Product Monograph

Including Patient Medication Information

[Pr]HIBSAGO

bepirovirsen injection

Solution

For Subcutaneous Use

150 mg/mL bepirovirsen (as bepirovirsen sodium) in a single-use pre-filled syringe

Antiviral

GlaxoSmithKline Inc.

100 Milverton Drive, Suite 800

Mississauga, Ontario
L5R 4H1

Date of Authorization:
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Control Number: 500584

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Recent Major Label Changes

None.

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Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

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Part 1: Healthcare Professional Information

1. Indications

HIBSAGO (bepirovirsen injection) is indicated as a finite treatment to achieve functional cure of chronic hepatitis B virus (HBV) infection in non-cirrhotic adult patients who have been on nucleos(t)ide analogue therapy for at least 6 months and with HBV DNA <90 IU/mL, and have hepatitis B surface antigen (HBsAg) levels ≤3,000 IU/mL.

Clinical efficacy is higher with lower baseline HBsAg levels, especially in patients with baseline HBsAg levels ≤1,000 IU/mL (see 14 Clinical Trials).

1.1. Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of HIBSAGO in pediatric patients has not been established.

1.2. Geriatrics

Geriatrics (≥65 years of age): The clinical experience in patients aged 65 years and older is limited. Based on population pharmacokinetic analyses, there was no difference in the pharmacokinetics of HIBSAGO in chronic hepatitis B (CHB) patients aged ≥65 years compared with those aged 18 to <65 years (see 7.1.4 Geriatrics).

2. Contraindications

HIBSAGO is contraindicated in patients:

- who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition, and Packaging.
- with Child-Pugh A, B or C cirrhosis.
- with platelet count below 100 x 10^9/L prior to initiation of treatment (see 7 Warnings and Precautions).

4. Dosage and Administration

4.1. Dosing Considerations

It is recommended that therapy is prescribed by a healthcare professional experienced in the management of hepatitis.

Healthcare professional should instruct patient to continue taking nucleos(t)ide analogue therapy while receiving HIBSAGO. Refer to the prescribing information of the medicinal product(s) that are administered in conjunction with HIBSAGO.

HIBSAGO is for subcutaneous use only.

The use of HIBSAGO is contraindicated in CHB patients with Child-Pugh A, B or C cirrhosis (see 2 Contraindications, 13 Pharmacokinetics, Hepatic Insufficiency).

Perform the following recommended tests prior to initiating treatment:

- Confirm the baseline HBsAg level ≤3,000 IU/mL.
- Baseline HBV DNA <90 IU/mL.
- Baseline hepatitis B e-antigen (HBeAg) status.
- Alanine transaminase (ALT) and total bilirubin (see **Table 1**, 7 Warnings and Precautions, Hepatic and 7 Warnings and Precautions, Monitoring and Laboratory Tests).
- Platelet count (see **Table 2**, 7 Warnings and Precautions, Hematologic and 7 Warnings and Precautions, Monitoring and Laboratory Tests).
- Urine albumin-creatinine ratio (uACR) and estimated glomerular filtration rate (eGFR) (see 7 Warnings and Precautions, Renal and 7 Warnings and Precautions, Monitoring and Laboratory Tests).

Patients with platelet count below the normal range prior to initiation of treatment

In patients with a platelet count below the normal range, particular care must be taken to exclude cirrhosis before initiating HIBSAGO (see 2 Contraindications).

4.2. Recommended Dose and Dosage Adjustment

HIBSAGO is a finite duration treatment that should be given over a period of 24 weeks.

Weeks 1 and 2

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

Weeks 3 to 24

The recommended dose is 300 mg of HIBSAGO (administered as two 150 mg subcutaneous injections) **once** a week.

Renal Impairment

No dose adjustment is required in patients with mild renal impairment (eGFR 60 to 89 mL/min/1.73m^2) (see 10.3 Pharmacokinetics, Renal Insufficiency). Insufficient data are available in patients with moderate or severe renal impairment (eGFR 15 to 59 mL/min/1.73m^2); therefore, the risks and benefits of HIBSAGO must be considered if used in patients with moderate or severe renal impairment (see 7 Warnings and Precautions).

Adjustments to dose and laboratory test monitoring

Before and during HIBSAGO treatment, laboratory test monitoring is required to detect and manage adverse reactions, with routine monitoring frequency described in **Table 5**, **Table 6**, and **Table 7** (see 7 Warnings and Precautions). Based on laboratory test values, adjustments to HIBSAGO dose and laboratory test monitoring frequency may be required as described in **Table 1**, **Table 2**, and **Table 3**.

Table 1: Adjustments to HIBSAGO dose and ALT and total bilirubin monitoring frequency according to liver laboratory values

ALT and/or total bilirubin	Dose	Monitoring frequency[a]
ALT: ≥12x ULN and	Pause treatment.	Twice weekly until ALT is on a downward trajectory.

ALT and/or total bilirubin	Dose	Monitoring frequency[a]
Total bilirubin: <1.5x ULN	When ALT is <10x ULN, resume treatment at 150 mg once a week. If ALT continues to decline, increase dose to 300 mg once a week.	
ALT: ≥10 to <12x ULN and **Total bilirubin:** <1.5x ULN	No adjustment required.	
ALT: ≥10x ULN for ≥4 weeks **OR** **ALT:** ≥3x ULN and **Total bilirubin:** ≥2x ULN	Permanently discontinue treatment.	
ALT: ≥3x ULN and **Total bilirubin:** 1.5 to <2x ULN	Pause treatment. When ALT is <10x ULN and total bilirubin is <1.5x ULN, resume treatment at 150 mg once a week. If ALT is on a downward trajectory, increase dose to 300 mg once a week.	

[a] For routine monitoring frequency, see **Table 5**.

Table 2: Adjustments to HIBSAGO dose and platelet monitoring frequency according to platelet count

Platelet count (x 10^9/L)[a]	Dose	Monitoring frequency[b]
100 to <140	No adjustment required.	Weekly
75 to <100	Pause treatment. When platelet count is ≥100 x 10^9/L, resume treatment at 300 mg once a week.	Weekly
50 to <75		Every 2-3 days until 3 consecutive platelet counts are ≥75 x 10^9/L
25 to <50	Permanently discontinue treatment and consider administering corticosteroids.	Every 2-3 days until 3 consecutive platelet counts are ≥75 x 10^9/L
<25		Daily until 2 consecutive platelet counts are ≥25 x 10^9/L

[a] Even if platelet count is ≥100 x 10^9/L, if platelet count decreases by ≥30% between consecutive readings, a platelet count must be repeated and reviewed before administering further doses of HIBSAGO.
[b] For routine monitoring frequency, see **Table 6**.

Table 3: Adjustments to HIBSAGO dose and urine albumin-creatinine ratio (uACR) and estimated glomerular filtration rate (eGFR) monitoring frequency according to renal laboratory values

uACR and/or eGFR	Dose	Monitoring frequency[a]
eGFR: reduced by >30%, from pretreatment level, for ≥2 consecutive readings	Pause treatment. When eGFR increases to within 15% of pretreatment levels, resume treatment at 300 mg once a week.	Weekly until eGFR and uACR stabilise or return to pretreatment levels.
uACR: ≥500 to <2000 mg/g	Pause treatment. When uACR is <500 mg/g, or if alternative cause identified, resume treatment at 300 mg once a week.	
uACR: ≥2000 mg/g	Pause treatment. If alternative cause is identified, resume treatment at 300 mg once a week. If alternative cause cannot be identified, permanently discontinue treatment.	

[a] For routine monitoring frequency, see **Table 7**.

4.4. Administration

After proper training in subcutaneous injection, a patient or a caregiver may subcutaneously administer HIBSAGO if their healthcare professional determines that it is appropriate (see Instructions for Use).

Ensure HIBSAGO has been at room temperature (below 30°C) for a minimum of 30 minutes before administration (see 11 Storage, Stability, and Disposal and Instructions for Use). Each 300 mg dose is administered as two 150 mg subcutaneous injections into the abdomen, thigh, or if administered by a caregiver or healthcare professional, the upper arm.

To receive the full 300 mg dose, both syringes must be administered, one immediately after the other. Two different anatomical sites can be used for each of the two injections. Alternatively, the same anatomical site can be used as long as the two injection sites are separated by at least 5 cm (2 inches).

For a 150 mg dose, one syringe must be administered.

Never give injections into areas where the skin is tender, bruised, red or hard. Rotation of injection sites is recommended to reduce the risk of injection site reactions (ISRs). Where possible, give each dose on the same day(s) each week for 24 weeks.

On completion of 24 weeks of treatment

- Stop HIBSAGO after completing 24 weeks of treatment.
- Continue nucleos(t)ide analogue therapy for an additional 24 weeks.
- Following the 24 weeks of further nucleos(t)ide analogue treatment, stop all hepatitis B-directed therapy provided the patient meets these criteria:
    - HBeAg negative (hepatitis B e-antigen).

- HBV DNA <LLOQ (less than 20 IU/mL).
- HBsAg not detectable (less than 0.05 IU/mL).
- ALT values ≤2xULN (alanine transaminase less than or equal to twice the upper limit of normal) (see 7 Warnings and Precautions).

Early On-treatment Response and Functional Cure

An early treatment response to HIBSAGO is defined using the following criteria:

- Patients with baseline HBsAg ≤1,000 IU/mL: HBsAg <1 IU/mL at Week 12.
- Patients with baseline HBsAg >1,000 IU/mL: HBsAg <0.05 IU/mL at Week 12.

HIBSAGO treatment duration is 24 weeks regardless of achievement of the early on-treatment response criteria. Week 12 HBsAg response has been evaluated as a potential predictor of subsequent functional cure in a post-hoc analysis (see 14 Clinical Trials). Results should be interpreted in conjunction with individual patient characteristics and clinical judgement.

4.5. Missed Dose

If a dose of HIBSAGO is missed, then 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.

5. Overdose

Single doses of 600 mg (2 times the recommended dose) were administered subcutaneously in a clinical trial to 5 healthy adults. Two participants developed tolerability issues at this dose, with symptoms including headache, nausea, vomiting, myalgia and dizziness which lasted 24 to 48 hours despite symptomatic treatment.

There is no specific treatment for an overdose of HIBSAGO. If overdose occurs, the patient is to be treated supportively with appropriate monitoring.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 4: Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength / Composition	Non-Medicinal Ingredients
Subcutaneous Use	Solution, 150 mg/mL bepirovirsen (as bepirovirsen sodium) in a single-use pre-filled syringe	hydrochloric acid, sodium hydroxide, water for injection

Description

HIBSAGO is a clear, colourless to yellow solution that is free of particles, with a pH of approximately 8, available in a single-use, pre-filled syringe pre-assembled with a safety syringe device and a chlorobutyl elastomeric plunger stopper.

HIBSAGO is available in a carton containing two pre-filled syringes. Each pre-filled syringe delivers 150 mg bepirovirsen (as bepirovirsen sodium) in 1 mL (150 mg/mL).

