Product Monograph

Including Patient Medication Information

PrHEPCLUDEX®

Bulevirtide for injection

Powder for solution, 2 mg bulevirtide (as bulevirtide acetate) / vial, subcutaneous injection

Antivirals for systemic use, other antivirals

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Sections or subsections that are not applicable at the time of authorization are not listed.

Part 1: Healthcare Professional Information

1 Indications

HEPCLUDEX (bulevirtide) is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in adults with compensated liver disease.

1.1 Pediatrics

Pediatrics (< 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics: Clinical studies of HEPCLUDEX did not include any patients aged 65 or over to determine whether they respond differently from younger patients.

2 Contraindications

HEPCLUDEX 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.

3 Serious Warnings and Precautions Box

Exacerbation of Hepatitis After Discontinuation of Treatment

- Severe acute exacerbations of HDV and hepatitis B virus (HBV) infection may occur after HEPCLUDEX is discontinued. Monitor hepatic function closely with both clinical and laboratory follow-up for at least several months in patients who discontinue HEPCLUDEX. In certain circumstances, resumption of antiviral therapy may be warranted (see 7 Warnings and Precautions).

4 Dosage and Administration

4.1 Dosing Considerations

Healthcare professionals should train patients or caregivers in the proper technique for reconstituting HEPCLUDEX with Sterile Water for Injection and self-administering subcutaneous injections using a syringe. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Instruct the patient or caregiver to read the Instructions For Use (contained within the Patient Medication Information) at the time they receive a prescription for HEPCLUDEX and as needed for ongoing administration of HEPCLUDEX. Emphasize the following instructions to the patient or caregiver:

- HEPCLUDEX must be stored in the refrigerator prior to preparation and administration.
- HEPCLUDEX needs to be reconstituted with Sterile Water for Injection prior to administration.

- The Sterile Water for Injection, syringe, and needles for preparation and injection are provided separately from HEPCLUDEX; all materials should be stored out of the reach of children.
- HEPCLUDEX must be administered by subcutaneous injection. Do not administer by any other route (see 4.3 Reconstitution and 4.4 Administration).

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage in adults is HEPCLUDEX 2 mg once daily administered by subcutaneous injection.

The optimal treatment duration is unknown. Treatment should be continued as long as associated with clinical benefit.

In all patients, manage the underlying HBV infection simultaneously as clinically appropriate. HBV-DNA levels should be closely monitored during treatment with HEPCLUDEX.

Pediatrics

The safety and efficacy of HEPCLUDEX in patients younger than 18 years of age have not been evaluated. Health Canada has not authorized an indication for pediatric use.

Geriatrics

No data are available on which to make a dose recommendation for patients over the age of 65 years.

Renal Impairment

No studies that evaluate the safety and efficacy of HEPCLUDEX in patients with renal impairment have been conducted. Based on limited clinical data and population pharmacokinetics (PK) analysis, no dosage adjustment of HEPCLUDEX is required in patients with mild renal impairment (creatinine clearance [CrCl] ≥ 60 and < 90 mL/min). No data are available on which to make a dose recommendation for patients with CrCl < 60 mL/min. Administration of HEPCLUDEX is associated with elevations in blood bile acids, which may be enhanced in patients with renal impairment due to renal elimination of bile acids. Monitoring of patients with renal impairment while receiving HEPCLUDEX is recommended.

Hepatic Impairment

No dosage adjustment of HEPCLUDEX is required in patients with mild hepatic impairment (Child-Pugh A). No studies that evaluate the safety and efficacy of HEPCLUDEX in patients with Child-Pugh B or C hepatic impairment or patients with decompensated liver disease have been conducted and therefore no data are available on which to make dosing recommendations for these patients.

4.3 Reconstitution

Emphasize the following instructions to the patient or caregiver:

Reconstitution Instructions

- Aseptically reconstitute HEPCLUDEX lyophilized powder by adding 1 mL of Sterile Water for Injection to the HEPCLUDEX vial. The resulting concentration will be 2 mg/mL.
- Carefully swirl or roll the vial between the hands to dissolve the powder. Complete dissolution might take up to 3 minutes.

