EPIC EHR
CHRONIC HEPATITIS B VIRUS INFECTION
Toolkit for Analysts

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INDICATION

HIBSAGO is indicated in combination with nucleos(t)ide analog reverse transcriptase inhibitor (NrtI) therapy to treat chronic hepatitis B virus (HBV) infection in adults without cirrhosis who have been on NrtI therapy for ≥6 months with suppressed HBV DNA and who have HBV surface antigen (HBsAg) levels ≤3,000 IU/mL as determined by an FDA-authorized test.

IMPORTANT SAFETY INFORMATION

WARNING: ON-TREATMENT HEPATIC FLARES AND THROMBOCYTOPENIA

On-Treatment Hepatic Flares

HIBSAGO may cause on-treatment hepatic flares with increases in alanine aminotransferase (ALT) of >20-40x upper limit of normal (ULN) associated with decline in HBsAg. Some cases were associated with hyperbilirubinemia. Most occurred within the first 12 weeks and resolved when treatment was interrupted or discontinued. Do not initiate HIBSAGO in patients with evidence of acute hepatic impairment or cirrhosis. ALT and total bilirubin must be measured prior to treatment and frequently monitored during treatment. Treatment interruption, followed by dose reduction or discontinuation, may be necessary based on liver laboratory results.

Thrombocytopenia

HIBSAGO may cause reductions in platelet counts that may result in sudden and unpredictable thrombocytopenia, which can be life-threatening. Obtain platelet count prior to treatment; HIBSAGO is contraindicated in patients with platelet count <100 x 10^9/L. Monitor platelet counts weekly during treatment and more frequently if platelet count falls <75 x 10^9 /L. Do not re-dose unless platelet count returns to ≥100 x 10^9/L. Permanently discontinue HIBSAGO if platelet count falls <50 x 10^9/L.

EHR = electronic health record.

Please see additional Important Safety Information for HIBSAGO throughout.

Please see full Prescribing Information, including Boxed Warning, for HIBSAGO.

HIBSAGO (bepirovirsen)
Subcutaneous Use 150 mg/mL

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IMPORTANT SAFETY INFORMATION (CONT'D)

CONTRAINDICATIONS

HIBSAGO is contraindicated in patients:

- with acute hepatic impairment or cirrhosis who have mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C).
- with a platelet count <100 x 10^9/L prior to initiation of treatment.

ALT = alanine transaminase; eGFR = estimated glomerular filtration rate; OPA = OurPractice Advisory.

Please see additional Important Safety Information for HIBSAGO throughout.

Please see full Prescribing Information, including Boxed Warning, for HIBSAGO.

HIBSAGO (bepirovirsen)
Subcutaneous Use 150 mg/mL



PURPOSE, SCOPE, AND CLINICAL REQUIREMENTS

Toolkit Overview and Limitations

This toolkit is intended to help Epic users configure and use selected EHR functionality relevant to HIBSAGO, including non-oncology therapy plan build and OPA alerts. These instructions are suggestions only and are not meant to replace institutional expertise, guidance, or independent clinical judgment. These instructions support the following and are not appropriate for other conditions, treatments, therapeutic areas, or for other EHR systems:

- Implementing Clinical Decision Support (CDS) Alerts
  - Configure an Epic OPA to surface workflow reminders and support review of relevant testing and treatment-related considerations at the point of care
- Ordering HIBSAGO (bepirovirsen) within the EHR
  - Build an Epic non-oncology therapy plan to organize treatment-related orders, relevant laboratory monitoring, and other recurring workflow elements within a longitudinal care process

The customer shall be solely responsible for implementing, testing, monitoring, and maintaining any EHR tools to ensure proper function in its own EHR environment. Capabilities, functionality, and set-up vary across institutions and Epic configurations. While EHRs may assist providers in identifying appropriate patients for consideration of assessment and treatment, the decision and action should ultimately be decided by a provider in consultation with the patient after review of the patient's records to determine eligibility.

Rather than prescribing a single build approach, the toolkit provides modular, step-by-step guidance, CDS examples, and workflows that organizations can adapt based on their Epic maturity, governance structure, and local practice patterns. Each section is described in detail in this document.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS

On-Treatment Hepatic Flares

Increases in ALT ≥3x ULN to 69x ULN were observed during treatment with HIBSAGO, most within the first 12 weeks. Isolated cases of ALT increases associated with an increase in total bilirubin resolved when treatment was permanently discontinued.

Please see additional Important Safety Information for HIBSAGO throughout.

Please see full Prescribing Information, including Boxed Warning, for HIBSAGO.

HIBSAGO (bepirovirsen)
Subcutaneous Use 150 mg/mL

PURPOSE, SCOPE, AND CLINICAL REQUIREMENTS

Why This Matters

HIBSAGO is a hepatitis B virus (HBV) mRNA-directed antisense oligonucleotide (ASO) indicated in combination with nucleos(t)ide analog reverse transcriptase inhibitor (NrtI) therapy for treatment of chronic HBV infection in adult patients without cirrhosis[1]:

- 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

Quantitative HBsAg testing measures the amount of HBV surface protein circulating in the blood (IU/mL), providing a more precise and clinically meaningful measure than qualitative testing alone.[2,3] Quantitative HBsAg levels inform prognosis, support treatment eligibility assessments, and allow clinicians to monitor therapy response and help track a patient's progress toward functional cure.[3]

Because HIBSAGO treatment is tied to specific clinical, laboratory, and safety considerations,[1] successful implementation may require coordinated EHR support. Therapy plan content, CDS alerts implementation, and quantitative HBsAg testing can each support a different part of the care process.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Thrombocytopenia

In addition to sudden and unpredictable thrombocytopenia, a gradual, dose-dependent decline in platelet count was observed in most patients that continued to worsen while on HIBSAGO. If a patient develops signs or symptoms of thrombocytopenia, pause HIBSAGO and obtain a platelet count as soon as possible. Instruct patients to report any symptoms of thrombocytopenia to their healthcare provider immediately. Consider the risks and benefits of treatment with HIBSAGO when treating patients who may be particularly susceptible to platelet count decreases.

FDA = U.S. Food and Drug Administration.

Please see additional Important Safety Information for HIBSAGO throughout.

Please see full Prescribing Information, including Boxed Warning, for HIBSAGO.

HIBSAGO (bepirovirsen)
Subcutaneous Use 150 mg/mL

DECIDE: ORDER SET OR THERAPY PLAN

- Each health system should determine whether an order set, a therapy plan, or both best align with the Epic configuration and operating model. The examples below are suggestions only and are not intended to establish a required or preferred approach
- The same suggested content may be considered for either an order set or a therapy plan, including the HIBSAGO medication order, ongoing lab orders, order comments, and monitoring intervals. If a health system builds both, it should identify which workflow is the source of truth for scheduled monitoring to help avoid duplicate ordering
- If the health system chooses to build a HIBSAGO order set, the order set can house the HIBSAGO medication order and selected ongoing labs using locally approved medication records, lab records, order comments, and monitoring intervals. This can make suggested orders available for standalone ordering or OPA follow-up actions, depending on local workflow design

Reminder: Whether content is delivered through an order set, therapy plan, or both is a local decision. The records and content below may be applied to any approach.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Worsening Renal Function

Mean estimated glomerular filtration rate (eGFR) declined within 4 weeks of initiation and continued to decline during treatment. These changes were generally reversible after treatment discontinuation.

Obtain eGFR and urine albumin-creatinine ratio (uACR) in all patients prior to initiation of treatment. Monitor eGFR frequently during and after treatment; treatment interruption or discontinuation may be necessary. Although no cases of glomerulonephritis were observed with HIBSAGO, glomerulonephritis has been observed with other antisense oligonucleotides; if suspected or confirmed, permanently discontinue HIBSAGO.

ORDER SET AND THERAPY PLAN CLINICAL BACKGROUND

Therapy plans may contain notes, referrals, imaging studies, lab orders and bundles, medications, immunizations, patient education, coding and billing information, and other orderable items used to manage a condition, problem, or age-specific need. Protocols may improve the user experience and help reduce practice variation. They will need to be built by a clinical analyst or an information technology (IT) colleague.

Therapy plans are typically created and modified at the health system level to help reduce practice variation. Engage the proper committees and stakeholders for clinical input and review well ahead of the planned implementation date.