7. Warnings and Precautions

General

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

Co-infections

Human Immunodeficiency Virus (HIV)

It is recommended that patients who are taking nucleos(t)ide analogue therapy for HIV and HBV are instructed not to stop taking the nucleos(t)ide analogue therapy unless a HIV healthcare professional has directed them to do so.

Hepatitis D

There are no data on the safety and efficacy of HIBSAGO in CHB patients co-infected with hepatitis D virus. HIBSAGO is not recommended in co-infected patients because of the potential for an exacerbated risk of clinically relevant ALT increases.

Hepatitis C

Compared with patients with HBV infection alone, patients with chronic hepatitis B and hepatitis C co-infection may present with higher ALT levels. No clinical trial data are available for this population because patients with HBV/HCV co-infection were excluded from the clinical studies.

Driving and Operating Machinery

There have been no studies to investigate the effect of HIBSAGO on the ability to perform tasks that require judgement, motor or cognitive skills. A detrimental effect on such activities would not be anticipated from the pharmacology of HIBSAGO. The clinical status of the patient and the adverse event profile of HIBSAGO should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills.

Hematologic

Patients with platelet count below the normal range prior to initiation of treatment

In patients with a platelet count below the normal range, particular care must be taken to exclude cirrhosis before initiating HIBSAGO (see 2 Contraindications).

Platelet count decreases and thrombocytopenia

HIBSAGO is associated with reductions in platelet count (see 8 Adverse Reactions). Platelet counts typically return to pretreatment levels after treatment with HIBSAGO has been completed, paused or permanently discontinued (see 7 Warnings and Precautions, Monitoring and Laboratory Tests).

It is recommended that patients are instructed to report to their healthcare professional immediately if they experience any signs of unusual or prolonged bleeding, or any symptoms of bleeding in the brain. If a patient develops signs or symptoms of thrombocytopenia, HIBSAGO treatment must be paused and a platelet count obtained as soon as possible (see **Table 2**).

The risks and benefits of HIBSAGO must be considered when treating patients who may be particularly susceptible to bleeding, e.g. elderly patients, or patients with bleeding diathesis/ coagulopathy, history of major bleeding events or patients taking antiplatelets, anticoagulants, or medicinal products that lower platelet count (see 9 Drug Interactions).

Hepatic/Biliary/Pancreatic

Alanine aminotransferase (ALT) increases

During HIBSAGO treatment, transient increases in ALT ≥3 x ULN have been observed in clinical studies (see 8 Adverse Reactions). Most increases occurred in the first 12 weeks of treatment, typically between Weeks 5 and 10, and were temporally associated with a preceding or concurrent decline in HBsAg. Most events resolved or began to resolve within approximately 2 weeks, were not associated with clinical signs or symptoms of hepatic dysfunction, and were not accompanied by increases in total bilirubin. Most events were managed without permanent treatment discontinuation; however, some patients required additional monitoring, temporary treatment interruption, or permanent discontinuation in accordance with protocol-defined hepatic stopping criteria (see 7 Warnings and Precautions, Monitoring and Laboratory Tests and 8.4 Abnormal Laboratory Findings, ALT Increased).

Immune

Inflammatory and Immune Effects

In HIBSAGO studies, influenza-like symptoms (see 8 Adverse Reactions) and laboratory test changes (e.g. decreases in complement factor C3 and C4) were observed. Events consistent with immune complex-mediated inflammation were also observed. These events included dermatological effects (purpuric leg rashes, cutaneous leukocytoclastic vasculitis, dermatitis, pruritus/erythematous plaque) and rheumatological effects (polyarthralgia). In addition, serious inflammatory and immune adverse reactions have been reported, including immune thrombocytopenia, auto-immune haemolytic anaemia and systemic inflammatory response syndrome and a cryoglobulinaemic flare.

The risks and benefits of HIBSAGO must be considered when treating patients that may be more susceptible to inflammatory and/or immune effects, e.g. solid organ transplant recipients, patients with autoimmune hepatitis, or patients with a history of vasculitis or conditions associated with vasculitis (e.g. systemic lupus erythematosus, cryoglobulinemia, or rheumatoid arthritis). The risks and benefits of HIBSAGO must also be considered in patients with a history of, or suspected, extrahepatic disorders related to HBV immune-mediated effects (including but not limited to nephrotic syndrome or any type of glomerulonephritis).

If signs and symptoms suggestive of vasculitis/immune-associated events occur, and no alternative cause is identified, permanently discontinue HIBSAGO treatment.

Monitoring and Laboratory Tests

ALT and Total Bilirubin

ALT and total bilirubin must be measured prior to initiation of treatment and according to the monitoring schedule in **Table 5**.

Table 5: Schedule for ALT and total bilirubin monitoring

Week	Monitoring schedule
2 to 24	Weekly: Weeks 2 to 12 Every other week: Weeks >12 to 24
>24	Weeks 28, 36 and 48

Recommendations for adjustments to HIBSAGO dose and ALT and total bilirubin monitoring frequency, are specified in **Table 1** (see 4 Dosage and Administration).

Platelet Count

Platelet count must be measured prior to initiation of treatment (see 2 Contraindications) and according to the monitoring schedule in **Table 6**.

Table 6: Schedule for platelet count monitoring

Week	Monitoring schedule
2 to 24	Every other week
>24	Week 28

Recommendations for adjustments to HIBSAGO dose and platelet count monitoring frequency, are specified in **Table 2** (see 4 Dosage and Administration).

eGFR, Urine Protein and uACR

eGFR and uACR must be measured prior to initiation of treatment. Once treatment commences, monitor eGFR, and urine protein by dipstick, according to the schedule in **Table 7**.

Table 7: Schedule for eGFR and urine protein monitoring

Week	Monitoring schedule
2 to 24	Every other week (eGFR) Every 4 weeks (urine protein)
>24	Weeks 28 and 36

If urine protein dipstick is abnormal, a uACR test must be performed. Recommendations for adjustments to HIBSAGO dose as well as eGFR and uACR monitoring frequency, are specified in **Table 3** (see 4 Dosage and Administration). Early initiation of immunosuppressive therapy must be considered if a diagnosis of glomerulonephritis is suspected or confirmed.

Renal

Renal toxicity has been observed after administration of antisense oligonucleotides (ASOs) and declines in eGFR have been observed during HIBSAGO treatment (see 8 Adverse Reactions). eGFR typically returns to pretreatment levels after treatment with HIBSAGO is completed or paused (see 7 Warnings and Precautions, Monitoring and Laboratory Tests).

The risks and benefits of HIBSAGO must be considered when treating patients at increased risk of renal toxicity (see 4 Dosage and Administration, and 9 Drug Interactions).

Reproductive Health

- **Fertility**

  There are no data on the effects of HIBSAGO on human fertility. No effects of HIBSAGO on male or female fertility have been observed in animal studies (see 16 Non-Clinical Toxicology).

7.1. Special Populations

7.1.1. Pregnancy

There are insufficient data on the use of HIBSAGO in pregnant women. There was no evidence of embryo-foetal harm or adverse pregnancy outcomes in animal studies at clinically relevant exposures (see 16 Non-Clinical Toxicology).

HIBSAGO should not be used during pregnancy unless the expected benefits to the mother outweigh the potential risks to the foetus.

7.1.2. Breastfeeding

There are insufficient data on the presence of HIBSAGO in human milk. HIBSAGO was present in the milk of lactating mice without an effect on offspring (see 16 Non-Clinical Toxicology).

A decision must be made whether to discontinue breast-feeding or to discontinue from HIBSAGO therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

7.1.3. Pediatrics

The safety and efficacy of HIBSAGO have not been established in patients less than 18 years of age.

7.1.4. Geriatrics

No age-based dose adjustment is required in patients aged 65 years and older (see 10.3 Pharmacokinetics, Geriatrics).

8. Adverse Reactions

8.1. Adverse Reaction Overview

The safety of HIBSAGO in the treatment of chronic HBV infection has been evaluated across a clinical program including two pooled, Phase 3, placebo-controlled randomized trials (B-Well 1 and B-Well 2) in which 1,223 HIBSAGO-treated patients who received at least one subcutaneous dose of HIBSAGO (300

mg, twice weekly during Weeks 1 and 2, followed by once weekly during Weeks 3 to 24), while 611 patients received matching placebo.

During the first 24 weeks, the most commonly reported adverse reactions (≥10%) with HIBSAGO included injection site reactions, ALT increased, pyrexia, platelet count decreased, and AST increased. Serious adverse events were reported in 4% of patients with HIBSAGO compared to 1% in placebo. No treatment-related deaths were reported. Permanent treatment discontinuation due to AEs occurred in 3% of patients treated with HIBSAGO. The most common adverse reactions leading to treatment discontinuation were injection site erythema and occurred in <1% (5/1,223) of patients receiving HIBSAGO in the primary safety population.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

The incidence of adverse reactions in the pooled safety data set in the primary safety population (Weeks 1 to 36) with HIBSAGO is shown in **Table 8**.

Table 8: Adverse Reactions Reported in ≥2% of Patients Treated with HIBSAGO in B-Well 1 and B-Well 2 Trials (Weeks 1 to 36)

System organ class/preferred term	HIBSAGO (bepirovirsen) n = 1,223 (%)	Placebo n = 611 (%)
General Disorders and Administration Site Conditions		
Injection site reactions	651 (53)	84 (14)
Pyrexia	242 (20)	22 (4)
Fatigue	115 (9)	31 (5)
Injection site discoloration	101 (8)	3 (<1)
Asthenia	58 (5)	6 (<1)
Chills	30 (2)	3 (<1)
Malaise	30 (2)	9 (1)
Hepatobiliary Disorders		
Alanine aminotransferase (ALT) increased	270 (22)	19 (3)
Aspartate aminotransferase (AST) increased	184 (15)	8 (1)
Blood and lymphatic system disorders		
Platelet count decreased	185 (15)	7 (1)
Thrombocytopenia	101 (8)	10 (2)
Neutrophil count decreased[b]	31 (3)	4 (<1)

System organ class/preferred term	HIBSAGO (bepirovirsen) n = 1,223 (%)	Placebo n = 611 (%)
White blood cell count decreased[b]	37 (3)	4 (<1)
Musculoskeletal and connective tissue disorders		
Myalgia	97 (8)	22 (4)
Renal and urinary disorders		
Glomerular filtration rate decreased	67 (5)	14 (2)
Skin and subcutaneous tissue disorders		
Pruritus	60 (5)	14 (2)
Rash	42 (3)	5 (<1)
Gastrointestinal disorders		
Nausea	43 (4)	10 (2)
Vomiting	28 (2)	8 (1)

[a] 300 mg, twice weekly during Weeks 1 and 2, and once weekly during Weeks 3 to 24.
[b] Not associated with events suggestive of increased risk of infection and did not require medical intervention.

Injection Site Reactions (ISRs)

ISRs were the most common adverse reactions in HIBSAGO clinical program (652/1223 [53%] vs. 84/611 [14%] in placebo) including injection site erythema, injection site pain, and injection site pruritus. The frequency of ISRs reduced over time and the majority were mild to moderate. No serious ISRs were observed. There were 9 (<1%) patients who withdrew from HIBSAGO dosing due to ISR. Eight of the 9 were in the first 12 weeks.