- Completely dissolved HEPCLUDEX should be clear without foam. If the HEPCLUDEX solution appears foamy, allow more time for the powder to dissolve.
- If there are bubbles in the solution, gently tap the vial until they disappear.
- If there are particles in the solution once the powder is (completely) dissolved (after approximately 5 minutes), do not use that vial of solution.
- Use reconstituted product immediately. Do not refrigerate.

4.4 Administration

Emphasize the following instructions to the patient or caregiver:

Administration Instructions

- Administer by subcutaneous injection into the upper thigh, lower abdomen, or back of the upper arm (only if administered by a caregiver).
- Change the injection site frequently to minimize potential injection site reactions.

IMPORTANT:

- Do not reuse the vials, syringe, needles, or any remaining Sterile Water for Injection.

4.5 Missed Dose

If a dose is missed, that dose should be taken as soon as possible on that day. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

5 Overdose

There are no data on human overdose with HEPCLUDEX. If overdose occurs, the patient must be monitored for evidence of toxicity and given standard supportive treatment as necessary.

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 1. Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous Injection	Powder for solution, 2 mg/vial (2 mg/mL when reconstituted)	Mannitol, sodium carbonate anhydrous, sodium hydrogen carbonate, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment

Each 2 mg single-dose vial contains a sterile, preservative-free lyophilized powder that is to be reconstituted with 1 mL of Sterile Water for Injection. The powder is white to off-white. Following reconstitution, each vial contains bulevirtide acetate equivalent to 2 mg bulevirtide

with a pH of approximately 9.0 and osmolality of approximately 300 mOsm/kg.

Packaged in a Type 1 clear glass vial, an elastomeric closure, and an aluminum overseal with a flip-off cap.

7 Warnings and Precautions

See 3 Serious Warnings and Precautions Box.

General

Treatment with HEPCLUDEX should be initiated and monitored by a physician experienced in the management of viral hepatitis.

Healthcare professionals should train patients or caregivers in the proper technique for reconstituting or administering HEPCLUDEX (see 4.1 Dosing Considerations, 4.3 Reconstitution and 4.4 Administration).

Co-infection with Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV)

No data are available from HCV co-infected patients. Limited data are available from HIV co-infected patients.

Driving and Operating Machinery

No studies on the effects of HEPCLUDEX on the ability to drive and use machines have been performed. Inform patients that dizziness has been reported during treatment with HEPCLUDEX.

Exacerbation of Hepatitis After Discontinuation of Treatment

Severe acute exacerbations of HDV and HBV infection may occur after HEPCLUDEX is discontinued. Monitor hepatic function closely with both clinical and laboratory follow-up for at least several months in patients who discontinue HEPCLUDEX. In certain circumstances, resumption of antiviral therapy may be warranted.

HDV and HBV Genotype

The predominant HBV/HDV genotype isolated from patients with chronic HDV infection in clinical studies was HBV-D/HDV-1, found in 84.6% of patients. Clinical data for rarer HBV and HDV genotypes is limited. Therefore, it is uncertain whether HBV or HDV genotype affects clinical response to HEPCLUDEX.

7.1 Special Populations

7.1.1 Pregnancy

There are no adequate and well-controlled studies with HEPCLUDEX in pregnant women. HEPCLUDEX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In non-clinical reproductive toxicity studies, bulevirtide demonstrated no adverse effect on embryofetal development when administered to pregnant rats and rabbits at systemic exposures (AUC) 12- and 124-fold relative to exposure in humans at the recommended human dose.

7.1.2 Breastfeeding

It is unknown whether HEPCLUDEX is secreted in human milk. Measurements of bulevirtide in the plasma of pups or in the milk of nursing animals were not performed in the non-clinical pre- and post-natal developmental rat studies. However, due to its high protein binding, liver tropism, and high specificity for the sodium taurocholate co-transporting polypeptide (NTCP), bulevirtide is not likely to be secreted in milk.