Suggested Order Set and Therapy Plan Content

HIBSAGO is a hepatitis B virus (HBV) mRNA-directed antisense oligonucleotide (ASO) indicated in combination with nucleos(t)ide analog reverse transcriptase inhibitor (NrtI) therapy for treatment of chronic HBV infection in adult patients without cirrhosis[1]:

- 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

Key clinical details from the HIBSAGO Prescribing Information are included in this section and may be incorporated as part of creating/updating the therapy plan based on steps in the instructions sections that follow. It is strongly recommended that clinical and operational leadership align the therapy plan contents with the expectations and goals of the organization. The organization may add or edit any details as desired to align with governing EHR policies and standards.

Please consult the most recent version of the HIBSAGO Prescribing Information for full treatment details.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Inflammatory and Immune Effects

Influenza-like symptoms, laboratory test changes (eg, decreases in complement factors C3 and C4), purpuric leg rashes, cutaneous leukocytoclastic vasculitis, dermatitis, pruritus/erythematous plaque, and polyarthralgia were observed. In addition, serious inflammatory and immune adverse reactions were reported, including immune thrombocytopenia, autoimmune hemolytic anemia, systemic inflammatory response syndrome, and a cryoglobulinemic flare.

Consider the risks and benefits of HIBSAGO in patients who may be susceptible to inflammatory and immune effects, including solid organ transplant recipients, patients with autoimmune hepatitis, patients with a history of or conditions associated with vasculitis, or extrahepatic disorders related to HBV immune-mediated effects. If signs and symptoms suggestive of vasculitis/immune-associated events occur, and no alternative cause is identified, permanently discontinue treatment with HIBSAGO.

AST = aspartate aminotransferase.

THERAPY PLAN BUILD

Instructions for Creating or Updating a Therapy Plan

Therapy plans may be used to set up HIBSAGO in the Epic EHR. Administrative user rights are required to access these build tools. An existing therapy plan may be used as the foundation for a new one. Consider modifying an existing therapy plan as a starting template, while saving the original.

There are 4 steps to create or update a therapy plan.

Step 1. Create a New Therapy Plan Record

Create a new therapy plan record, ideally by copying an existing therapy plan. Follow the same build approach and use the same tools that your organization uses for other therapy plans while also considering unique HBV workflows that may affect build.

1. In **Hyperspace**, navigate to the **Therapy Protocol Builder (Epic button > Admin > Beacon Admin > Therapy Protocol Builder)**
2. Search for an existing **HBV protocol** (or another similar protocol record) and open it
   Note: Alternatively, if a similar protocol does not exist, select the **Create New** button
3. After opening the existing protocol, select the **Save As** button
4. Give the new protocol an ID and name that conform to your organization's build standards. For example:
   - HIBSAGO for adult patients on nucleos(t)ide analog therapy with HBV infection (without cirrhosis) with HBsAg levels ≤3,000 IU/mL
5. Update the **Comment** field, if your organization uses it for Therapy Plans. Consider the suggestion below or select another description to align with internal standards
   - HIBSAGO is for the treatment of adult patients receiving nucleos(t)ide analog therapy, for treatment of chronic hepatitis B virus (HBV) infection (without cirrhosis) with hepatitis B surface antigen (HBsAg) levels ≤3,000 IU/mL
6. Update the **Synonyms** for the protocol. Consider adding regimen acronyms, generic names, transplant type, and other values specific to the protocol. Options include:
   - **HIBSAGO**
   - **Bepirovirsen**
   - **Any potential common misspellings of HIBSAGO or its generic name**
   - **Hepatitis B virus infection**
   - **HBV**
   - **Hepatitis B surface antigen**
   - **HBsAg**
7. Add the necessary **Therapy Plan Episode Types** (eg, Therapy Plan A, Therapy Plan B) for the navigator records that will need access to the Therapy Plan
8. Update the **Review Scheme** as necessary if your organization requires periodic reviews of active therapy plans
9. Update the **Clinical Study Reference** for HIBSAGO (consider a link to the Clinical Studies [14] section of the HIBSAGO Prescribing Information)

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Serious Adverse Reaction with Improper Administration

Improper HIBSAGO administration, including not rotating injection sites, has been associated with the serious adverse reaction of omental infarction in one participant. Ensure injection sites are rotated from one week to the next and that the two injections making up each dose are separated by at least 2 inches (5 cm). Never inject into areas where the skin is tender, bruised, red, or hard.

THERAPY PLAN BUILD (CONT'D)

Step 2. Create or Update the Order Groups

As part of this step, multiple order groups related to HIBSAGO may be created/updated. Order groups for HIBSAGO and premedications may be created, as well as any other desired order groups (eg, schedulable orders, treatment conditions, monitoring and hold parameters, warnings and precautions, supportive care, healthcare provider [HCP] communications, hydration). Review your organization's governing rules and principles regarding therapy plan builds and adjust the groups as appropriate. The same order groups may be used in different therapy plans. If working from a copy of an existing order group, be sure to create a copy to avoid inadvertently affecting other therapy plans.

HIBSAGO Order Group

1. Review the **Regimen Category Order Group** to confirm that **Medications, Premedications, Treatment Conditions, and Supportive Medications** (or similar sections that already exist, following your organization's protocol build standards) are values in the category list
2. In **Hyperspace**, navigate to the **Order Group Builder (Epic button > Admin > Beacon Admin > Order Group Builder)**
3. Create a new order group named "**HIBSAGO for adult patients on nucleos(t)ide analog therapy with HBV infection (without cirrhosis) with HBsAg levels ≤3,000 IU/mL**" or follow your organization's standard naming conventions

   Note: If you started by copying an existing protocol in the Step 1 section on page 7, it may be easier and more efficient to create copies of existing order groups and modify them, when necessary. To do this, right-click on the order group within the protocol record, select **Open**, then select the **Save As** button. Next, follow the steps starting below for each order group
4. Set the default category to **Treatment Medications** or whichever equivalent treatment category is used for treatment medications in your organization
5. Add the details for HIBSAGO to the order group. The following content is from the HIBSAGO package insert[1]:

   Dosage and Administration Overview

   - HIBSAGO therapy should be prescribed only when appropriate laboratory monitoring can be performed to manage the treatment regimen. Close laboratory monitoring is required to assess for toxicities that may necessitate dose modification, treatment interruption, or permanent discontinuation of HIBSAGO
   - HIBSAGO must be administered under the guidance and supervision of a healthcare provider for the initial dose to ensure proper injection technique
   - Patients or caregivers may administer HIBSAGO after their healthcare provider determines that it is appropriate and with medical follow-up, including laboratory testing. Healthcare providers must provide proper training in subcutaneous injection technique before the patient or caregivers can administer HIBSAGO. The maximum recommended duration of HIBSAGO treatment is 24 weeks.

   Testing Prior to Initiation for Patient Selection

   Prior to initiation of HIBSAGO for treatment of chronic HBV infection, test all patients to quantify HBsAg levels in serum or plasma to identify patients with baseline HBsAg levels less than or equal to 3,000 IU/mL. In addition, test patients for HBV DNA, ALT, AST, bilirubin, platelet count, urine albumin-creatinine ratio (uACR), and estimated glomerular filtration rate (eGFR) prior to initiation of treatment and as directed while on treatment and following treatment completion.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Post-Treatment Exacerbations of HBV Infection After NrtI Discontinuation

Severe acute exacerbations of HBV infection may occur after discontinuation of anti-HBV therapy. If NrtI therapy is discontinued after completing HIBSAGO treatment, frequent monitoring is recommended for at least one year to detect acute exacerbations of HBV infection and the possible need for resumption of HBV treatment.

THERAPY PLAN BUILD (CONT'D)

Step 2. Create or Update the Order Groups (cont'd)

HIBSAGO Order Group (cont'd)

Recommended Dosage[1]

HIBSAGO is for subcutaneous use only. The maximum recommended duration of HIBSAGO treatment is 24 weeks.

HIBSAGO must be used in combination with NrtI therapy. Refer to the NrtI prescribing information for additional information.

Weeks 1 and 2

The recommended dosage of HIBSAGO is 300 mg (administered as two 150 mg subcutaneous injections) **twice** a week allowing 3 or 4 days between each dose.

Weeks 3 to 24

The recommended dosage of HIBSAGO is 300 mg (administered as two 150 mg subcutaneous injections) **once** a week on the same day each week.

Early cessation of HIBSAGO may be considered in patients who have not achieved HBsAg <1 IU/mL by Treatment Week 12.

Contraindications[1]

HIBSAGO is contraindicated in patients:

- with acute hepatic impairment, or cirrhosis who have mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C)
- with a platelet count <100 x 10^9/L prior to initiation of treatment

Warnings and Precautions

For warnings and precautions, see Section 5 of the HIBSAGO Prescribing Information.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Risk of Human Immunodeficiency Virus-1 (HIV-1) Virologic Failure in Patients with HBV/HIV-1 Coinfection Who Discontinue NrtI Therapy

Patients who are taking NrtI for HIV-1 and HBV coinfection must not stop taking their NrtI unless an HIV healthcare provider has directed them to do so.