8.3. Less Common Clinical Trial Adverse Reactions

Adverse Reactions Occurring in Less than 2% of Patients Receiving HIBSAGO in the Phase 3 Trial:

Blood and lymphatic system disorders: Neutropenia, leukopenia

Immune system disorders: Hypersensitivity

Skin and subcutaneous tissue disorders: Cutaneous vasculitis

Cutaneous Vasculitis

Cutaneous vasculitis occurred in <1% of patients, and was reversible on withdrawal of bepirovirsen treatment. Less than 1% of patients permanently discontinued treatment because of cutaneous vasculitis, which could have presented as dermatological effects (purpuric leg rashes, cutaneous leukocytoclastic vasculitis, dermatitis, pruritus/erythematous plaque) or rheumatological effects (polyarthralgia). Cases generally occurred early during treatment and presented with purpuric rash with or without arthralgia. In some cases, biopsy findings were consistent with leukocytoclastic vasculitis. Events resolved following treatment discontinuation and appropriate medical management, including corticosteroid therapy.

8.4. Abnormal Laboratory Findings

Laboratory Abnormalities are presented in **Table 9**.

Table 9: Selected Laboratory Abnormalities[a] (Worsened from Baseline) Reported in Patients in B-Well 1 and B-Well 2 Trials (Weeks 1-36)

Laboratory Categories	HIBSAGO N = 1,223	Placebo N = 611
ALT		
≥3xULN to <5xULN	10%	<1%
≥5xULN to <10xULN	8%	0
≥10xULN to <20xULN	4%	0
≥20xULN	2%	<1%
AST		
≥3xULN to <5xULN	6%	<1%
≥5xULN to <10xULN	4%	<1%
≥10xULN to <20xULN	1%	<1%
≥20xULN	<1%	0
Total bilirubin		
≥ULN to <1.5xULN	8%	11%
≥1.5xULN to <2xULN	2%	2%
≥2xULN	<1%	<1%
Platelets ($x10^9$/L)		
≥100 to <140	37%	7%
≥75 to <100	8%	<1%
≥50 to <75	2%	<1%
≥25 to <50	<1%	0
<25	<1%	0
ANC cells/mm^3		
≥500 to <1,000	8%	3%
≥100 to <500	1%	<1%
<100	0	0
eGFR		
≥15 to <30% decline from baseline	51%	30%
≥30 to <50% decline from baseline	17%	6%

Laboratory Categories	HIBSAGO N = 1,223	Placebo N = 611
≥50% decline from baseline	1%	<1%
uACR		
≥300 mg/g	2%	1%

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ANC = absolute neutrophil count; eGFR = estimated glomerular filtration rate; uACR = urine albumin-to-creatinine ratio, ULN = upper limit of normal.
Note: Each patient is only counted once per parameter with the laboratory value that represents their largest change from baseline in Weeks 1-36.
Note: Japanese Society of Nephrology-Chronic Kidney Disease Initiatives (JSN-CKDI) equation was used to calculate eGFR for Japanese patients.
[a] Information based on laboratory values reported from the central laboratory for B-Well 1 and B-Well 2 (local laboratory results were not included).

ALT Increased

During the first 24 weeks of treatment with HIBSAGO, 24% of patients developed ALT elevations ≥3x ULN, and 6% had ALT elevations ≥10x ULN. Less than 1% (n = 1) of HIBSAGO recipients had ALT ≥3x ULN with bilirubin ≥2x ULN (>35% direct bilirubin) and permanently discontinued treatment. Three other patients also permanently discontinued treatment because of ALT ≥10 x ULN for 4 or more weeks. No events met the criteria for drug induced liver injury (see 7 Warnings and Precautions).

Thrombocytopenia and Platelet Count Decreases

In patients treated with HIBSAGO, during the first 24 weeks, decline in platelet count was mostly of Grade 1 or 2 severity. 1% had platelet counts <75 x 10^9/L (Grade 2) and <1% (n = 2) had platelet counts <50 x 10^9/L (≥Grade 3); one of whom developed platelet counts <25 x 10^9/L (Grade 4). This patient was assessed as having developed immune thrombocytopenia based on the rapid decline in platelet count from one week to the next and the fast recovery of platelet count upon permanent discontinuation of HIBSAGO and initiation of corticosteroid treatment (see 7 Warnings and Precautions).

eGFR Decreased

During the first 24 weeks, in patients treated with HIBSAGO, 4% had an eGFR decrease >30% of pretreatment levels for 2 or more consecutive readings and <1% (one patient) experienced such declines more than 24 weeks after completion of HIBSAGO treatment (see 7 Warnings and Precautions).

9. Drug Interactions

9.2. Drug Interactions Overview

HIBSAGO is primarily metabolized by nucleases and not by cytochrome P450 (CYP450) system. HIBSAGO was not a substrate or inducer of major CYP450 enzymes or drug transporters *in vitro*. HIBSAGO was not an inhibitor of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5 or UGT enzymes, nor an inhibitor of transporters MATE1, MATE2-K, OAT3, OATP1B1, OATP1B3, OCT2, OAT1, and OCT1 *in vitro*. HIBSAGO inhibited CYP2C8 (IC_{50} > 100 µM) and MRP2 (IC_{50} of 8.49 µM) *in vitro*, however, clinically relevant drug interactions are not expected based on model risk assessments. No formal clinical drug interaction studies have been conducted with HIBSAGO.

9.3. Drug-Behaviour Interactions

The interaction of HIBSAGO with individual behavioural risks has not been studied.

9.4. Drug-Drug Interactions

As HIBSAGO is not a substrate, inducer or inhibitor of major cytochrome P450 (CYP) enzymes, or drug transporters, clinically relevant pharmacokinetic interactions are not expected and subsequently there are no established or potential drug-drug interactions.

Anticoagulants, antiplatelets and medicinal products that decrease platelet count

Due to the risk of thrombocytopenia, consider the risks and benefits of HIBSAGO when used concomitantly with anticoagulants, antiplatelets or medicinal products that decrease platelet count, such as acetylsalicylic acid, clopidogrel, warfarin, direct oral anticoagulants (e.g. apixaban, dabigatran) and heparin (see 7 Warnings and Precautions and 8 Adverse Reactions).

Medicinal products that impair renal function

The risks and benefits of HIBSAGO must be considered when HIBSAGO is used concomitantly with medicinal products that may impair renal function, e.g. acetylsalicylic acid and other non-steroidal anti-inflammatory drugs, diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aminoglycosides, vancomycin, beta-lactams, cephalosporins quinolones, acyclovir, ganciclovir, tenofovir disoproxil or adefovir (see 7 Warnings and Precautions and 8 Adverse Reactions).

Peginterferon alfa

There are no data on the safety and efficacy of HIBSAGO co-administration with peginterferon alfa. Concomitant use of HIBSAGO and peginterferon alfa is not recommended due to the potential for an exacerbated risk of increased ALT, decreased platelet count and immune-mediated effects.

Nucleos(t)ide analogue

In clinical studies, concomitant administration of HIBSAGO with nucleos(t)ide analogue did not result in changes in HIBSAGO exposure. In addition, HIBSAGO did not impact the exposure of nucleos(t)ide analogues (such as entecavir, tenofovir disoproxil fumarate, tenofovir alafenamide fumarate, lamivudine, emtricitabine, and adefovir).

9.5. Drug-Food Interactions

Not applicable as the drug is administered subcutaneously.

9.6. Drug-Herb Interactions

Not applicable as the drug is administered subcutaneously.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

HIBSAGO (bepirovirsen) is a chimeric 2'-methoxyethyl-modified phosphorothioate antisense oligonucleotide (ASO) with antiviral activity. It is designed to bind to a conserved 20-nucleotide sequence present in HBV messenger RNAs, including pregenomic RNA, resulting in ribonuclease H-mediated degradation of these transcripts and a reduction in HBV DNA and viral proteins, including HBsAg. Bepirovirsen also has innate immunostimulatory activity which may contribute to its therapeutic effect.

Immunostimulant activity

In non-clinical studies, bepirovirsen has demonstrated innate immune activities, potentially via toll-like receptor 8 (TLR8) among other pattern recognition receptors. Activation of the TLR8 pathway by bepirovirsen was shown in an *in vitro* TLR8 overexpressing reporter cell line and *in vivo* human TLR8 knock-in- (hTLR8-KI) mice. Increased cytokine expression upon bepirovirsen treatment was mainly localised to non-parenchymal cells in the liver of hTLR8-KI mice.

In clinical studies, administration of bepirovirsen was associated with activation of innate and adaptive immune pathways, including increased expression of cytokines and chemokines such as interleukin-12 (IL-12), tumour necrosis factor (TNF), interferon gamma (IFN-gamma) and CXC motif chemokine ligand 9 and 10 (CXCL9, CXCL10). Bepirovirsen treatment also increased total IgM suggesting a stimulatory effect on B cells. In addition, immunophenotypic changes in peripheral immune cell populations were observed, including increases in Ki67 positive B and T cells, and increases in frequency of granzyme B positive CD8 T cells. Some of these responses generally appeared to be more prominent among patients with greater HBsAg reductions.

10.2. Pharmacodynamics

See 15 Microbiology for information on Antiviral Activity and Resistance.

Cardiac Electrophysiology

The effect of bepirovirsen at doses up to 600 mg on the QTc interval was evaluated in a Phase 1, randomised, placebo-controlled, double-blind, parallel group QT study in 46 healthy subjects. Subjects received a single subcutaneous administration of placebo or a supratherapeutic dose of bepirovirsen (450 or 600 mg). Bepirovirsen administration did not have a clinically meaningful effect on the QTc interval.

10.3. Pharmacokinetics

The pharmacokinetic parameters of bepirovirsen are shown in **Table 10**, derived from observed pharmacokinetic data and population pharmacokinetics (PK) analyses.

Table 10: Summary of bepirovirsen pharmacokinetic parameters

C_{max}, ss	T_{max}	$t_{½}$	$AUC_{(0\text{-}tau)}$,ss	CL/F	Vd/F
9.14 mcg/mL	3 hours (2 – 5 hours)	29 days	102 h*mcg/mL	2.99 L/h	70.9 L

C_{max}, ss – Maximum concentration at steady-state

T_{max} – Time of occurrence of C_{max}
T½ – Terminal phase half-life
$AUC_{(0\text{-}tau)}$, ss – Area under the concentration-time curve over the dosing interval, at steady-state
CL/F – Apparent clearance
Vd /F – Apparent volume of distribution

HBV infection status (healthy participants vs CHB patients) was evaluated as a covariate in the population PK model and was not identified as a covariate on bepirovirsen PK, indicating that PK bepirovirsen PK are similar in healthy participants and CHB patients.