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Clinical studies of HEPCLUDEX did not include any patients aged 65 or over to determine whether they respond differently from younger patients.

8 Adverse Reactions

8.1 Adverse Reaction Overview

The safety of HEPCLUDEX for the treatment of chronic HDV infection in adult patients with compensated liver disease was primarily evaluated in a randomized, open-label Phase 3 trial (MYR301) which enrolled 49 patients in the HEPCLUDEX 2 mg arm and 51 patients in a delayed treatment (control) arm. The safety profile is further supplemented by three Phase 2 studies (MYR202, MYR203, and MYR204) which collectively enrolled 382 patients with chronic HDV infection. Across these studies, 43 patients received HEPCLUDEX 2 mg as a HDV monotherapy, and 65 patients received HEPCLUDEX 2 mg with pegylated interferon α-2a (Peg-IFNα).

In the Study MYR301 Week 48 analysis, 2 of 49 patients (4.1%) in the HEPCLUDEX 2 mg treatment group experienced serious adverse events (SAEs), compared to 1 of 51 patients (2.0%) in the control group; none of the SAEs were considered related to HEPCLUDEX. The most common AEs observed in greater than 10% of patients and at a higher frequency in the HEPCLUDEX 2 mg treatment group versus control at Week 48 were: headache, fatigue, pruritis, eosinophilia, and injection site reactions. Through Week 48, no AEs led to premature discontinuation of HEPCLUDEX or death.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 2 describes the adverse reactions (all grades) that were reported in ≥ 3% of patients treated with HEPCLUDEX 2 mg in Study MYR301, and at a higher frequency in the HEPCLUDEX 2 mg group versus control; frequencies are based on adverse events observed by Week 48.

Table 2. Adverse Reactions (All Grades) Reported in ≥ 3%[a] of Patients With Chronic Hepatitis Delta (CHD) and Compensated Liver Disease in Study MYR301 (Week 48 Analysis)

	Delayed Treatment (Control)[b] (N=51)	HEPCLUDEX 2 mg (N=49)
Gastrointestinal disorders		
Nausea	2 (3.9%)	3 (6.1%)
General disorders and administration site conditions		
Injection site reactions[c]	0%	9 (18.4%)
Fatigue	1 (2.0%)	5 (10.2%)
Nervous system disorders		
Headache	0%	9 (18.4%)
Dizziness	0%	2 (4.1%)
Skin and subcutaneous tissue disorders		
Pruritus	0%	6 (12.2%)

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events regardless of causality
b. Patients who received delayed treatment in Study MYR301.
c. Grouped term including injection site reaction, injection site erythema, injection site pain, injection site pruritus, injection site rash, injection site hematoma, and injection site swelling.

The safety profile of HEPCLUDEX 2 mg in Phase 2 Study MYR202 and Phase 2 Study MYR203, where 28 and 15 participants received HEPCLUDEX 2 mg for 24 weeks and 48 weeks, respectively, was generally consistent with that observed in Study MYR301 through Week 48.

In Study MYR301, the safety profile of HEPCLUDEX 2 mg when administered through up to 144 weeks of treatment was consistent with that observed in the Week 48 analysis.

Across Phase 2 studies MYR203 and MYR204, after 65 patients received HEPCLUDEX 2 mg in combination with Peg-IFNα for 48 weeks, the most common adverse events reported (≥ 10%) in participants receiving HEPCLUDEX 2 mg + Peg-IFNα included cytopenias (leukopenia, thrombocytopenia, neutropenia, lymphopenia, neutrophil count decreased, white blood cell count decreased, platelet count decreased), bile acids increased, influenza-like illness, alanine aminotransferase (ALT) increased, aspartate aminotransferase increased, pyrexia, asthenia, and injection site reactions, in line with the safety profile of the individual components (HEPCLUDEX 2 mg and Peg-IFNα).