Risk of Hepatitis Flare in Patients with HBV/Hepatitis D (HDV) Virus Coinfection

HIBSAGO is not recommended in patients with HDV coinfection due to the potential for an exacerbated risk of clinically significant ALT increases.

Unknown Effect on Preventing Transmission of HBV

There are no data on the effect of HIBSAGO in preventing transmission of HBV. Patients must be advised to use appropriate precautions to prevent transmission of HBV.

THERAPY PLAN BUILD (CONT'D)

Step 2. Create or Update the Order Groups (cont'd)

HIBSAGO Order Group (cont'd)

1. Adding an outpatient version of HIBSAGO to the same order group is strongly recommended. This order will cause HIBSAGO to appear on the patient's home medication list after administration, which will ensure transparency and continuity of care in case of unexpected admissions or ancillary office visits after the procedure. To add the outpatient details to the order group
   - Right-click in the empty field at the bottom of the window
   - Select **Add Orders**, and under the **Outpatient Medications** section in the preference search window, choose HIBSAGO
   - In the **Duration** field, enter "**24 weeks**"
   - In the **Order Class** field, select **No Print** (or your organization's equivalent)
   - In the **Comments** field, enter "**FOR DOCUMENTATION PURPOSES ONLY. Not for ordering, dispensing, or administration.**" If your organization does not have the Comments field enabled, add this to the Additional Sig Instructions instead
   - Fill in any remaining fields, such as dose, route, or frequency, based on the information in the Prescribing Information
2. Once all the desired information is added, release and migrate the order group to the production environment after completing testing

IMPORTANT SAFETY INFORMATION (CONT'D)

ADVERSE REACTIONS

The most common adverse reactions (≥10%), excluding laboratory abnormalities, reported with HIBSAGO included injection site reactions, pyrexia, fatigue, and headache.

Selected laboratory abnormalities worsened from baseline, including but not limited to, increases in ALT and total bilirubin, decreases in platelets and eGFR.

Please see additional Important Safety Information for HIBSAGO throughout.

Please see full Prescribing Information, including Boxed Warning, for HIBSAGO.

HIBSAGO (bepirovirsen)
Subcutaneous Use 150 mg/mL

THERAPY PLAN BUILD (CONT'D)

Step 2. Create or Update the Order Groups (cont'd)

Lab Monitoring Order Groups

1. Create a new order group named **"HIBSAGO Quantitative HBsAg Testing"** or follow your organization's standard naming conventions
   - Set the default category to **Labs** or whichever equivalent treatment category is used for labs in your organization
   - Add the quantitative HBsAg lab record used in your organization
   - Set the frequency to **Once**
   - Add an **Order Comment** of **"See current HIBSAGO Prescribing Information regarding consideration of early cessation if HBsAg <1 IU/mL has not been achieved."**
2. Create a new order group named **"HIBSAGO ALT Testing"** or follow your organization's standard naming conventions
   - Repeat steps in #1 above using the ALT lab record used in your organization
   - Add an **Order Comment** of **"See HIBSAGO package insert for guidance if ALT result ≥3x upper limit of normal (ULN)"**
3. Create a new order group named **"HIBSAGO Total Bilirubin Testing"** or follow your organization's standard naming conventions
   - Repeat steps in #1 above using the total bilirubin lab record used in your organization
   - Add an **Order Comment** of **"See HIBSAGO package insert for guidance if bilirubin result ≥1.5x ULN"**
4. Create a new order group named **"HIBSAGO Platelet Testing"** or follow your organization's standard naming conventions
   - Repeat steps in #1 above using the platelet lab record used in your organization
   - Add an **Order Comment** of **"See HIBSAGO package insert for guidance if platelet result <100x10^9/L"**
5. Create a new order group named **"HIBSAGO Serum Creatinine Testing"** or follow your organization's standard naming conventions
   - Repeat steps in #1 above using the serum creatinine lab record used in your organization
   - Add an **Order Comment** of **"See HIBSAGO package insert for guidance for estimated glomerular filtration rate (eGFR) reduction of ≥30% of baseline from pre-treatment levels for ≥2 consecutive tests"**

Additional Order Groups

1. Create additional order groups for any other desired orderable procedures and information for the protocol. This may include information for HIBSAGO treatment conditions, monitoring and hold parameters, warnings and precautions, procedure orders, schedulable orders, HCP communications, and any other pertinent information
2. Once all the desired information is added, release and migrate the order group to the production environment after completing testing

IMPORTANT SAFETY INFORMATION (CONT'D)

DRUG INTERACTIONS

- Monitor patients for signs of bleeding and thrombocytopenia if HIBSAGO is taken concomitantly with anticoagulants, antiplatelets, or drugs that decrease platelet count.
- Monitor patients for signs of worsening renal function during concomitant administration of HIBSAGO with drugs that may impair renal function.
- Concomitant administration of HIBSAGO and peginterferon alfa-2a is not recommended due to the potential for an exacerbated risk of increased ALT, decreased platelet count, and immune-mediated effects.

THERAPY PLAN BUILD (CONT'D)

Step 3. Add Order Instructions and Links for the Prescribing Information and Other Resources

Add links for the Prescribing Information, Patient Enrollment Form, and other resources to the medication record.

1. In **Hyperspace**, open the **SmartText Editor**
   - Create a new **SmartText** called "**HIBSAGO Specialty Pharmacy Prescribing Order Instructions**" or follow your organization's standard naming conventions
   - Add a **SmartText** type of MR Order Instructions
   - In the **text field**, add the following:

     Use the following pharmacy information for prescribing:

     PANTHERx Rare Pharmacy
     Phone: 855-726-8479
     Fax: 855-246-3986
     ERx NCPDP: 6008002
     Address: 1120 Stevenson Mill Road, Coraopolis, PA 15108
     Website: https://pantherxrare.com
   - **Save** and release the **SmartText**
2. Log in to the **Medication Master File (ERX)** with authorized user credentials
3. Use the search feature in the **Medication Master File** to search for and select **HIBSAGO**
4. Page down to the **Order Instructions** screen
   - Add the **SmartText** record created in Step 1 above to the **Order Instructions SmartText** field
5. Page down to the **Inpatient Reference Links** screen and add 4 new rows
   - Row 1: For Display Name, enter "HIBSAGO Prescribing Information"
     In the URL field, enter this hyperlink:
     https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Hibsago/pdf/HIBSAGO-PI-MG-IFU.PDF
   - Row 2: For Display Name, enter "Additional Resources for Healthcare Professionals"
     In the URL field, enter this hyperlink:
     https://hibsagohcp.com/resources/
   - Row 3: For Display Name, enter "Patient Enrollment Form"
     In the URL field, enter this hyperlink:
     https://www.togetherwithgsk.com/hibsago/hibsago/
6. Close the medication record to save the changes

IMPORTANT SAFETY INFORMATION (CONT'D)

USE IN SPECIFIC POPULATIONS

Pregnancy and Lactation

There are insufficient data on HIBSAGO use in pregnancy or during breastfeeding. Consider the benefits of breastfeeding together with the mother's clinical need for HIBSAGO.

THERAPY PLAN BUILD (CONT'D)

Step 4. Add the Order Groups Created in Step 2 to the New Therapy Plan

Add the order groups created in Step 2 beginning on page 8 to the new protocol or therapy plan and fill in the protocol/therapy plan details.