Absorption

Following subcutaneous administration of 300 mg bepirovirsen to CHB patients, the median time to maximum plasma concentrations (T_{max}) was 3 hours. Following weekly dosing, the mean steady-state maximum plasma concentration (C_{max}) was 9.14 mcg/mL, area under the concentration-time curve over the dosing interval ($AUC_{(0\text{-}tau)}$) was 102 mcg*h/mL and pre-dose (trough) concentration (C_{trough}) at the end of the dosing interval was 0.022 mcg/mL. Following multiple dose administration, bepirovirsen exposure increased proportionally over the 150 mg to 300 mg dose range.

Distribution

Bepirovirsen was highly bound to human plasma protein (≥95%), with a higher fraction bound at lower concentrations. The typical apparent volume of distribution estimated from population PK analyses was 70.9 L.

Metabolism

Bepirovirsen is not a substrate for CYP-mediated metabolism and is metabolised in tissues by endonucleases to form shorter oligonucleotides that are then substrates for additional metabolism by exonucleases.

Elimination

Bepirovirsen is eliminated by metabolism in the tissue and renal elimination of chain shortened fragments. Following subcutaneous administration, the terminal elimination half-life was approximately 29 days, and based on population pharmacokinetic analyses, the typical apparent clearance (CL/F) was 2.99 L/h.

Based on population PK analyses, development of anti-drug antibodies (ADAs) was associated with a 26.6% reduction in CL/F (see 10.4 Immunogenicity).

Special populations and conditions

Based on population pharmacokinetic analyses, following subcutaneous administration, there were no clinically meaningful changes in the pharmacokinetics of bepirovirsen by race, ethnicity, sex, body weight, ADA status, baseline HBsAg level, HBV genotype, or injection site location.

- **Pediatrics:**

  The pharmacokinetics of bepirovirsen in patients less than 18 years of age have not been studied.

- **Geriatrics:**

  Based on population pharmacokinetic analyses, there was no difference in the pharmacokinetics of bepirovirsen in CHB patients aged ≥65 years compared with those aged 18 to <65 years.

- **Hepatic Insufficiency:**

  CHB patients: The pharmacokinetics of bepirovirsen have not been evaluated in patients with Child-Pugh A, B or C cirrhosis (see 2 Contraindications).

  Non-CHB individuals: No difference in pharmacokinetic parameters of bepirovirsen is expected in individuals with mild hepatic impairment compared to individuals with normal hepatic function. There was a 33% reduction in C_{max} and a 31% reduction in area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time ($AUC_{(0-\infty)}$) in individuals with moderate hepatic impairment compared to individuals with normal hepatic function.

- **Renal Insufficiency:** Based on population PK analysis, bepirovirsen pharmacokinetics were similar between CHB patients with eGFR 60 to 89 mL/min/1.73m^2 compared to those with eGFR ≥90 mL/min/1.73 m^2. Insufficient data are available in patients with moderate or severe renal impairment (eGFR 15 to 59/min/1.73m^2).

10.4. Immunogenicity

In the Phase 3 B-Well studies, 43% (517/1203) of bepirovirsen-treated patients tested positive for ADAs. There was no evidence of an association of ADAs with any impact on the safety or efficacy (see 10.3 Pharmacokinetics).

11. Storage, Stability, and Disposal

Prior to dispensing: Store in a refrigerator (2°C to 8°C). Do not freeze. Store in the original carton to protect from light. Do not shake.

After dispensing: Store at room temperature (below 30°C). Do not freeze. Store in the original carton to protect from light. Do not shake. Discard if the expiry date has passed, or it has been 12 weeks since carton was received, whichever comes first.

Each pre-filled syringe must be administered within 6 hours once removed from the carton. Discard if not administered within 6 hours.

12. Special Handling Instructions

Any unused medicinal product or waste material must be disposed of in accordance with local requirements.

Part 2: Scientific Information

13. Pharmaceutical Information

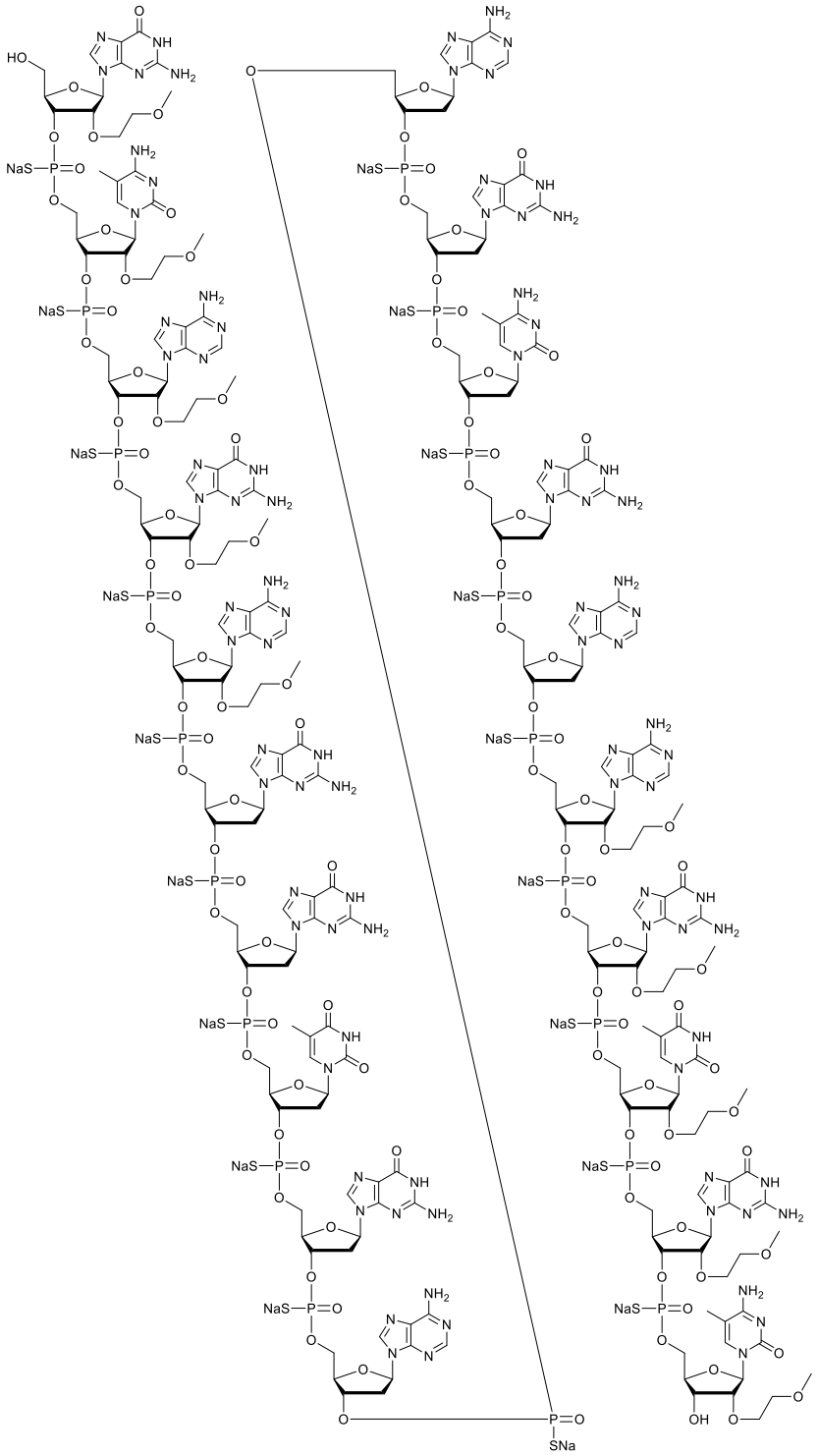
Drug Substance

Non-proprietary name of the drug substance: bepirovirsen sodium

Chemical name: *all-P-ambo*-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-O-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-O-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methylcytidine, nonadeca sodium salt.

Molecular formula and molecular mass: $C_{230}H_{290}N_{88}Na_{19}O_{115}P_{19}S_{19}$ and 7761.89 Da

Structural formula:



Physicochemical properties: Bepirovirsen sodium is a white to yellow solid, freely soluble in water, phosphate buffered saline, artificial interstitial fluid, and aqueous sodium hydroxide, but insoluble in ethanol and isopropyl alcohol.

14. Clinical Trials

14.1. Clinical Trials by Indication

Functional cure of chronic hepatitis B virus (HBV) infection (without cirrhosis)

Table 11: Summary of Trial Designs of Phase 3 Pivotal Clinical Trials in Chronic Hepatitis B Infected Patients

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age (range)	Sex
202009 (B-Well 1)	Phase 3, multicenter, randomized, Double-Blind, Placebo-Controlled	300 mg Subcutaneous (SC) Twice weekly on Weeks 1 and 2, and once weekly on Weeks 3 to 24	Study arm: 653 Placebo: 328	21-87 years	Female: 293 Male: 688
219288 (B-Well 2)	Phase 3 Multicenter, Randomized, Double-Blind; Placebo-Controlled	300 mg Subcutaneous (SC) Twice weekly on Weeks 1 and 2, and once weekly on Weeks 3 to 24	Study arm: 571 Placebo: 286	22-79 years	Female: 241 Male: 616

The efficacy and safety of HIBSAGO in the treatment of chronic HBV infection were evaluated in two identically designed multicentre, Phase 3, randomised, double-blind, placebo-controlled studies (B-Well 1 [study 202009] and B-Well 2 [study 219288]). All patients were aged ≥18 years, had documented chronic HBV infection for ≥6 months, were receiving stable nucleos(t)ide analogue therapy (defined as no changes due to loss of virologic control for ≥6 months before the start of the study and no plans for changes over the duration of the study), and had serum HBsAg >100 to ≤3,000 IU/mL. Patients were excluded from the study if they had a history, suspicion or evidence of cirrhosis.

Patients were randomised 2:1 to receive 24 weeks of HIBSAGO (300 mg, twice weekly on Weeks 1 and 2, and once weekly on Weeks 3 to 24), or placebo, together with their background nucleos(t)ide analogue therapy. From Week 25 to 48, patients continued to receive their nucleos(t)ide analogue therapy without HIBSAGO or placebo.

At Week 48, eligible patients discontinued nucleos(t)ide analogue therapy. To be eligible for nucleos(t)ide analogue cessation, patients had to demonstrate an absence of cirrhosis at Week 36, HBV DNA <LLOQ and undetectable HBsAg from Week 24 to 46, and HBeAg-negative status with ALT values ≤2x ULN at Week 46. Additionally, they must have remained on stable nucleos(t)ide analogue therapy for the preceding 48 weeks.

At Week 72, twenty-four weeks after cessation of nucleos(t)ide analogue treatment, the primary endpoint assessed patients with baseline HBsAg ≤3,000 IU/mL achieving functional cure, and a key secondary endpoint assessed patients with baseline HBsAg ≤1,000 IU/mL achieving functional cure.

Functional cure was defined as sustained suppression (24 weeks or longer) of HBV DNA (<LLOQ) and HBsAg not detected, with or without hepatitis B surface antibodies, after a finite duration of therapy and off all HBV treatment. At Week 96, forty-eight weeks after cessation of nucleos(t)ide analogue treatment, patients continued to be monitored to evaluate the long-term durability of functional cure.