8.3 Less Common Clinical Trial Adverse Reactions

No additional adverse reactions have been identified for HEPCLUDEX.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

Clinical Trial Findings

Eosinophil Count Increased

Increases in eosinophil counts were commonly observed in patients receiving HEPCLUDEX 2 mg; there were no associated clinical sequelae, hepatic adverse reactions, or significant liver-related laboratory abnormalities. For participants who experienced treatment-emergent adverse events of eosinophilia, peak post-baseline absolute eosinophil counts ranged from 0.91 x 10^9/L to 1.53 x 10^9/L; all were Grade 1.

Total Bile Salts Increased

Asymptomatic bile salt elevations, associated with the mechanism of action of HEPCLUDEX, were very commonly observed in clinical studies of HEPCLUDEX 2 mg; the bile salt elevations resolved upon discontinuation of HEPCLUDEX. Median (Q1, Q3) change from baseline in bile salt concentrations at Week 48 was +5.5 µmol/L (–3.5, 16.5 µmol/L) and Week 144 was +2.7 µmol/L (–3.8, 12.0 µmol/L).

8.5 Post-Market Adverse Reactions

In addition to adverse reactions from clinical studies, the following adverse reactions were identified during post-approval use of HEPCLUDEX. Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

IMMUNE SYSTEM DISORDERS
Hypersensitivity, including anaphylactic reaction

9 Drug Interactions

9.1 Drug Interactions Overview

Bulevirtide acts as an inhibitor of NTCP. *In vitro*, it has been shown that certain medicinal products can inhibit bulevirtide target NTCP. The co-administration of such medicinal products (e.g. sulfasalazine, irbesartan, ezetimibe, ritonavir, simvastatin and cyclosporin A) is not recommended.

As a precautionary measure, close clinical monitoring is warranted when NTCP substrates are co-administered with bulevirtide. When possible, co-administration of these substrates should be avoided.

In a clinical PK drug interaction study in healthy volunteers, there was no significant effect of bulevirtide on the PK of TDF, a potential concomitant medication for the treatment of HBV infection.

In clinical PK drug interaction studies in healthy volunteers, there was no impact of bulevirtide alone on the PK of the CYP3A4 substrate midazolam. However, an approximate 40% increase in midazolam exposure was observed when administered in combination with bulevirtide and tenofovir which was not observed upon administration of tenofovir alone. As a precautionary measure, close clinical monitoring is warranted when bulevirtide is co-administered with tenofovir and narrow-therapeutic-index drugs which are sensitive CYP3A4 substrates (e.g. cyclosporine, carbamazepine, sirolimus, and tacrolimus).

In a clinical PK drug interaction study in healthy volunteers, there was minimal impact of bulevirtide on the PK of the OATP1B1/3 and NTCP substrate pravastatin, or of pravastatin on the PK of bulevirtide.

9.4 Drug-Drug Interactions

In vitro studies have shown that no clinically relevant interactions are expected for the most common efflux transporters (MDR1, BCRP, BSEP, MATE1, and MATE2K) and uptake transporters (OATP2B1, OAT1, OAT3, OCT1, and OCT2). *In vitro* bulevirtide inhibited the organic anion transporting polypeptides, OATP1B1 and OATP1B3, with IC_{50} values of 0.5 and 8.7 µM, respectively. In clinical studies, at the recommended 2 mg dose of bulevirtide, maximum plasma concentrations at steady state were up to 26 nM, and thus no clinically relevant interaction is expected with OATP1B1 and OATPB1B3.

In vitro studies have shown that bulevirtide does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. No *in vitro* induction of CYP1A2, CYP2B6, or CYP3A4 by bulevirtide was observed.

Bulevirtide administered at 10 mg once daily (administered as two consecutive 5 mg doses) to 12 healthy volunteers did not impact the PK of TDF in a dedicated drug interaction study.