1. Open the therapy plan record created in Step 1 beginning on page 7
2. Select **Add -> Order Group**
3. Search for the order groups created in Step 2 beginning on page 8 and add them to the therapy plan
4. Fill in the details below for each order group. These fields will appear immediately after adding the order group to the plan and can also be accessed in the header of each order by clicking the summary sentence
   - Note: The monitoring schedules below represent the minimum recommended routine on-treatment monitoring intervals. More frequent monitoring may be necessary based on laboratory results. Additional testing following abnormal results should be ordered by the provider as clinically appropriate
5. For the **HIBSAGO Quantitative HBsAg Testing** order group, fill in the following details:
   - **Interval:** Once
   - **Defer until:** S+84
6. For the **HIBSAGO ALT Testing** and **HIBSAGO Total Bilirubin Testing** order groups, fill in the following details:
   - **Interval:** Weekly, for 1 time per week
   - **Minimum separation:** 6 days
   - **Duration:** 11 treatments (for weeks 2 through 12)
   - **Defer until:** S+7
7. Repeat Step 6 to create orders for weeks 12 to 24 and fill in the following details:
   - **Interval:** Daily, every 14 days
   - **Minimum separation:** 13 days
   - **Duration:** 7 treatments (for weeks 12 to 24)
   - **Defer until:** S+84
8. Conditional post-treatment ALT and total bilirubin testing is not preconfigured in the standard therapy plan. Consider adding a communication order with the following instruction:
   "If ALT or total bilirubin values are abnormal when HIBSAGO is discontinued, obtain follow-up testing at 4, 12, and 24 weeks post-treatment to assess for recovery of values to within the normal range, as appropriate. See the current HIBSAGO Prescribing Information."
   - **Interval:** Once
   - **Defer until:** S+196
     - Create copies of this group with **Defer until** as S+252 and S+336
9. For the **HIBSAGO Platelet Testing** order group, fill in the following details:
   - **Interval:** Daily, every 7 days
   - **Minimum separation:** 6 days
   - **Duration:** 23 treatments (for Treatment Weeks 2 through 24)
   - **Defer until:** S+7
10. Conditional post-treatment platelet testing is not preconfigured in the standard therapy plan. Consider adding a communication order with the following instruction:
    "If platelet values are abnormal when HIBSAGO is discontinued, obtain repeat testing at 4 and 12 weeks post-treatment to assess for recovery, as appropriate. See the current HIBSAGO Prescribing Information."
    - **Interval:** Daily, every 56 days
    - **Minimum separation:** 55 days
    - **Duration:** 2 treatments (for weeks 28 and 36)
    - **Defer until:** S+196

IMPORTANT SAFETY INFORMATION (CONT'D)

USE IN SPECIFIC POPULATIONS (CONT'D)

Pediatric Use

HIBSAGO's safety and effectiveness have not been established in patients under 18 years of age.

Please see additional Important Safety Information for HIBSAGO throughout.
Please see full Prescribing Information, including Boxed Warning, for HIBSAGO.

HIBSAGO (bepirovirsen)
Subcutaneous Use 150 mg/mL

THERAPY PLAN BUILD (CONT'D)

Step 4. Add the Order Groups Created in Step 2 to the New Therapy Plan (cont'd)

11. For the **HIBSAGO Serum Creatinine Testing** order group, fill in the following details:

- **Interval:** Daily, every 14 days
- **Minimum separation:** 13 days
- **Duration:** 12 treatments (for weeks 2 through 24)
- **Defer until:** S+7

12. Conditional post-treatment eGFR testing is not preconfigured in the standard therapy plan. Consider adding a communication order with the following instruction:
"If eGFR values are abnormal when HIBSAGO is discontinued, obtain follow-up testing at 4 and 12 weeks post-treatment to monitor for renal function recovery, as appropriate. See the current HIBSAGO Prescribing Information."

- **Interval:** Daily, every 56 days
- **Minimum separation:** 55 days
- **Duration:** 2 treatments (for weeks 28 and 36)
- **Defer until:** S+196

13. For all other order groups, fill in the following details:

- **Interval:** Weekly, for 2 times per week
- **Minimum separation:** 3 days
- **Duration:** 4 treatments (for weeks 1 and 2)
- **Dose (for HIBSAGO order only):** 300 mg

14. Repeat Step 13 to create orders for weeks 3 to 24 and fill in the following details:

- **Interval:** Weekly, for 1 time per week
- **Minimum separation:** 3 days
- **Duration:** 22 treatments (for weeks 3 to 24)
- Defer until: S+14
- **Dose (for HIBSAGO order only):** 300 mg

15. Click **Save**

16. Release the therapy plan and migrate it to the production environment after completing testing

IMPORTANT SAFETY INFORMATION (CONT'D)

USE IN SPECIFIC POPULATIONS (CONT'D)

Renal Impairment

HIBSAGO can cause worsening renal function. No dosage adjustment is recommended for mild renal impairment. Data are insufficient for moderate or severe renal impairment or end-stage renal disease (ESRD).

BUILD THE ORDER SET

Step 1. Confirm the Source Records

1. Confirm the HIBSAGO medication record, including the outpatient documentation-only version
2. Confirm the lab records for the monitored labs: HIBSAGO Quantitative HBsAg Testing, HIBSAGO ALT Testing, HIBSAGO Total Bilirubin Testing, HIBSAGO Platelet Testing, and HIBSAGO Serum Creatinine Testing
3. Confirm with the Beaker or Orders team that each lab is interfaced and files to discrete result values

Step 2. Create the Order Set Record

1. In **Hyperspace**, open the **Order Set Composer** (or **Preference List Composer** if your organization builds advisory-linked orders as a preference list)
2. Before creating a new record, check whether an existing order set, SmartSet, SmartGroup, preference list, or related Epic record may be modified. If an existing record is appropriate, follow the health system's standard process for updating it. If no appropriate record exists, create a new record
3. Create a locally approved record name, such as **"HIBSAGO"** or use the health system's standard naming convention
4. If building as a preference list for OPA use, set the list type to **Procedures** and the sub-type to **BestPractice**
5. Set the record status to testing or the health system's equivalent non-production status while the build, validation, and review are in progress
6. Create two sections: **HIBSAGO Treatment** and **Ongoing Safety-Monitoring Labs**
7. The health system may consider an EHR newsletter, tip sheet, or other local communication to notify end users if a HIBSAGO order set, therapy plan, or OPA workflow is made available
8. Add **Synonyms:**
   - **HIBSAGO**
   - **Bepirovirsen**
   - **Any potential common misspellings of HIBSAGO or its generic name**
   - **Hepatitis B virus infection**
   - **HBV**
   - **Hepatitis B surface antigen**
   - **HBsAg**
9. Release the record to production only after the health system completes its standard clinical review, build validation, user acceptance testing, and approval process

IMPORTANT SAFETY INFORMATION (CONT'D)

CONTRAINDICATIONS

HIBSAGO is contraindicated in patients:

- with acute hepatic impairment or cirrhosis who have mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C).
- with a platelet count <100 x 10^9/L prior to initiation of treatment.

Please see additional Important Safety Information for HIBSAGO throughout.
Please see full Prescribing Information, including Boxed Warning, for HIBSAGO.

HIBSAGO (bepirovirsen)
Subcutaneous Use 150 mg/mL

BUILD THE ORDER SET (CONT'D)

Step 3. Add the HIBSAGO Treatment Order

1. In the **HIBSAGO Treatment** section, add the HIBSAGO medication record and set the default category to **Treatment Medications**, or whichever equivalent treatment category your organization uses
2. Build the dosage per the Prescribing Information, with separate orderable lines for each phase[1]:
   - Weeks 1 and 2: 300 mg (administered as two 150 mg subcutaneous injections) **twice** a week, allowing 3 or 4 days between each dose
   - Weeks 3 to 24: 300 mg (administered as two 150 mg subcutaneous injections) **once** a week on the same day each week
3. Confirm the dosage form and strength[1]: injection, 150 mg/mL solution in a single-dose, prefilled syringe. Route is subcutaneous use only
4. Add contraindication text so it is visible at the point of ordering[1]: HIBSAGO is contraindicated in patients with acute hepatic impairment, or cirrhosis who have mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C), and in adults with a platelet count <100 x 10^9/L prior to initiation of treatment. The indicated population is also limited to patients without cirrhosis
5. Add a missed-dose comment[1]: If a dose of HIBSAGO is missed at any time during treatment (weeks 1–24), the missed dose must be administered as soon as possible, unless the next scheduled dose is due in less than three days, in which case the missed dose must be skipped and the next dose administered as scheduled
6. Link the **HIBSAGO Specialty Pharmacy Prescribing Order Instructions** SmartText and the reference links on the medication record, so Prescribing Information, Additional Resources for Healthcare Professionals, and the Patient Enrollment Form are available from the order set
7. Add the outpatient documentation-only version of HIBSAGO as a second line:
   - **Duration:** 24 weeks
   - **Order Class:** No Print (or your organization's equivalent)
   - **Comments:** "FOR DOCUMENTATION PURPOSES ONLY. Not for ordering, dispensing, or administration." If the Comments field is not enabled, add this to Additional Sig Instructions instead

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS

On-Treatment Hepatic Flares

Increases in ALT ≥3x ULN to 69x ULN were observed during treatment with HIBSAGO, most within the first 12 weeks. Isolated cases of ALT increases associated with an increase in total bilirubin resolved when treatment was permanently discontinued.

Please see additional Important Safety Information for HIBSAGO throughout.