Baseline demographics in both studies were similar across study arms (see **Table 12**).

Table 12: Summary of baseline demographics in the full analysis set[a]

	B-Well 1		**B-Well 2**	
	HIBSAGO (N=650)	Placebo (N=328)	HIBSAGO (N=570)	Placebo (N=286)
Male, n (%)	458 (70)	227 (69)	414 (73)	202 (71)
Mean age (standard deviation)	50.2 (11.8)	49.2 (10.6)	48.7 (10.4)	49.2 (11.4)
Race, n (%)				
Asian	438 (67)	229 (70)	387 (68)	195 (68)
White	167 (26)	78 (24)	149 (26)	78 (27)
Black or African American	31 (5)	18 (5)	25 (4)	11 (4)
HBV genotype, n (%)				
A	70 (11)	24 (7)	56 (10)	39 (14)
B	164 (25)	80 (24)	144 (25)	74 (26)
C	195 (30)	105 (32)	181 (32)	93 (33)
D	163 (25)	94 (29)	155 (27)	62 (22)
E	13 (2)	6 (2)	6 (1)	6 (2)
F, G, H, I, or J	10 (1.5)	2 (<1)	0	1 (<1)
Other[b]	33 (5)	16 (5)	20 (4)	6 (2)
Missing[c]	2 (<1)	1 (<1)	8 (1)	5 (2)
HBeAg negative, n (%)	595 (92)	300 (91)	527 (92)	260 (91)
Serum HBsAg ≤1,000 IU/mL, n (%)	426 (66)	214 (65)	342 (60)	179 (63)
Serum ALT (IU/L) ≤ULN, n (%)	596 (92)	296 (90)	534 (94)	263 (92)
Background Nucleos(t)ide Analogue Therapy				
Entecavir	259 (40)	139 (42)	249 (44)	116 (41)
Tenofovir disoproxil fumarate	218 (34)	106 (32)	166 (29)	86 (30)
Tenofovir alafenamide fumarate	154 (24)	81 (25)	132 (23)	74 (26)

[a] Full analysis set, defined as all patients randomised who received at least one dose of HIBSAGO or placebo. Of note, 3 patients in B-Well 1, and 1 patient in B-Well 2 were randomised into the HIBSAGO group but did not receive HIBSAGO.

[b] Genotype results undetermined/unclassified and mixed genotypes.
[c] Genotype not evaluated/results not available.

Study Results

Within both studies, at Week 72 (twenty-four weeks after cessation of nucleos(t)ide treatment), the proportion of patients achieving a functional cure following HIBSAGO was statistically significantly superior to placebo, in patients with baseline HBsAg ≤3,000 IU/mL, and in patients with baseline HBsAg ≤1,000 IU/mL. **Table 13** and **Table 14** provide data for patients achieving functional cure and sustained suppression of HBV DNA, respectively.

Pooled Analysis

At Week 48, 295 of 1,220 (24%) HIBSAGO-treated patients discontinued nucleos(t)ide analogue therapy due to fulfilment of the criteria for nucleos(t)ide analogue discontinuation. No placebo-treated patients were eligible for nucleos(t)ide analogue cessation. An additional 13 HIBSAGO-treated patients were eligible for nucleos(t)ide analogue cessation but remained on nucleos(t)ide analogue therapy by patient or investigator choice. Among the 295 patients who discontinued nucleos(t)ide analogue therapy, 233 (79%) subsequently achieved functional cure at Week 72.

At Week 72 (twenty-four weeks after cessation of nucleos(t)ide treatment), the proportion of patients with baseline HBsAg ≤ 3,000 IU/mL achieving functional cure was 19.1% (233/1,220) following HIBSAGO and 0% (0/614) following placebo. At Week 72, the proportion of patients with baseline HBsAg ≤ 1,000 IU/mL achieving functional cure was 26.0% (200/768) following HIBSAGO and 0% (0/393) following placebo.

Table 13: Functional cure[a] 24 weeks after cessation of nucleos(t)ide treatment in the full analysis set

	B-Well 1		**B-Well 2**		**Pooled B-Well 1 and B-Well 2**	
	HIBSAGO n/N (%)	**Placebo** n/N (%)	**HIBSAGO** n/N (%)	**Placebo** n/N (%)	**HIBSAGO** n/N (%)	**Placebo** n/N (%)
Patients with baseline HBsAg ≤3,000 IU/mL (Primary endpoint)						
Functional cure	127/650 (19.5)	0/328	106/570 (18.6)	0/286	233/1220 (19.1)	0/614
Common risk difference (95% CI[f])	17.5% (14.6%, 20.3%)		13.3% (10.4%, 16.1%)		15.4% (13.4%, 17.4%)	
p-value[e]	<0.001		<0.001		<0.001	
Patients with baseline HBsAg ≤1,000 IU/mL (Key secondary endpoint)[b]						
Functional cure	105/426 (24.6)	0/214	95/342 (27.8)	0/179	200/768 (26.0)	0/393

	B-Well 1		B-Well 2		Pooled B-Well 1 and B-Well 2	
	HIBSAGO n/N (%)	**Placebo** n/N (%)	**HIBSAGO** n/N (%)	**Placebo** n/N (%)	**HIBSAGO** n/N (%)	**Placebo** n/N (%)
Risk Difference within the subgroup (95% CI[d])	24.6% (20.8%, 29.0%)		27.8% (23.3%, 32.8%)		26.2% (23.1%, 29.3%)	
p-value[f]	<0.001		<0.001		<0.001	
Patients with baseline HBsAg >1,000 to ≤3,000 IU/mL						
Functional cure	22/224 (9.8)	0/114	11/228 (4.8)	0/107	33/452 (7.3)	0/221
Risk Difference within the subgroup (95% CI[d])	9.8% (6.4%, 14.4%)		4.8% (1.3%, 8.4%)		7.3% (4.7%, 10.0%)	

[a] Functional cure, defined as sustained suppression (24 weeks or longer) of HBV DNA (<LLOQ) and HBsAg not detected, with or without hepatitis B surface antibodies, after a finite duration of therapy and off all HBV treatment (HIBSAGO/placebo and nucleos(t)ide analogue).
[b] Adjusted for multiple comparisons.
[c] CI: Confidence interval.
[d] Based on two-sided p-value (exact Cochran-Mantel Haenszel).
[e] Based on two-sided p-value (Boschloo's test).
[f] Miettinen-Nurminen common risk difference, a weighted average of the risk differences in the two strata.

Table 14: Sustained suppression of HBV DNA 24 weeks after cessation of nucleos(t)ide treatment in the full analysis set

	B-Well 1		B-Well 2		Pooled B-Well 1 and B-Well 2	
	HIBSAGO n/N (%)	**Placebo** n/N (%)	**HIBSAGO** n/N (%)	**Placebo** n/N (%)	**HIBSAGO** n/N (%)	**Placebo** n/N (%)
Patients with HBsAg ≤3,000 IU/mL (Key secondary endpoint)[a]						
	151/650 (23.2)	0/328	132/570 (23.2)	0/286	283/1220 (23.2)	0/614
Common risk difference (95% CI)[d]	21.0% (17.9%, 24.0%)		18.2% (15.1%, 21.3%)		19.6% (17.4%, 21.8%)	
p-value[b]	<0.001		<0.001		<0.001	

	B-Well 1		B-Well 2		Pooled B-Well 1 and B-Well 2	
	HIBSAGO n/N (%)	**Placebo** n/N (%)	**HIBSAGO** n/N (%)	**Placebo** n/N (%)	**HIBSAGO** n/N (%)	**Placebo** n/N (%)
Patients with HBsAg ≤1,000 IU/mL (Key secondary endpoint)[a]						
	124/426 (29.1)	0/214	113/342 (33.0)	0/179	237/768 (30.9)	0/393
Risk difference (95% CI)	29.1 % (25.0%, 33.6%)		33.0% (28.3%, 38.2%)		31.0% (27.7%, 34.2%)	
p-value[c]	<0.001		<0.001		<0.001	
Patients with HBsAg >1,000 to ≤3,000 IU/mL						
	27/224 (12.1)	0/114	19/228 (8.3)	0/107	46/452 (10.2)	0/221
Risk difference (95% CI)	12.1% (8.4%, 17.0%)		8.3% (4.8%, 12.7%)		10.5% (7.6%, 13.4%)	
p-value[c]	<0.001		<0.001		<0.001	

[a] Key secondary endpoint, adjusted for multiple comparisons.
[b] Based on two-sided p-value (exact Cochran-Mantel Haenszel).
[c] Based on two-sided p-value (Boschloo's test).
[d] Miettinen-Nurminen common risk difference, a weighted average of the risk differences in the two strata.

Baseline HBsAg levels are considered the most important predictor of achieving functional cure in clinical studies. Baseline HBeAg status was also an important predictor of functional cure in the B-Well studies. Both B-Well 1 and B-Well 2 studies demonstrated statistically significant superiority of HIBSAGO vs. placebo for functional cure, regardless of the HBeAg status. The number of patients with baseline HBeAg positive status was limited in the B-Well studies. The greatest functional cure rates were observed among patients who were both baseline HBeAg negative and had baseline HBsAg ≤1,000 IU/mL (**Table 15**).

Table 15: Functional cure in patients with different baseline HBeAg status in B-Well studies

	B-Well 1		B-Well 2		Pooled B-Well 1 and B-Well 2	
	HIBSAGO n/N (%)	**Placebo** n/N (%)	**HIBSAGO** n/N (%)	**Placebo** n/N (%)	**HIBSAGO** n/N (%)	**Placebo** n/N (%)
Patients with baseline HBsAg ≤3,000 IU/mL and HBeAg negative at baseline						
Functional cure[a]	121/595 (20.3)	0/300	104/527 (19.7)	0/260	225/1122 (20.1)	0/560
Posterior mean difference (95% CrI[b])	19.9% (16.8%, 23.3%)		19.3% (16.0%, 22.8%)		19.8% (17.6%, 22.3%)	
Patients with baseline HBsAg ≤3,000 IU/mL and HBeAg positive at baseline						
Functional cure	6/55 (10.9)	0/28	2/43 (4.7)	0/26	8/98 (8.2)	0/54
Posterior mean difference (95% CrI[b])	13.0% (5.1%, 21.8%)		6.9% (1.0%, 16.8%)		9.2% (4.2%, 16.2%)	
Patients with baseline HBsAg ≤1,000 IU/mL and HBeAg negative at baseline						
Functional cure	100/400 (25.0)	0/197	94/327 (28.7)	0/165	194/727 (26.7)	0/362
Posterior mean difference (95% CrI[b])	24.6% (20.5%, 28.9%)		28.1% (23.4%, 33.2%)		26.4% (23.2%, 29.7%)	
Patients with baseline HBsAg ≤1,000 IU/mL and HBeAg positive at baseline						
Functional cure	5/26 (19.2)	0/17	1/15 (6.7)	0/14	6/41 (14.6)	0/31
Posterior mean difference (95% CrI[b])	21.2% (9.2%, 33.9%)		13.0% (1.0%, 30.8%)		17.5% (7.1%, 28.7%)	

[a]Functional cure, defined as sustained suppression (24 weeks or longer) of HBV DNA (<LLOQ) and HBsAg not detected, with or without hepatitis B surface antibodies, after a finite duration of therapy and off all HBV treatment.
[b]Credible interval.