Bulevirtide administered at 5 mg twice daily to 19 healthy volunteers did not impact the PK of the CYP3A4 probe substrate midazolam. Bulevirtide administered at 10 mg once daily (administered as two consecutive 5 mg injections) in combination with once daily tenofovir (245 mg) to 12 healthy volunteers, increased midazolam AUC_{2-4} exposure by approximately 40% when compared to midazolam alone.

Bulevirtide administered at 5 mg twice daily to 19 healthy volunteers resulted in a 32% increase in the C_{max} and AUC of the OATP1B1/3 and NTCP substrate pravastatin administered in single doses of 40 mg in a dedicated clinical drug interaction study. This drug interaction is not considered clinically meaningful.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 Clinical Pharmacology

10.1 Mechanism of Action

Bulevirtide is a 47-amino acid, N-terminally myristoylated, HBV-L-protein derived, synthesized lipopeptide that acts as a potent, selective entry inhibitor of HDV. Bulevirtide blocks the entry of HBV and HDV into hepatocytes by binding to and inactivating the essential HBV and HDV entry receptor NTCP.

10.2 Pharmacodynamics

Effects on Electrocardiogram

Current non-clinical and clinical data do not suggest a risk of QT prolongation, but QT prolongation has not been fully evaluated in humans.

10.3 Pharmacokinetics

The PK properties of bulevirtide were characterized after intravenous and subcutaneous administration. The exposure of bulevirtide increased in a more than proportional manner with increasing doses (dose range: 300 mcg to 20 mg intravenous; 800 mcg to 10 mg subcutaneous). Following 14 days of dosing, accumulation ratios for the recommended 2 mg dose for C_{max} and AUC_{0-24h} were approximately 2-fold. Based on clinical results and PK analysis, no relationship could be identified between presence of ADA and bulevirtide PK. The steady state PK parameters of bulevirtide in Study MYR301 (based on population PK/pharmacodynamics (PD) analysis) are provided in Table 3.

Table 3. Steady State PK Parameters of Bulevirtide Following Subcutaneous Administration of HEPCLUDEX 2 mg in HDV-Infected Adults[a]

Parameter[b]	Geometric Mean (90% confidence Interval)
C_{max} (ng/mL)	22.1 (19.2 – 25.5) Min: 5.13; Max: 78.2
AUC_{0-24h} (h●ng/mL)	180 (162 –201) Min: 67.4; Max: 507

a. From Population PK/PD analysis simulations to generate exposure estimates of MYR301 study patients, N=49

Absorption

After subcutaneous injection, maximum plasma concentrations were reached between 0.5 and 3 hours.

The absolute bioavailability of bulevirtide after subcutaneous injection of HEPCLUDEX 2 mg has not been estimated. Absolute bioavailability following subcutaneous injection of 5 mg and 10 mg bulevirtide is estimated to be 48% and 57%, respectively.

Distribution:

In vitro protein binding is high with > 99% of bulevirtide bound to plasma proteins. Following multiple dosing with HEPCLUDEX 2 mg subcutaneous injection, the mean apparent volume of distribution was estimated to be 133 L in Study MYR203.

Metabolism:

No biotransformation study was performed for bulevirtide. Bulevirtide is a linear peptide consisting of L-amino acids, and it is expected to be catabolized by peptidases to amino acids. No active metabolites are expected.

Elimination

No bulevirtide excretion into urine was detected in healthy volunteers. Following multiple dosing with HEPCLUDEX 2 mg subcutaneous injection, total mean apparent systemic clearance of bulevirtide was estimated at 12.8 L/h in Study MYR203. After reaching peak

concentrations, plasma levels declined with $t_{1/2}$ of 3-7 hours.