Please see full Prescribing Information, including Boxed Warning, for HIBSAGO.

HIBSAGO (bepirovirsen)
Subcutaneous Use 150 mg/mL

BUILD THE ORDER SET (CONT'D)

Step 4. Add the Required Ongoing Labs

In the Ongoing Safety-Monitoring Labs section, add one line per monitored lab. Carry the order comments and monitoring intervals onto each line so a provider ordering from the order set gets the same schedule and guidance as a patient managed on a therapy plan.

Ongoing Safety-Monitoring Labs[1]

Lab order	Minimum on-treatment interval	Defer until	Order comment
HIBSAGO Quantitative HBsAg Testing	Once	S+84	See HIBSAGO Prescribing Information regarding consideration of early cessation if HBsAg <1 IU/mL has not been achieved. Do not use HBV DNA as a substitute for quantitative HBsAg
HIBSAGO ALT Testing	Weekly; minimum separation 6 days; 11 treatments (weeks 2–12) Then every other week; minimum separation 13 days; 7 treatments (weeks 12–24)	S+7 S+84	See HIBSAGO Prescribing Information for ALT and total bilirubin monitoring and dosage-modification guidance. ALT and total bilirubin should be evaluated together when determining monitoring frequency, treatment interruption, dose reduction, or discontinuation
HIBSAGO Total Bilirubin Testing	Same on-treatment schedule as ALT Weekly (weeks 2–12), then every other week (weeks 12–24)	S+7 S+84	See HIBSAGO Prescribing Information for ALT and total bilirubin monitoring and dosage-modification guidance when total bilirubin is ≥1.5x ULN or ≥2x ULN in combination with ALT elevation
HIBSAGO Platelet Testing	Weekly through week 24	S+7 S+196	See HIBSAGO Prescribing Information for platelet monitoring and dosage-modification guidance if platelet count is <100 x 10^9/L, including more frequent monitoring for platelet counts <75 x 10^9/L and permanent discontinuation thresholds below 50 x 10^9/L
HIBSAGO Serum Creatinine Testing	Every other week during treatment	S+7	See HIBSAGO Prescribing Information for guidance for eGFR reduction of ≥30% of baseline from pre-treatment levels for ≥2 consecutive tests

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Thrombocytopenia

In addition to sudden and unpredictable thrombocytopenia, a gradual, dose-dependent decline in platelet count was observed in most patients that continued to worsen while on HIBSAGO. If a patient develops signs or symptoms of thrombocytopenia, pause HIBSAGO and obtain a platelet count as soon as possible. Instruct patients to report any symptoms of thrombocytopenia to their healthcare provider immediately. Consider the risks and benefits of treatment with HIBSAGO when treating patients who may be particularly susceptible to platelet count decreases.

Please see additional Important Safety Information for HIBSAGO throughout.
Please see full Prescribing Information, including Boxed Warning, for HIBSAGO.

HIBSAGO (bepirovirsen)
Subcutaneous Use 150 mg/mL

BUILD THE ORDER SET (CONT'D)

Step 4. Add the Required Ongoing Labs (cont'd)

Conditional Post-Discontinuation Monitoring Labs for Patients With Abnormal Values at HIBSAGO Discontinuation[1]

In the Ongoing Safety-Monitoring Labs section, add one line per monitored lab. Carry the order comments and monitoring intervals onto each line so a provider ordering from the order set gets the same schedule and guidance as a patient managed on a therapy plan.

Lab	Post-discontinuation timing	Build note
ALT and total bilirubin	4, 12, and 24 weeks after HIBSAGO discontinuation	Assess recovery of ALT values to within the normal range, as appropriate
Platelet count	4 and 12 weeks after HIBSAGO discontinuation	Assess platelet count recovery, as appropriate
eGFR follow-up	4 and 12 weeks after HIBSAGO discontinuation	Assess for renal function recovery, as appropriate

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Worsening Renal Function

Mean estimated glomerular filtration rate (eGFR) declined within 4 weeks of initiation and continued to decline during treatment. These changes were generally reversible after treatment discontinuation.

Obtain eGFR and urine albumin-creatinine ratio (uACR) in all patients prior to initiation of treatment. Monitor eGFR frequently during and after treatment; treatment interruption or discontinuation may be necessary. Although no cases of glomerulonephritis were observed with HIBSAGO, glomerulonephritis has been observed with other antisense oligonucleotides; if suspected or confirmed, permanently discontinue HIBSAGO.

BUILD OPAS TO SUPPORT THE WORKFLOW

Step 1. Confirm Data Readiness

Before building any suggested lab-based OPA or monitoring workflow, confirm with the Laboratory, Interfaces, or EHR build team that the relevant lab results are available in the EHR and filed as discrete values.

Question	If yes	If no
Are results interfaced back to the EHR?	Proceed with build	Do not proceed — pursue an interfaced-result option with your interfaces team first
Are interfaced results filed to discrete result values (not PDF/image)?	Proceed with build	Build is still possible, but see operational impact below

Note: If lab results are not filed as discrete values, an OPA or report may only identify that an order was completed, not the result value. The health system should account for any manual follow-up needed before building on a non-discrete lab.

Step 2. Confirm Local Lab Thresholds

Because lab reference ranges can vary by health system, assay, lab vendor, and result component, confirm the local reference range before build. Use this worksheet to translate the approved threshold into the exact discrete value the OPA should evaluate in your organization's EHR.

Lab	Toolkit threshold	Local ULN / baseline	Calculated OPA value	Component / source to confirm	Build notes
ALT	≥3x ULN	____ U/L	____ U/L	ALT common name/ Laboratory Result Component (LRR) ID	Confirm assay-specific ULN
Total bilirubin	≥1.5x ULN	____ mg/dL	____ mg/dL	Bilirubin total component	Confirm unit and reference range
eGFR	≥30% decline, 2 consecutive results	Baseline: ____	30% decline value: ____	eGFR component/ calculation method	Define baseline window and confirm final-result logic
Platelet count	75 to <100 × 10^9/L; 50 to <75 × 10^9/L; 25 to <50 × 10^9/L; <25 × 10^9/L; and ≥30% decrease between consecutive readings	Baseline: ____	Configured according to selected OPA scenario: ____	Platelet count common name/Laboratory Result Component (LRR) ID	Confirm units, final-result logic, and which PI-defined platelet scenarios the organization elects to support

Recommended workflow: confirm the local ULN or baseline definition first; confirm the discrete lab component and units with the appropriate lab or EHR build team; then translate the confirmed value into the OPA criteria or rule logic. Do not rely on a generic ULN multiple alone when the local lab reference range varies.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Inflammatory and Immune Effects

Influenza-like symptoms, laboratory test changes (eg, decreases in complement factors C3 and C4), purpuric leg rashes, cutaneous leukocytoclastic vasculitis, dermatitis, pruritus/erythematous plaque, and polyarthralgia were observed. In addition, serious inflammatory and immune adverse reactions were reported, including immune thrombocytopenia, autoimmune hemolytic anemia, systemic inflammatory response syndrome, and a cryoglobulinemic flare.

Consider the risks and benefits of HIBSAGO in patients who may be susceptible to inflammatory and immune effects, including solid organ transplant recipients, patients with autoimmune hepatitis, patients with a history of or conditions associated with vasculitis, or extrahepatic disorders related to HBV immune-mediated effects. If signs and symptoms suggestive of vasculitis/immune-associated events occur, and no alternative cause is identified, permanently discontinue treatment with HIBSAGO.

Please see additional Important Safety Information for HIBSAGO throughout.
Please see full Prescribing Information, including Boxed Warning, for HIBSAGO.

HIBSAGO (bepirovirsen)
Subcutaneous Use 150 mg/mL

BUILD OPAS TO SUPPORT THE WORKFLOW

Clinical Decision Support Tools - OPAs

Consider using Epic's clinical decision support solution, an OPA, to create notifications that align with your organization's clinical preferences and workflows, either actively through pop-up alerts or passively through alerts displayed in the patient's Storyboard/sidebar. OPAs consist of a criteria record and a base record. Criteria records define the conditions under which an alert should appear. A base record defines an alert's overall behavior, display text, restrictions, workflow triggers, follow-up actions, and more by linking criteria records. While a single criteria record can contain multiple conditions, it is recommended that separate criteria records be created for each condition so they can be reused across multiple alerts.