Post-hoc Analysis of Early On-treatment Response and Functional Cure

In a post-hoc analysis of pooled B-Well study data, Week 12 HBsAg levels were evaluated as a potential predictor of subsequent functional cure following HIBSAGO treatment.

Among patients with baseline HBsAg ≤1,000 IU/mL, an early response was defined as HBsAg <1 IU/mL at Week 12. Of patients who achieved this early response, 42% (179/426) subsequently achieved functional cure whereas patients who lacked this early response had a 2.5% (7/280) probability of achieving functional cure. Among patients with baseline HBsAg >1,000 IU/mL, an early response was defined as HBsAg <0.05 IU/mL at Week 12. Functional cure was achieved by 20.8% (22/106) of patients who met this criterion compared with 1.4% (4/287) of patients who did not.

These findings should be interpreted with caution, as the analysis was conducted post-hoc and was not adjusted for multiplicity. The results were considered supportive in the development of the early treatment response assessment.

15. Microbiology

Antiviral Activity

The antiviral activity of bepirovirsen was determined in cell culture assays. In HepG2.2.15 cells, bepirovirsen reduced the level of HBV RNA transcripts in a dose-dependent manner (EC_{50} = 122 nM). In addition, in primary human hepatocytes, bepirovirsen inhibited secretion of HBsAg (EC_{50} = 47.1±0.7 nM) and HBeAg (EC_{50} = 29.8±2.9 nM). Combining bepirovirsen with entecavir (ETV) or tenofovir disoproxil fumarate (TDF) improved HBV DNA reduction over ETV or TDF alone in HepG2.2.15 cells.

Resistance

The frequency of patients with nucleotide polymorphisms in the bepirovirsen binding site in bepirovirsen-treated patients across B-Well 1 and 2 studies are depicted in **Table 16**. The clinical significance of these polymorphisms is unknown.

Table 16: Patients with nucleotide polymorphisms (allelic frequency >5%) in the bepirovirsen binding site

	Baseline		**Treatment emergent**	
	Nucleotide polymorphisms	**Frequency % (n/N[a])**	**Nucleotide polymorphisms**	**Frequency % (n/N[b])**
Patients with baseline HBsAg ≤3,000 IU/mL				
B-Well 1	A1583G, A1583T, C1589A, A1593C, T1596C, T1598C, G1599A	6 (7/123)	C1589A, A1593C	5 (2/42)
B-Well 2	C1587T, G1588T, C1589A, C1597_1599DEL, C1599A, C1600T	7 (7/104)	T1586G, A1593C	6 (2/31)
Patients with baseline HBsAg ≤1,000 IU/mL				
B-Well 1	A1583G, C1589A, A1593C	3 (2/69)	C1589A	5 (1/22)
B-Well 2	C1587T, G1588T, C1589A, C1597_1599DEL, C1600T	12 (6/50)		0 (0/10)

[a]N = number of patients with baseline HBV sequence.
[b]N = number of patients with paired baseline and post-baseline HBV sequences.

In vitro testing of selected single nucleotide polymorphisms showed 1.2 to 4.1-fold shifts in EC_{50} relative to wild-type. The clinical impact of reduced susceptibility to bepirovirsen in these variants is unknown.

16. Non-Clinical Toxicology

Repeat Dose Toxicology

In mice treated weekly with bepirovirsen at 3, 10, 30 or 60 mg/kg/dose subcutaneously for 26 weeks, the principal findings at ≥30 mg/kg/dose (equating to ≥0.49 times the maximum recommended human dose [MRHD] based on body surface area comparison [BSA]) were elevated liver enzymes and hepatocellular single cell necrosis/mitosis and glomerulopathy, only the latter being adverse. These effects are considered related to the increased sensitivity of rodents to the immunostimulatory effects of ASOs like bepirovirsen. The NOAEL was 10 mg/kg/dose, equating to 0.16 times the MRHD. In general, rodents are more sensitive to the pro-inflammatory effects of ASOs compared to primates (including humans) and are not considered appropriate for calculating systemic safety margins for this class of drug.

In monkeys treated weekly with bepirovirsen at 3, 6, 10 or 20 mg/kg/dose subcutaneously for 39 weeks, principle adverse findings related to treatment at ≥10 mg/kg/dose (equating to ≥4.9 times the MRHD, based on AUC comparison) were thrombocytopenia, hypoalbuminemia and vasculitis, and additionally at 20 mg/kg/dose (12.6 times the MRHD), glomerulonephritis. With the exception of thrombocytopenia, these effects are related to activation of the alternative pathway of complement and considered species-specific with low potential for clinical translation. An additional finding at ≥10 mg/kg/dose (≥4.9 times the MRHD) was bepirovirsen-related mortality, associated with platelet decreases resulting in hemorrhagic or thrombotic sequela and/or hypoproteinemia due to complement-mediated glomerulonephritis. The NOAEL was 6 mg/kg/dose, equating to 2.0 times the MRHD.

Mutagenicity/Genotoxicity

Bepirovirsen did not exhibit a genotoxic potential in a battery of studies, including an *in vitro* bacterial reverse mutation (Ames) test, mammalian cell chromosomal aberration test and an *in vivo* micronucleus test in mice.

Carcinogenicity

Weekly subcutaneous administration of bepirovirsen was assessed in a 2-year carcinogenicity study in mice at doses up to 0.49 times the MRHD (based on BSA). Treatment resulted in an increase in hepatocellular carcinomas/adenomas and liver/whole body hemangiosarcomas/haemangiomas (particularly in males, concordant with greater severity/incidence of hepatotoxicity in this sex), and injection site-associated fibrosarcomas from 0.16 times the MRHD. Additionally, liver hemangiosarcomas were seen in male mice at 0.05 times the MRHD. These tumours are considered specific to rodents treated with this class of oligonucleotide and are deemed to be of low clinical relevance.

Reproductive and Developmental Toxicology

Fertility: Subcutaneous administration of bepirovirsen to mice up to 0.7 times the weekly MRHD (based on BSA), did not have adverse effects on male or female mating or fertility.

Pregnancy and Lactation: Subcutaneous administration of bepirovirsen to pregnant mice during organogenesis only or throughout pregnancy and lactation at 0.7 times the weekly MRHD (based on BSA), had no adverse effects on embryo-foetal development, parturition, lactation or on the postnatal development of offspring. Bepirovirsen was detectable in milk of lactating mice and in the livers of their offspring at <1% of maternal liver exposure. When given to pregnant rabbits during organogenesis at

2.9 times the weekly MRHD (based on BSA), bepirovirsen was associated with decreased foetal weights which occurred in the presence of maternal toxicity.

Special Toxicity Studies

In mouse splenocytes treated *in vitro*, bepirovirsen caused concentration-dependent increases in cytokines (IP-10, MIP-1α and TNF-α) at 200 and/or 1,000 μg/mL.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]HIBSAGO

bepirovirsen injection

This Patient Medication Information is written for the person who will be taking **HIBSAGO**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **HIBSAGO** talk to a healthcare professional.

What HIBSAGO is used for:

- HIBSAGO is used with other medicines called "nucleos(t)ide analogues", to treat adults who have a long term (chronic) hepatitis B virus infection.

How HIBSAGO works:

Chronic hepatitis B is a long-term infection of the liver caused by the hepatitis B virus. It can lead to a condition called "cirrhosis" which is an advanced liver disease. This condition can lower your liver's ability to work. It can also increase the risk of liver cancer.

HIBSAGO contains the active substance bepirovirsen. Bepirovirsen is a type of medicine called an antisense oligonucleotide.

HIBSAGO lowers the levels of hepatitis B virus proteins and DNA in the blood. In some people, the virus becomes undetectable in the blood and remains under control after treatment is stopped. Your healthcare professional will decide whether you can stop long-term hepatitis B treatment.

The ingredients in HIBSAGO are:

Medicinal ingredient: bepirovirsen (as bepirovirsen sodium)

Non-medicinal ingredients: hydrochloric acid, sodium hydroxide, water for injection

HIBSAGO comes in the following dosage form(s):

150 mg/mL solution

Do not use HIBSAGO if:

- you have a type of liver disease called cirrhosis.
- blood tests done by your healthcare professional show you have low levels of platelets (cells that help your blood to clot to stop bleeding).
- You are allergic to bepirovirsen, any of the other ingredients of this medicine or any parts of the container (see **The ingredients in HIBSAGO are**).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take HIBSAGO. Talk about any health conditions or problems you may have, including if you:

- have or have had kidney problems.
- have or have had abnormal bleeding or bruising, low numbers of blood platelets or thrombocytopenia (a condition where you have a low number of blood platelets).
- have or have had an organ transplant.
- have or have had any problems where your immune system attacks healthy body tissue, a condition called "autoimmune disease".
- have or have had blood vessel inflammation, a condition called "vasculitis".
- have or have had hepatitis C (an infection of the liver, caused by the hepatitis C virus).
- have or have had hepatitis D (an infection of the liver, caused by the hepatitis D virus).
- have a human immunodeficiency virus (HIV) infection and are taking medicines for it.
- are pregnant, planning to become pregnant, or planning to have a child with your partner.
- are breastfeeding or plan to breastfeed.
- are taking medicines that affect blood clotting. See **The following may interact with HIBSAGO** for more information.

Other warnings you should know about:

Check-ups and testing:

Your healthcare professional will do blood and urine tests to check on how your liver and kidneys are working.

They will also do tests to check the number of platelets you have. These are the cells in your body that help your blood clot, which stops bleeding.

Bleeding Problems:

Tell your healthcare professional immediately if you experience:

- unusual bleeding.
- a long period of bleeding.
- symptoms of bleeding of the brain such as a severe headache, vomiting, drowsiness, losing consciousness, dizziness, slurred speech, confusion or loss of movement on one side of the body.

Your healthcare professional may pause your use of HIBSAGO if you experience these events.

Immune System Problems:

Tell your healthcare professional if you experience:

- changes in your skin like rashes, red or purple spots, swelling, discomfort, itchiness, scaley patches, raised or red patches.
- joint paint that does not go away on its own.
- flu like symptoms like a fever, feeling aches, fast heartbeats or fast breathing.
- feeling weak or tired all the time, pale skin, shortness of breath.

These may be symptoms of your immune system attacking your body or inflammation of your blood vessels, which could be caused by HIBSAGO. Your healthcare professional may stop your use of HIBSAGO if you experience these symptoms.

Pregnancy:

- Talk to your healthcare professional before taking this medicine if you are pregnant, think you may be pregnant or are planning to have a baby.
- Your healthcare professional will decide if HIBSAGO is right for you based on the benefits to you and the risk to your baby while you are pregnant.