Special Populations and Conditions

- **Age, Sex, and Race:** Based on population PK/PD modeling, age, sex, or race did not have a clinically relevant impact on the systemic exposure of bulevirtide. This analysis was conducted in patients aged 18-65 of which 67% were male, 89% were White, and 8.9% were Asian.
- **Geriatrics:** The PK of bulevirtide have not been evaluated in the elderly (65 years of age and older).
- **Hepatic Insufficiency:** There is no clinically relevant impact of mild hepatic impairment (Child-Pugh A) on bulevirtide PK. The PK of bulevirtide have not been evaluated in patients with moderate and severe hepatic impairment (Child-Pugh B and C, respectively).
- **Renal Insufficiency:** There is no clinically meaningful impact of mild renal impairment (CrCl ≥ 60 and < 90 mL/min at baseline) on bulevirtide PK based on population PK/PD modeling. The PK of bulevirtide have not been evaluated in patients with moderate and severe renal impairment (CrCl < 60 mL/min), or in patients with end-stage renal disease, including those on dialysis. As bulevirtide is > 99 % protein bound, dialysis is not expected to alter exposures of bulevirtide.

10.4 Immunogenicity

All therapeutic peptides, including HEPCLUDEX, have the potential to induce antidrug antibodies (ADA). The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sampling handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of incidence of ADA across studies or to other products may be misleading. In HEPCLUDEX clinical studies, incidence of ADA was measured using an enzyme-linked immunosorbent assay (ELISA). In Studies MYR203 and MYR301, a total of 64 patients who were treated with HEPCLUDEX 2 mg monotherapy for 48 weeks were eligible for assessment of ADA prevalence; 18 of these patients (28.1%) were positive for ADA prevalence, of which 3 patients (4.7%) were positive for ADA at baseline. There is no evidence that the PK of bulevirtide, or safety or effectiveness of HEPCLUDEX were altered in these patients.

11 Storage, Stability, and Disposal

In order to protect from light, keep the vials in the outer carton. Before reconstitution, the product should be stored in a refrigerator (2°C-8°C).

After reconstitution, chemical and physical in-use stability has been demonstrated for 2 hours at room temperature (up to 25°C). From a microbiological point of view, it is recommended that the product should be used immediately.

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

Part 2: Scientific Information

13 Pharmaceutical Information

Drug Substance

Proper Name: bulevirtide acetate (INNM)

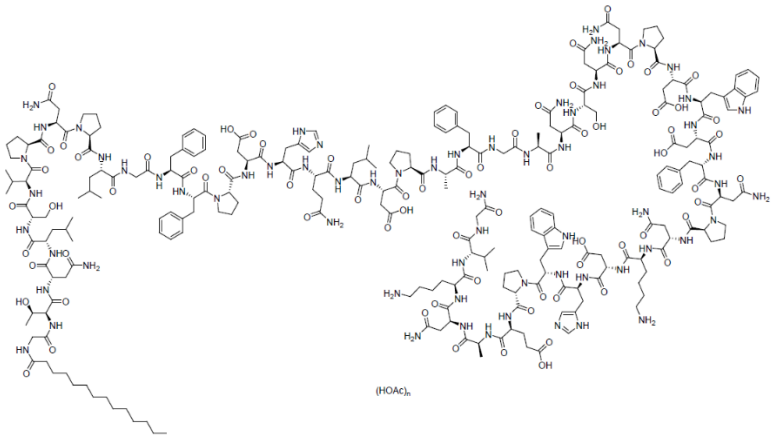
Chemical name:

N-Tetradecanoylglycyl-L-threonyl-L-asparaginyl-L-leucyl-L-seryl-L-valyl-L-prolyl-L-asparaginyl-L-prolyl-L-leucyl-glycyl-L-phenylalanyl-L-phenylalanyl-L-prolyl-L-aspartyl-L-histidyl-L-glutaminyl-L-leucyl-L-aspartyl-L-prolyl-L-alanyl-L-phenylalanyl-glycyl-L-alanyl-L-asparaginyl-L-seryl-L-asparaginyl-L-asparaginyl-L-prolyl-L-aspartyl-L-tryptophanyl-L-aspartyl-L-phenylalanyl-L-asparaginyl-L-prolyl-L-asparaginyl-L-lysyl-L-aspartyl-L-histidyl-L-tryptophanyl-L-prolyl-L-glutamyl-L-alanyl-L-asparaginyl-L-lysyl-L-valylglycinamide, acetate salt