OPA 1: Chronic HBV infection without a recent quantitative HBsAg assessment

1. Include chronic HBV infection diagnosis grouper
2. Include positive qualitative HBsAg lab results
3. Exclude active quantitative HBsAg lab orders
4. Exclude patients with quantitative HBsAg results in the past year

OPA 2: Quantitative HBsAg ≤3,000 IU/mL and not currently receiving HIBSAGO

1. Include quantitative HBsAg results ≤3,000 IU/mL in the past year
2. Exclude current medication orders for HIBSAGO
3. Exclude an active HIBSAGO therapy plan

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Serious Adverse Reaction with Improper Administration

Improper HIBSAGO administration, including not rotating injection sites, has been associated with the serious adverse reaction of omental infarction in one participant. Ensure injection sites are rotated from one week to the next and that the two injections making up each dose are separated by at least 2 inches (5 cm). Never inject into areas where the skin is tender, bruised, red, or hard.

Please see additional Important Safety Information for HIBSAGO throughout.
Please see full Prescribing Information, including Boxed Warning, for HIBSAGO.

HIBSAGO (bepirovirsen)
Subcutaneous Use 150 mg/mL

BUILD OPAS TO SUPPORT THE WORKFLOW (CONT'D)

Clinical Decision Support Tools - OPAs (cont'd)

Step 1. Create the Criteria Records

Chronic HBV Infection

1. **Chart Search** for **OurPractice Advisory Editor**
2. Create a new **Criteria record** and enter a unique name (eg, "CL EDG Include Chronic HBV Infection" or follow your organization's naming conventions)
3. Add criteria for **Diagnosis Grouper**
4. In the **Include Diagnosis Grouper** field, add your organization's grouper for Chronic HBV infection
5. Select the **Released** checkbox
6. Click **Accept**

HBV Qualitative Lab Positive

1. **Chart Search** for **Rule Editor**
2. Create a new **Rule record** and enter a unique name (eg, "Prior abnormal HBV qualitative result" or follow your organization's naming conventions)
3. In the **property field**, search for **Lab Result: Has Abnormal Result**
4. Enter the **Base Name(s)** and/or **Common Name(s)** used for the HBV Qualitative lab results used in your organization
   - Consult with the Beaker or Orders teams if you need assistance identifying the appropriate base or common names depending on your lab build strategy
5. Enter a large value in the **lookback field** (eg, 9999 days)
6. **Save** and **Accept** the record
7. **Chart Search** for **OurPractice Advisory Editor**
8. Create a new **Criteria** record and enter a unique name (eg, "CL CER Include Abnormal HBV Qualitative Result" or follow your organization's naming conventions)
9. Add criteria for **Rules**
10. In the **Include Rule field**, add the rule record created in Step 2 above
11. Select the **Released** checkbox
12. Click **Accept**

Quantitative HBsAg Lab Ordered

1. **Chart Search** for **OurPractice Advisory Editor**
2. Create a new **Criteria record** and enter a unique name (eg, "CL EAP Exclude Quantitative HBsAg Lab" or follow your organization's naming conventions)
3. Add criteria for **Procedure**
4. In the **Exclude Procedures** field, add the procedure records used for the Quantitative HBsAg Lab record(s) in use in your organization
5. Select the **Released** checkbox
6. Click **Accept**

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Post-Treatment Exacerbations of HBV Infection After NrtI Discontinuation

Severe acute exacerbations of HBV infection may occur after discontinuation of anti-HBV therapy. If NrtI therapy is discontinued after completing HIBSAGO treatment, frequent monitoring is recommended for at least one year to detect acute exacerbations of HBV infection and the possible need for resumption of HBV treatment.

Please see additional Important Safety Information for HIBSAGO throughout.
Please see full Prescribing Information, including Boxed Warning, for HIBSAGO.

HIBSAGO (bepirovirsen)
Subcutaneous Use 150 mg/mL

BUILD OPAS TO SUPPORT THE WORKFLOW (CONT'D)

Clinical Decision Support Tools - OPAs (cont'd)

Step 1. Create the Criteria Records (cont'd)

HBV Recent Quantitative Lab Result in the Last Year

1. **Chart Search** for **Rule Editor**
2. Create a new rule record and enter a unique name (eg, "Quantitative HBsAg Lab Result Exists in the Past Year" or follow your organization's naming conventions)
3. In the **property** field, search for **Lab Result: Last Lab Result (Numeric)**
4. Enter the **Base Name(s)** and/or **Common Name(s)** used for the Quantitative HBsAg lab results used in your organization
   - Consult with the Beaker or Orders teams if you need assistance identifying the appropriate base or common names depending on your lab build strategy
5. In the **Lookback** field, enter **365 days (or 1 year)**
6. In the **Comparison** field, enter <> (not equal to)
7. Leave the **Value** field blank
8. **Chart Search** for **OurPractice Advisory Editor**
9. Create a new **Criteria** record and enter a unique name (eg, "CL CER Exclude Recent HBV Quantitative Result in the Last Year" or follow your organization's naming conventions)
10. Add criteria for **Rules**
11. In the **Exclude Rule** field, add the rule record created in Step 2 above
12. Select the **Released** checkbox
13. Click **Accept**

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Risk of Human Immunodeficiency Virus-1 (HIV-1) Virologic Failure in Patients with HBV/HIV-1 Coinfection Who Discontinue NrtI Therapy

Patients who are taking NrtI for HIV-1 and HBV coinfection must not stop taking their NrtI unless an HIV healthcare provider has directed them to do so.

Please see additional Important Safety Information for HIBSAGO throughout.
Please see full Prescribing Information, including Boxed Warning, for HIBSAGO.

HIBSAGO (bepirovirsen)
Subcutaneous Use 150 mg/mL

BUILD OPAS TO SUPPORT THE WORKFLOW (CONT'D)

Clinical Decision Support Tools - OPAs (cont'd)

Step 1. Create the Criteria Records (cont'd)

Quantitative HBsAg Lab ≤3,000 IU/mL

1. **Chart Search** for **Rule Editor**
2. Create a new rule record and enter a unique name (eg, "Last Quantitative HBsAg Result ≤3,000 IU/mL" or follow your organization's naming conventions)
3. In the **property** field, search for **Lab Result: Last Lab Result (Numeric)**
4. Enter the **Base Name(s)** and/or **Common Name(s)** used for the Quantitative HBsAg lab results used in your organization
   - Consult with the Beaker or Orders teams if you need assistance identifying the appropriate base or common names depending on your lab build strategy
5. In the **Lookback** field, enter **365 days (or 1 year)**
6. In the **Comparison** field, enter ≤
7. In the **Value** field, enter **3,000**
8. **Save** and **Accept** the record
9. **Chart Search** for **OurPractice Advisory Editor**
10. Create a new **Criteria** record and enter a unique name (eg, "CL CER Include Quantitative HBsAg Result ≤3,000 IU/mL" or follow your organization's naming conventions)
11. Add criteria for **Rules**
12. In the **Include Rule** field, add the rule record created in Step 2 above
13. Select the **Released** checkbox
14. Click **Accept**

HIBSAGO Ordered

1. **Chart Search** for **OurPractice Advisory Editor**
2. Create a new **Criteria** record and enter a unique name (eg, "CL ERX Exclude Active HIBSAGO order" or follow your organization's naming conventions)
3. Add criteria for **Medications**
4. In the **Exclude Medications** field, add the medication (ERX) records for HIBSAGO used in your organization
5. Select the **Released** checkbox
6. Click **Accept**

Exclude Active Therapy Plan for HIBSAGO

1. **Chart Search** for **Rule Editor**
2. Create a new **Rule** record and enter a unique name (eg, "HIBSAGO Active Therapy Plan" or follow your organization's naming conventions)
3. In the property field, search for **Active Therapy Plan**
4. Enter the name of the **Therapy Plan built for HIBSAGO** [see Therapy Plan section of this build guide]
5. In the **Comparison** field, enter = (equal to)
6. **In the Value field, enter Yes**

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Risk of Hepatitis Flare in Patients with HBV/Hepatitis D (HDV) Virus Coinfection

HIBSAGO is not recommended in patients with HDV coinfection due to the potential for an exacerbated risk of clinically significant ALT increases.

Unknown Effect on Preventing Transmission of HBV

There are no data on the effect of HIBSAGO in preventing transmission of HBV. Patients must be advised to use appropriate precautions to prevent transmission of HBV.

BUILD OPAS TO SUPPORT THE WORKFLOW (CONT'D)

Clinical Decision Support Tools - OPAs (cont'd)

Step 2. Create the Base Records

Below is a list of recommended alerts designed to support the management of patients with chronic HBV, along with suggested alert text for clinicians. These recommendations should be reviewed and modified as needed to align with your organization's workflows, clinical preferences, and intended users.