Breastfeeding:

- Talk to your healthcare professional before taking this medicine if you are breastfeeding or planning to breastfeed as HIBSAGO may pass into breast milk.

Preventing the spread of Hepatitis B:

HIBSAGO will NOT stop you from infecting people through sex or transfer of blood or body fluids.

Continue to take precautions to prevent passing on your hepatitis B to other people.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with HIBSAGO:

- medicines that stop your blood from clotting or lower your blood platelet levels or function, such as:
  - acetylsalicylic acid
  - clopidogrel
  - warfarin
  - apixaban
  - dabigatran
  - heparin
- medicines that may lower your kidney function, such as:
  - painkillers like acetylsalicylic acid, ibuprofen or naproxen.
  - medicines that treat high blood pressure.
  - medicines that treat bacterial infections like antibiotics.
  - medicines that treat other viral infections.
- peginterferon, a medicine used to treat hepatitis B.

If you are also taking medicines for an HIV (human immunodeficiency virus) infection, keep doing so unless the healthcare professional treating your HIV infection has told you to stop.

How to take HIBSAGO:

Read the Instructions for Use for detailed steps and information on how to inject HIBSAGO.

You will receive your first dose of HIBSAGO under the guidance and supervision of your healthcare professional.

Your healthcare professional will show you or your caregiver how to inject HIBSAGO. Your healthcare professional may then decide if you or your caregiver may inject HIBSAGO. Take HIBSAGO exactly as your healthcare professional tells you.

HIBSAGO is given as an injection under your skin (subcutaneously only).

- A 300 mg dose is given as 2 injections (2 syringes).
- A 150 mg dose is given as 1 injection (1 syringe).

- Keep the syringes at room temperature (below 30°C) for at least 30 minutes before you plan to inject HIBSAGO.
- Keep the syringes in the original carton until you are ready to use them, to protect them from light.
- **Do NOT** inject HISBAGO into a vein or muscle.
- If you are giving yourself the injections, you can inject into your upper leg (thigh) or stomach area (abdomen).
- A caregiver can inject into the upper arm, thigh or abdomen.
- Look at the medicine in the HIBSAGO syringes through the inspection windows. The medicine should be clear and colourless to yellow.
  - **Do NOT** use if the HIBSAGO solution in the syringes is cloudy, discoloured or has particles.
- If two injections are needed, inject the second syringe immediately after the first.
- You can use two different places to inject your two syringes.
  - For example, you can give one in the thigh and the other in the abdomen.
  - You can also use the same place as long as you leave at least 5 cm (2 inches) between each injection site.
- **Do NOT** inject where the skin is bruised, tender, red, or hard.

- Between doses, change where you inject HIBSAGO to lower the risk of getting reactions to the injections.
- Where possible, give each dose on the same day(s) each week.
  - Keep track of the day(s) of the week you inject HIBSAGO so you remember to inject your next dose on the same day(s) the following week.

Usual dose:

Always use HIBSAGO exactly as your healthcare professional has told you to. Check with your healthcare professional if you are not sure.

Treatment with HIBSAGO typically lasts 24 weeks.

Recommended dose		
When	**How much**	**How often**
Weeks 1 and 2	300 mg (complete contents of **2** syringes)	**Twice** a week Allow 3 or 4 days between each dose. Where possible, give each dose on the same days each week.
Weeks 3 to 24	300 mg (complete contents of **2** syringes)	**Once** a week Where possible, give each dose on the same day each week.

The usual dose of HIBSAGO is 300 mg. You will have blood and urine tests while you are taking HIBSAGO. Your healthcare professional may decide to change your dose, pause your treatment or stop your treatment early based on the results of the tests done while you are taking HIBSAGO.

- If your dose is 300 mg dose of HIBSAGO, you will need 2 syringes.
- If your dose is 150 mg dose of HIBSAGO, you will need 1 syringe.

While you are taking HIBSAGO, you will have to continue taking your nucleos(t)ide analogue treatment for as long as your healthcare professional recommends.

After you use HIBSAGO:
You will continue to have blood and urine tests done by your healthcare professional but these will happen less often.

Overdose:

If you think you, or a person you are caring for, have taken too much HIBSAGO, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you miss a dose, and your next dose is due in 3 days or more:

- inject the missed dose as soon as you remember. Then continue your treatment as before.

If you miss a dose, and your next dose is due in less than 3 days:

- skip the missed dose and inject the next one at the usual time. Then continue your treatment as before.

Use HIBSAGO for as long as your healthcare professional recommends. Do not stop unless your healthcare professional tells you to stop or you experience serious side effects.

Possible side effects from using HIBSAGO:

These are not all the possible side effects you may have when taking HIBSAGO. If you experience any side effects not listed here, tell your healthcare professional.

- injection site reactions, such as:
    - redness
    - itchiness
    - pain at the injection site
    - skin colour changes at injection site
- high temperature (fever)
- changes to your blood test results
    - decreases in platelets (blood cells that help your blood to clot to stop bleeding).
    - increases in two substances called "alanine aminotransferase" and "aspartate aminotransferase," both made by your liver.
    - lower number of neutrophils (neutropenia), a type of white blood cell that protects your body from infections.
    - lower number of white blood cells (leukopenia)
    - lower kidney function

- itching
- rash
- muscle pain
- lack of energy (fatigue)
- feeling cold
- feeling weak (asthenia)
- feeling generally unwell or sick (malaise)
- allergic reactions (hypersensitivity)
- inflammation of blood vessels in the skin (cutaneous vasculitis)
- nausea
- vomiting

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Unknown			
Serious liver injury: jaundice (yellow skin or eyes), dark urine, nausea or vomiting, loss of appetite, bloated or painful stomach.		X	X
Thrombocytopenia (very low blood platelets): • unusual bruising or bleeding, e.g. petechiae (red or purple flat pinhead spots under your skin), bright red patches on the white of your eye, bleeding from your nose or gums, blood in your urine or stools (poo) or any bleeding that doesn't stop. • bleeding in the brain**:** confusion, dizziness, vomiting, fits (seizures), severe headache, weakness or numbness on one side of the body.		X	X
Inflammation in your blood vessels, or anaemia (low number of red blood cells)		X	X

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
• skin changes away from where HIBSAGO is injected (e.g. purple rashes, red-purple spots, swelling, discomfort, itchiness, scaley patches, raised or red patches) • joint pain that doesn't go away by itself • flu-like symptoms (such as high temperature and feeling achy), that don't get better with painkillers, or are accompanied by other symptoms, such as a fast heartbeat or fast breathing • feeling weak or tired all the time, having pale skin, shortness of breath on exertion, or a fast heartbeat.			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature (below 30°C).
- **Do NOT** freeze.
- Store in the original carton to protect from light.

- **Do NOT** shake.
- Throw away if the expiry date has passed, or it has been 12 weeks since you received your carton, whichever comes first.
- Each pre-filled syringe must be administered within 6 hours once removed from the carton. Throw away if not administered within 6 hours.
- **Do NOT** use HIBSAGO after the expiry date shown on the pack.
- Keep out of reach and sight of children.

If you want more information about HIBSAGO:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.gsk.ca; or by calling 1-800-387-7374.

This leaflet was prepared by GlaxoSmithKline Inc.

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INSTRUCTIONS FOR USE

HIBSAGO

bepirovirsen injection

For subcutaneous use

150 mg/mL

Each carton contains 2 pre-filled syringes (150 mg / mL each)

This Instructions for Use contains information on how to inject HIBSAGO.

Read this section first

Read this Instructions for Use before you start using HIBSAGO and each time you get another prescription. There may be new information. Before using your HIBSAGO syringe, it is important that your healthcare professional explains your HIBSAGO dosing instructions and shows you (or your caregiver) how to use the syringe the right way. If you do not follow these instructions, you may not get all your medicine.

Important Information

- 2 HIBSAGO syringes are required to complete the usual 300 mg dose.
- If your healthcare professional lowers your dose to 150 mg, only one syringe is required.
- HIBSAGO is for use **under the skin only** (subcutaneous). Do NOT inject HIBSAGO into a vein or muscle.

Do NOT use HIBSAGO syringe if:

- it has been frozen
- it has been stored above 30°C
- it has been dropped or damaged
- the security seal on the carton has been broken
- the expiry date (EXP) has passed or it has been 12 weeks since you received your HIBSAGO carton, whichever comes first

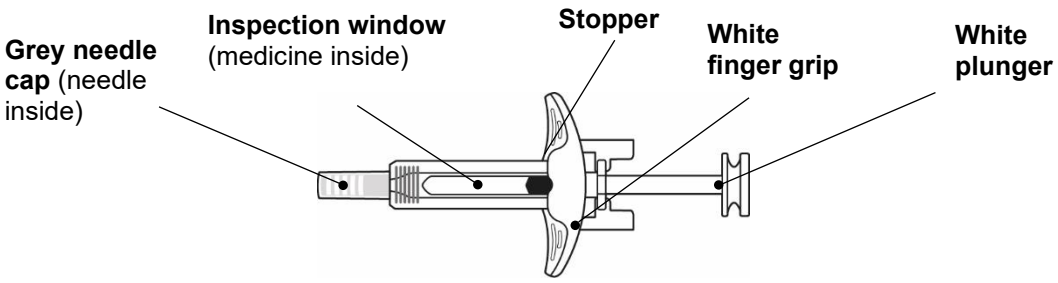
Do NOT:

- shake HIBSAGO syringe
- share or reuse your syringe
- expose your syringe to heat or direct sunlight

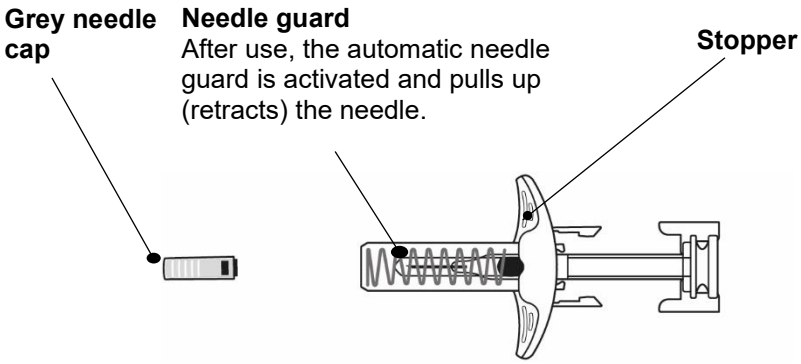
If any of these happen, throw away the HIBSAGO syringe in a sharps disposal container and use a new HIBSAGO syringe. **Keep out of reach of children. Contains small parts.**

Get to know your HIBSAGO syringes

Before Use



After Use



Storage

Syringes stored in the carton

- Store HIBSAGO at room temperature up to 30°C until you are ready to use it. Keep in the original carton until you are ready to use it, to protect from light.
- Keep HIBSAGO at room temperature for at least 30 minutes before using it.
- Throw away HIBSAGO in a sharps disposal container after 12 weeks of storage at room temperature.

