of a decline in renal function in patients with moderate or severe renal impairment.

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

- 5075-6 Conduct a clinical trial to evaluate the pharmacokinetics, safety, and treatment response of 24 weeks of bepirovirsen in participants with moderate or severe renal impairment and chronic hepatitis B virus (HBV) infection (without cirrhosis), HBV surface antigen (HBsAg) levels $\leq 3,000$ IU/mL and receiving nucleos(t)ide reverse transcriptase inhibitor treatment. The trial must follow participants after completing therapy to document renal parameters off-treatment.

The timetable you submitted on October 1, 2026, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2027
Trial Completion:	05/2032
Final Report Submission:	11/2032

³ 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>.

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 122685 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 FD&C Act 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(a)(1) of the FD&C Act, 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(a)(1) 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 FD&C Act 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:

- 5075-7 Conduct cell culture phenotypic characterization of bepirovirsen binding site polymorphisms identified in bepirovirsen-treated participants across the B-Well 1 (Trial 202009) and B-Well 2 (Trial 219288) clinical trials for which phenotypic data are not currently available. Specifically, assess bepirovirsen susceptibility (EC₅₀ value fold change relative to wild type) of the following uncharacterized polymorphisms using the validated primary human hepatocyte assay system previously employed: A1583G, T1586G, C1587T, G1588T, T1591C, A1593C, T1598C, G1599A, and A1593G.

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>.

The timetable you submitted on October 1, 2026, states that you will conduct this study according to the following schedule:

Study Completion:	10/2027
Final Report Submission:	01/2028

- 5075-8 Conduct nonclinical assessments of relevant TLR8 gene polymorphisms to determine whether they influence bepirovirsen-mediated TLR8 activation.

The timetable you submitted on October 1, 2026, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2027
Study Completion:	03/2029
Final Report Submission:	06/2029

- 5075-9 Conduct clinical biomarker and genetic analyses, to complement the nonclinical findings, using data from B-Well 1 (Trial 202009) and B-Well 2 (Trial 219288) to characterize TLR8 pathway activation and its association with HBsAg decline and/or sustained suppression of HBV DNA <LLOQ and HBsAg not detected at 24 weeks off all treatment, including: (1) TLR8 genetic variant associations; (2) TLR8 expression; (3) mediation analysis of serum proteins and treatment response; and (4) sex-stratified analysis of TLR8 genetic variants and expression.

The timetable you submitted on October 1, 2026, states that you will conduct this study according to the following schedule:

Final Report Submission:	03/2027
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A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 122685 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/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be 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 guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.

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.⁵ Information and Instructions for completing the form can be found at FDA.gov.⁶

REPORTING REQUIREMENTS

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

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.⁷

REQUESTED ENHANCED PHARMACOVIGILANCE (EPV)

We request that for Hibsago you submit all serious cases of hepatic flare and thrombocytopenia – whether domestic or foreign – as though they were 15-day “Alert reports” (which are described under 21 CFR 314.80(c)(1)) through the 3rd year following initial U.S. approval date.

When you receive new information about a report of hepatic flare or thrombocytopenia that has been previously reported, we request that you submit a follow-up individual case safety report (ICSR) containing the new information and using the same unique case identification number as the initial report (as described in 21 CFR 314.80(f)(5)(viii)).

We request that you provide a narrative summary including analyses of serious cases of hepatic flare and thrombocytopenia events as part of your required periodic safety reports (e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)), quarterly during the first 3 years post-approval.

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁶ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁷ <https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products>

Your analyses should include interval and cumulative data relative to the date of approval of Hibsago and include line listings of the cases in addition to your narrative summary. Your analyses should provide an assessment of causality, with documentation of indication, temporal association, dosage and duration of therapy, associated signs and symptoms, relevant investigations (including laboratory testing and imaging), concomitant medications (including dosage, duration, and indication when available), confounders, underlying risk factors, treatment given for the adverse event, outcome, and dechallenge/rechallenge. We also request you include interval and cumulative drug utilization information.

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.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website⁸.

⁸ <https://www.uspnf.com/>

If you have any questions, contact Stephanie Fuda, Regulatory Project Manager, at 240-402-3769 or Stephanie.Fuda@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information
 - Medication Guide
 - 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
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