1. Patients who have a positive qualitative test result for chronic HBV infection without a quantitative HBsAg lab ordered within the past year
2. Patients with a quantitative HBsAg result of ≤3,000 IU/mL within the past year who are not on HIBSAGO

Chronic HBV Infection without Quantitative HBsAg Titer ordered

1. **Chart Search** for **OurPractice Advisory Editor**
2. Create a **Base** record with a unique name (eg, "BASE CHRONIC HEPATITIS B VIRUS INFECTION – NO QUANTITATIVE HBsAg LAB ORDERED" or follow your organization's naming conventions)
3. Start editing the record and click **+ Add Criteria Type**
4. Add the **Criteria** records created in Step 1 on page 22 in the **Linked Criteria:**
   - Line 1: CL EDG Include Chronic HBV Infection
   - Line 2: CL CER Include Abnormal Qualitative HBsAg Result
   - Line 3: CL EAP Exclude Quantitative HBsAg Lab
   - Line 4: CL CER Exclude Recent Quantitative HBsAg Result in the Last Year
   - In the Logic section, enter: **(1 OR 2) AND 3 AND 4**
5. In the **Display** section:
   - Select **Yes** for **Display to User** (If your organization does not want the OPA to display within the provider workflow and only wishes to have an InBasket message sent to the provider, you can select **No** instead)
6. Enter a **Summary Text** to describe the **Advisory**
7. For the **Unformatted Display Text**, enter suggested message: "**Patient has diagnosis of chronic HBV infection or positive Hepatitis B Surface Antigen (HBsAg) qualitative test result without a quantitative lab order. Recommend ordering quantitative HBsAg lab**"
8. Click the **Restrictions** tab to narrow the target audience. In the **Encounter Limitation Inclusion and/or Exclusion** grid, set the Specialty, Department, and Provider Type as necessary. The selections may vary depending on how the organization was set up in the EHR and the intended audience for the alert
9. Set the desired **Triggers** for the OPA per institutional conventions
10. Set the desired **Actions**. Consider selecting **Single Orders** with a link to the **Quantitative HBsAg lab orders** or **SmartSet** with the orders. If an InBasket message is preferred, select the **InBasket Message** option
11. Set any **Acknowledgment Reason**, if desired
12. Preview the **OPA** to confirm the expected display result as a **Pop-Up** or **Navigator OPA**
13. Select the **Test** activity and complete any **Testing (Troubleshooting)**, if needed, and consider additional end user testing before releasing the OPA
14. Release after satisfactory testing has been completed

IMPORTANT SAFETY INFORMATION (CONT'D)

ADVERSE REACTIONS

The most common adverse reactions (≥10%), excluding laboratory abnormalities, reported with HIBSAGO included injection site reactions, pyrexia, fatigue, and headache.

Selected laboratory abnormalities worsened from baseline, including but not limited to, increases in ALT and total bilirubin, decreases in platelets and eGFR.

BUILD OPAS TO SUPPORT THE WORKFLOW (CONT'D)

Clinical Decision Support Tools - OPAs (cont'd)

Quantitative HBsAg ≤3,000 IU/mL and not on HIBSAGO

1. **Chart Search** for **OurPractice Advisory Editor**
2. Create a **Base** record with a unique name (eg, "BASE QUANTITATIVE HBsAg ≤3,000 IU/mL – NOT ON HIBSAGO" or follow your organization's naming conventions)
3. Start editing the record and click **+ Add Criteria Type**
4. Add the **Criteria** records created in Step 1 on page 22 in the **Linked Criteria:**
   - Line 1: CL CER Last Quantitative HBsAg Result ≤3,000 IU/mL
   - Line 2: CL ERX Exclude Active HIBSAGO order
   - Line 3: CL CER Exclude Active HIBSAGO Therapy Plan
   - In the Logic section, enter: **1 AND 2 AND 3**
5. In the **Display** section:
   - Select **Yes** for **Display to User** (If your organization does not want the OPA to display within the provider workflow and only wishes to have an InBasket message sent to the provider, you can select **No** instead)
6. Enter a **Summary Text** to describe the **Advisory**
7. For the **Unformatted Display Text**, enter suggested message: "**Patient has a recent quantitative HBsAg result of ≤3,000 IU/mL and not currently on HIBSAGO therapy. Recommend ordering HIBSAGO therapy plan**"
8. Click the **Restrictions** tab to narrow the target audience. In the **Encounter Limitation Inclusion and/or Exclusion** grid, set the Specialty, Department, and Provider Type as necessary. The selections may vary depending on how the organization was set up in the EHR and the intended audience for the alert
9. Set the desired **Triggers** for the OPA per institutional conventions
10. Set the desired **Actions**. Consider selecting either a) Follow-up Activity with a link to the Therapy Plan ordering activity record in use in your organization, or b) Single Orders with a link to the HIBSAGO SmartSet with the orders, depending on organizational preferences. If an InBasket message is preferred, select the **InBasket Message** option
11. Set any **Acknowledgment Reason**, if desired
12. Preview the **OPA** to confirm the expected display result as a **Pop-Up** or **Navigator OPA**
13. Select the **Test** activity and complete any **Testing (Troubleshooting)**, if needed, and consider additional end user testing before releasing the OPA
14. Release after satisfactory testing has been completed

IMPORTANT SAFETY INFORMATION (CONT'D)

DRUG INTERACTIONS

- Monitor patients for signs of bleeding and thrombocytopenia if HIBSAGO is taken concomitantly with anticoagulants, antiplatelets, or drugs that decrease platelet count.
- Monitor patients for signs of worsening renal function during concomitant administration of HIBSAGO with drugs that may impair renal function.
- Concomitant administration of HIBSAGO and peginterferon alfa-2a is not recommended due to the potential for an exacerbated risk of increased ALT, decreased platelet count, and immune-mediated effects.

Please see additional Important Safety Information for HIBSAGO throughout.
Please see full Prescribing Information, including Boxed Warning, for HIBSAGO.

HIBSAGO (bepirovirsen)
Subcutaneous Use 150 mg/mL

BUILD OPAS TO SUPPORT THE WORKFLOW (CONT'D)

Step 3. Build a SmartSet for Multi-Order Follow-Up (Optional)

1. If a single advisory should offer more than one follow-up order (for example, repeat ALT and total bilirubin together), create a scenario-specific SmartSet containing only the applicable follow-up labs rather than linking the full HIBSAGO treatment order set
2. Group orders by safety scenario so the SmartSet mirrors the Base records
3. Add the corresponding order comments and any required order-specific questions

Step 4. Attach the Appropriate Follow-Up Action to the OPA

1. Open the **Base** record for the applicable scenario in the **OurPractice Advisory Editor**
2. For a post-discontinuation monitoring OPA, do not link the full HIBSAGO treatment order set. In the **Actions** section, select **Single Orders** and link the specific follow-up lab order that matches the advisory
3. If the scenario requires multiple follow-up labs, select **SmartSet** and link a scenario-specific SmartSet containing only those applicable post-discontinuation orders
4. Where an In Basket workflow is preferred over provider ordering, select the **InBasket Message** action and route to the pharmacist or specialty pool instead
5. Confirm that the linked action matches the lab or labs for the specific post-discontinuation scenario. For example, an ALT and total bilirubin follow-up advisory may link both labs, while a platelet follow-up advisory should not default to the full monitoring panel unless that is the intended organizational workflow
6. For patient-identification advisories, the health system may separately consider linking the full HIBSAGO treatment order set so the provider can initiate HIBSAGO and its associated monitoring together

Step 5. Create a Criteria Record for the HIBSAGO Treatment Context

1. Open the **OurPractice Advisory** activity and create a new record with a type of Criteria
2. Add a **Criteria Type of Medications** (or Diagnosis, if more appropriate), referencing the HIBSAGO medication record or diagnosis directly
3. Select the **Released** checkbox

Step 6. Create a Criteria Record for Each Monitored Lab Value

Worked example — ALT:

1. Open the **OurPractice Advisory** activity and create a new record with a type of Criteria
2. Add a **Criteria Type** of **Lab Components**
3. Enter the ALT component using its common name or LRR ID (confirm with your Beaker/Lab team if unknown). Common name is preferred where multiple assay-specific components need to be checked with one line
4. Set the Function to **GREATER THAN OR EQUAL TO** and the **Additional Info** field to the applicable ULN multiple (3), with an appropriate lookback

Note: If ULN varies by assay or lab rather than one fixed number, or if you need to check only the most recent value across several common names, use a rule-type Criteria record instead.