Syringes removed from the carton

- HIBSAGO syringes must be used within 6 hours after you take them out of the carton. If they are not used within 6 hours, throw them away in a sharps disposal container.

Keep out of the reach of children. Contains small parts.

A. Prepare



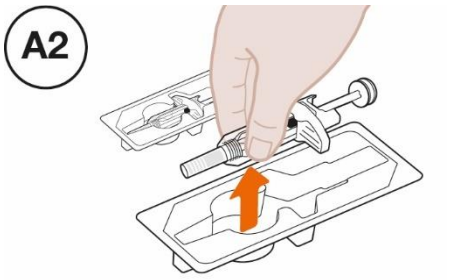
Gather supplies

Supplied

- 2 HIBSAGO syringes

Not supplied

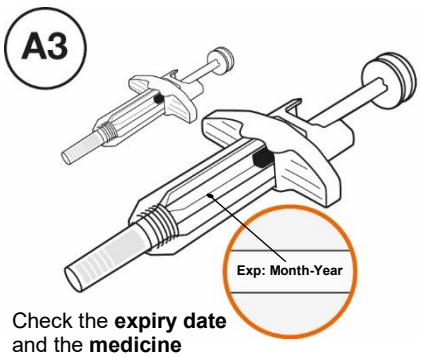
- 2 Alcohol swabs
- 2 Cotton balls or gauzes
- 2 Adhesive bandages
- Sharps disposal container
  (see **Section C** for disposal instructions).



Take the **syringes out** of the tray

Take out your syringes

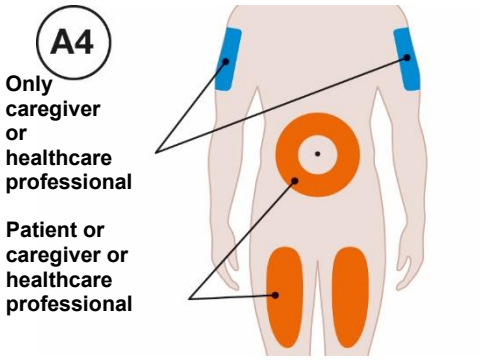
- Peel off the clear plastic cover from the corner of the tray.
- Hold the **middle** of the syringes (near the inspection window) and carefully take the syringes out of the trays.
- **Do NOT** handle the syringes by the white plunger when removing from the tray, or at any point when handling the syringes.
- **Do NOT** remove the grey needle caps at this step.
- **Do NOT** use the syringes if they have been dropped or damaged.



Check the **expiry date** and the **medicine**

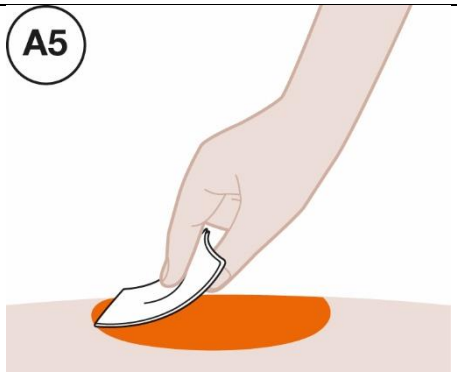
Check your syringes

- Check the expiry date. **Do NOT** use if the expiry date has passed or it has been 12 weeks since you received your HIBSAGO carton, whichever comes first.
- Ensure that HIBSAGO has been at room temperature up to 30°C for **at least 30 minutes** before using it. Cold medicine is more painful to inject.
- Look at the medicine in the HIBSAGO syringes through the inspection windows. The medicine should be clear and colourless to yellow.
- It is normal to see air bubbles. You don't need to do anything about it.
- **Do NOT** use if the HIBSAGO solution in the syringes is cloudy, discoloured, or has particles.
- **Do NOT** shake the syringes.



Choose your injection sites

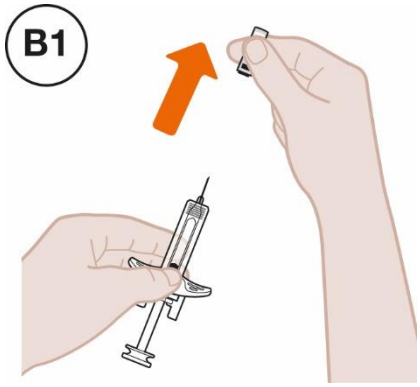
- For a 300 mg dose, you will need **2 injections** to complete your dose.
- For a 150 mg dose, you will need **1 injection** to complete your dose.
- If you are giving yourself the injection, you can inject into your thighs or stomach (abdomen).
- A caregiver can inject into the upper arm, thigh, or abdomen.
- If you need 2 injections to complete your dose, leave at least 5 cm (2 inches) between each injection site. You can use 2 different injection sites for your 2 syringes to complete your dose.
- **Do NOT** inject yourself in the upper arm, as it is more difficult to avoid syringe movement during the injection.
- **Do NOT** inject where the skin is bruised, tender, red, or hard.
- **Do NOT** inject within 5 cm (2 inches) of your belly button.



Clean the injection sites

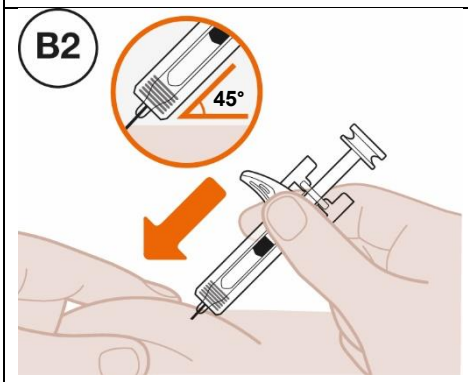
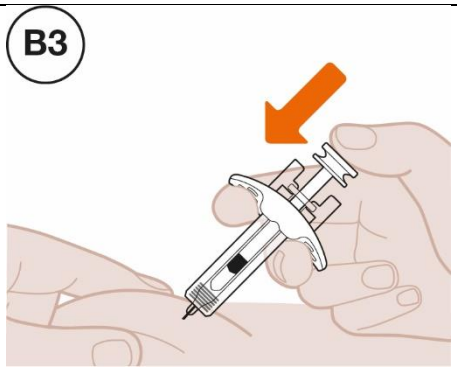
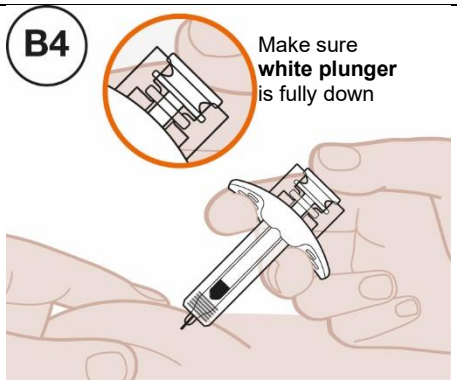
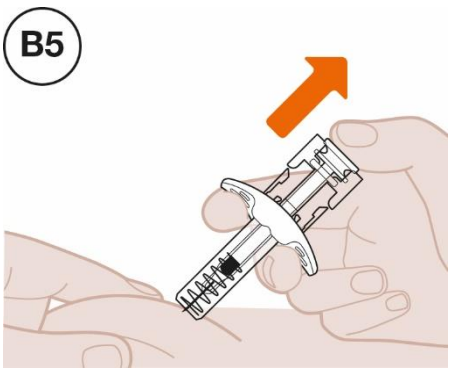
- Wash your hands with soap and water.
- Clean the injection sites with an alcohol swab. Allow skin to air dry.
- **Do NOT** fan or blow on the cleaned injection sites.
- **Do NOT** touch the cleaned injection sites again until you have finished your injections.

B. Inject

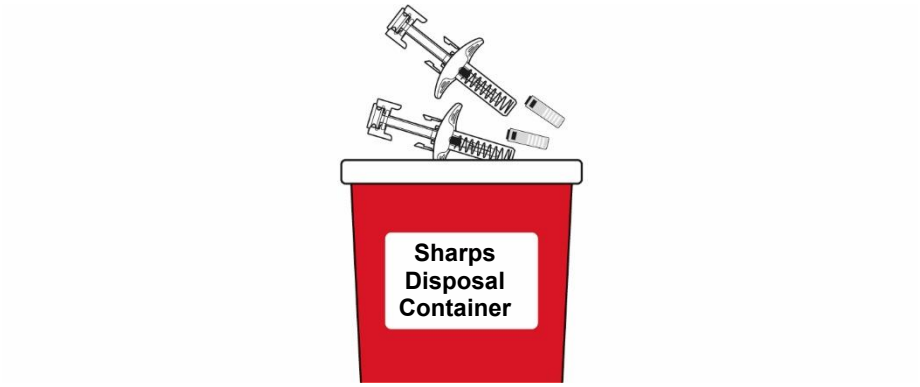


Pull off the grey needle cap

- Remove the grey needle cap from 1 syringe by pulling it straight off, away from the needle (as shown). It may take some force to remove the grey needle cap.
- Inject within 5 minutes after you remove the grey needle cap.
- **Do NOT** remove both needle caps from both syringes at the same time.
- Only remove the grey needle cap from the second syringe when you are ready to use it and if your dose is 300 mg.
- **Do NOT** handle the syringe by the white plunger while removing the grey needle cap.
- **Do NOT** let the needle touch any surface.
- **Do NOT** touch the needle.

	• **Do NOT** try to remove any air bubbles from the syringe. • **Do NOT** put the grey needle cap back onto the syringe. This could cause a needle injury.
	**Position the syringe at the injection site** • Use your free hand to gently **pinch** the skin around the cleaned injection site. • Keep pinching the skin throughout the injection. • Hold the **middle** of the syringe and insert the entire needle into the pinched skin at a 45-degree angle using a dart like motion, as shown. • **Do NOT** handle the syringe by the white plunger while inserting the needle into the pinched skin.
	**Start the injection** • Move your thumb to the white plunger and use your other fingers to hold onto the white finger grip, as shown. • Slowly push down on the white plunger **using your thumb** to inject the full syringe.
	**Fully press the white plunger** • Make sure the white plunger is pushed all the way down until the stopper reaches the bottom of the syringe and all of the medicine is injected.
	**Slowly lift thumb after injection completes** • Slowly lift your thumb up. This will allow the white plunger to come up and the needle to automatically pull up (retract) into the needle guard. • After removing the syringe from the injection site, release the pinched skin. • There may be a small drop of blood at the injection site. This is normal. Press a cotton ball or gauze on the area and apply an adhesive bandage if you need it. • **Do NOT** rub the injection site.

	• **Do NOT** put the grey needle cap back onto the HIBSAGO syringe.
	**Repeat with second syringe for 300 mg dose** • For a 300 mg dose, give your second injection **immediately**, to complete your dose, by repeating all Inject steps (Steps B1 through B5). • **Do NOT** inject the second injection within 5 cm (2 inches) of the first injection site.

C. Throw Away

Throw away any unused medicinal product or waste material in accordance with local requirements. **Keep your used syringes and needle caps out of the sight and reach of children.**