IMPORTANT SAFETY INFORMATION (CONT'D)

USE IN SPECIFIC POPULATIONS

Pregnancy and Lactation

There are insufficient data on HIBSAGO use in pregnancy or during breastfeeding. Consider the benefits of breastfeeding together with the mother's clinical need for HIBSAGO.

Pediatric Use

HIBSAGO's safety and effectiveness have not been established in patients under 18 years of age.

BUILD OPAS TO SUPPORT THE WORKFLOW (CONT'D)

Step 6. Create a Criteria Record for Each Monitored Lab Value (cont'd)

Repeat this approach only for OPA criteria the health system chooses to support. Separate patient-identification criteria from on-treatment safety-monitoring criteria, and confirm final logic, thresholds, audience, and workflow through local clinical and informatics governance before build.

Criterion	Use case	Function / logic	Value / threshold	Build note
Quantitative HBsAg	Patient identification/ eligibility assessment	Less than or equal to	3,000 IU/mL	Use quantitative HBsAg. Avoid generic "HBV quantitative" wording, which could be interpreted as HBV DNA
Quantitative HBsAg	Week 12 assessment, if included	Less than	1 IU/mL	Consider adding this threshold if the workflow is intended to support Week 12 assessment and potential early-cessation discussion. The PI states to consider early cessation in patients who have not achieved HBsAg <1 IU/mL by Treatment Week 12
ALT with total bilirubin	On-treatment monitoring/dosage modification	Rule-type logic recommended	Evaluate ALT and total bilirubin together using PI-aligned thresholds: ALT <3x ULN; ALT ≥10x to <12x ULN with total bilirubin <1.5x ULN; ALT ≥12x ULN with total bilirubin <1.5x ULN; ALT ≥3x ULN with total bilirubin ≥1.5 to <2x ULN; ALT ≥3x ULN with total bilirubin ≥2x ULN	ALT and total bilirubin are interdependent and should be evaluated together rather than as standalone criteria
Platelets	Pre-initiation contraindication and on-treatment monitoring	Rule-type logic recommended	Pre-initiation: platelet count <100 x 10^9/L. During treatment: platelet count 75 to <100 x 10^9/L, 50 to <75 x 10^9/L, 25 to <50 x 10^9/L, or <25 x 10^9/L	Align monitoring and action to the PI, including increased monitoring below 75 x 10^9/L and permanent discontinuation thresholds below 50x 10^9/L
eGFR	On-treatment renal monitoring	Rule-type only	≥30% decline, 2 consecutive results	Requires baseline definition, final-result logic, and consecutive-result evaluation

For end-user and provider-facing builds, keep the alert focused on the specific clinical scenario it is intended to support. Clearly separate criteria used to identify potentially appropriate patients from criteria used for on-treatment safety monitoring. Before activation, confirm the final threshold logic, local lab values, and intended alert audience through the health system's standard clinical, informatics, and governance review process.

IMPORTANT SAFETY INFORMATION (CONT'D)

USE IN SPECIFIC POPULATIONS (CONT'D)

Renal Impairment

HIBSAGO can cause worsening renal function. No dosage adjustment is recommended for mild renal impairment. Data are insufficient for moderate or severe renal impairment or end-stage renal disease (ESRD).

Please see additional Important Safety Information for HIBSAGO throughout.
Please see full Prescribing Information, including Boxed Warning, for HIBSAGO.

HIBSAGO (bepirovirsen)
Subcutaneous Use 150 mg/mL

BUILD OPAS TO SUPPORT THE WORKFLOW (CONT'D)

Step 7. Rule-Type Criteria Record for eGFR, ALT/Bilirubin, and Other Interdependent Logic

1. Create a new **Patient OPA Locator** rule
2. Add the Last Lab Value property (or, for the decline calculation, build custom logic that pulls the baseline and most recent qualifying values)
3. Add the eGFR component using Base/Common names or an LRR grouper, with an appropriate lookback period
4. Define the baseline window and whether baseline is a single, closest, or averaged pre-treatment result
5. Calculate percentage decline: ([baseline − current] / baseline) x 100; require two consecutive qualifying final results before the rule returns true
6. Link the rule to your Criteria record and select the **Released** checkbox
7. For ALT and total bilirubin, build rule-type logic when the threshold requires evaluating both values together. This helps avoid treating ALT or bilirubin as isolated triggers when the label logic requires combined interpretation

Note: This step may require support from the appropriate clinical informatics, rules, or EHR build team if local configuration cannot be completed through standard point-and-click setup.

Step 8. Create a Base Record for Each Safety Scenario

1. Create a new OPA record with a type of **Base**
2. Link the relevant treatment-context and lab Criteria records; set **Logic** to **1 and 2** (and 3, if a suppression criterion is added for the overdue advisory)
3. **Restrictions:** use the **Include Encounter Restriction** table to scope the OPA to appropriate provider types (eg, Physician, Physician Assistant, Nurse Practitioner, Resident, Fellow) and department/specialty, entering each combination as its own OR-logic line
4. **Triggers:** choose how and where the alert appears
   - Open Patient Chart: interruptive pop-up on chart opening
   - General BPA Section: non-interruptive navigator-line display
   - Header BPA Notifications: appears in the patient Storyboard; provider clicks to expand

   Default to General BPA Section or Header BPA Notifications; reserve Open Patient Chart for scenarios with explicit prescribing-information and governance support
5. **Actions:** add applicable actions — link to the HIBSAGO therapy plan or Prescribing Information, suggest a repeat or follow-up lab order from the order set, or route an In Basket message to a pharmacist or specialty pool
6. **Acknowledgment:** give providers a documented decline or acknowledgment reason, and optionally lock the OPA from reappearing for a defined interval after acknowledgment
7. **Display:** configure alert text using the Base record's text fields or an approved SmartLink. Use health-system-approved clinical language and align with applicable Prescribing Information
8. Select the **Released** checkbox to activate for testing

Build one Base record per scenario (quantitative HBsAg, ALT, bilirubin, platelets pre-initiation, sustained eGFR decline) rather than one combined record, so firing and acknowledgment trends can be reviewed by scenario in the **Our Practice Alert Usage** report.

IMPORTANT SAFETY INFORMATION (CONT'D)

CONTRAINDICATIONS

HIBSAGO is contraindicated in patients:

- with acute hepatic impairment or cirrhosis who have mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C).
- with a platelet count <100 x 10^9/L prior to initiation of treatment.

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BUILD OPAS TO SUPPORT THE WORKFLOW (CONT'D)

Step 9. Add an Overdue-Monitoring OPA

To prompt ordering when a monitored lab has not been checked within the expected interval:

1. Save a copy of a safety-scenario Base record
2. Create a new Criteria record with a type of **Rule**
3. Create a new **Patient OPA Locator** rule using the **Last Lab Date** property; add the relevant Base/Common names or LRR grouper and set the lookback to at least the monitoring interval (do not set it shorter than roughly the interval itself)
4. Use the **less than** operator with a value such as M-6 (or the applicable interval) to flag dates older than the expected window, a missing or null date also evaluates true, so this correctly flags patients with no result on file
5. Add the new criterion to the copied Base record and update the logic accordingly
6. Optionally add a **Single Order** action built from the ongoing safety-monitoring lab lines in the order set
7. If this could fire alongside the threshold-exceeded OPA for the same lab, invert the logic on 1 of the 2 records so only one fires per situation

This OPA and a therapy plan's passive overdue-lab display are not meant to replace each other, and do not need cross-suppression. The therapy plan view is the reference for someone already reviewing the plan, while this OPA is the safety net for chart-open, results-review, and covering-provider scenarios where the plan was never opened. A provider seeing the same overdue result in both places is not a conflict.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS

On-Treatment Hepatic Flares

Increases in ALT ≥3x ULN to 69x ULN were observed during treatment with HIBSAGO, most within the first 12 weeks. Isolated cases of ALT increases associated with an increase in total bilirubin resolved when treatment was permanently discontinued.

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DISCLAIMERS

- The user (eg, physician, medical group, integrated delivery network) shall be solely responsible for implementation, testing, and monitoring of the instructions to ensure proper orientation in each user's EHR system
- Capabilities, functionality, and set-up (customization) for each individual EHR system vary. GSK shall not be responsible for revising the implementation instructions it provides to any user if user modifies or changes its software or the configuration of its EHR system after such time as the implementation instructions have been initially provided by GSK
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References: 1. HIBSAGO (bepirovirsen). Prescribing Information. GSK; 2026. **2.** Cornberg M, et al. *J Hepatol*. 2017;66(2):398-411. **3.** Vachon A, et al. *Viruses*. 2021;13(6):951.

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