Empirical formula: $C_{248}H_{355}N_{65}O_{72}$ (net, acetate excluded)

Formula weight: 5398.9 g/mol (average mass, net peptide, acetate excluded)

Structural formula:



Physicochemical properties:

Description: Bulevirtide acetate is a white to off-white powder.

Solubility: The solubility of bulevirtide acetate in 50% v/v acetic acid in water is 1 mg/mL.

14 Clinical Trials

14.1 Clinical Trials by Indication

Patients with Chronic Hepatitis Delta (CHD) and Compensated Liver Disease

Pivotal Study (MYR301 Study)

The efficacy of HEPCLUDEX 2 mg for CHD in patients with compensated liver disease was primarily evaluated in a Phase 3, randomized, open-label, multicentre, parallel-group trial, MYR301. In Study MYR301, 100 of 150 patients with CHD were randomized to receive immediate treatment with once daily HEPCLUDEX 2 mg (N=49) or to have treatment (10 mg/day) delayed for 48 weeks (N=51). Randomization was stratified by the presence or absence of compensated cirrhosis. The proportion of patients achieving combined response at Week 48 was the primary endpoint. Combined response was defined as undetectable HDV RNA or decrease in HDV RNA by ≥ 2 $\log_{10}$ IU/mL from baseline and ALT normalization. The key secondary endpoint was the proportion of patients with undetectable HDV RNA at Week 48.

Patients were included if they met the following criteria: CHD (≥ 6 months prior to screening) and positive polymerase chain reaction results for serum/plasma HDV RNA, with or without liver cirrhosis; elevated ALT (> 1 to < 10 × ULN); Child-Pugh score of ≤ 7 points; serum albumin > 28 g/L; creatinine clearance ≥ 60 mL/min (Cockcroft-Gault formula); and total bilirubin < 34.2 µmol/L at screening. Patients with current or previous (within the past 2 years) decompensated liver disease were excluded. Patients with controlled HIV coinfection were allowed. All 100 patients had hepatitis delta genotype 1.

Baseline characteristics were balanced among the immediate and control groups. During the study (through Week 48), 63% of these patients, received concomitant therapy according to the standard care for their underlying HBV infection: the most common concomitant medications were TDF-containing or tenofovir alafenamide-containing products (49%) and entecavir (14%).

The summary of trial design and demographics and baseline characteristics of patients in MYR301 are provided in Table 4 and Table 5.

Table 4. Summary of Patient Demographics for Clinical Trials in MYR301

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
MYR301	Phase 3, Randomized, open-label, multicentre, parallel-group trial	Delayed Treatment for 48 weeks followed by HEPCLUDEX 10 mg/day subcutaneously for 96 weeks (follow-up 96 weeks)	51	41 years (range: 27 to 61)	26 males, 25 females
		HEPCLUDEX 2 mg/day subcutaneously for 144 weeks (follow-up 96 weeks)	49	44 years (range: 19 to 62)	30 males, 19 females

Table 5. Summary of Demographics and Baseline Characteristics in Study MYR301

	Delayed Treatment (Control) (N=51)	HEPCLUDEX 2 mg (N=49)
Demographic Characteristics		
Race		
Asian	11 (21.6%)	8 (16.3%)
Black or African American	0	0
White	40 (78.4%)	41 (83.7%)
Body Mass Index (kg/m^2)		
Mean (SD)	25.26 (3.863)	24.40 (3.086)
Baseline Disease Characteristics		
Previous IFN therapy		
No	22 (43.1%)	23 (46.9%)
Yes	29 (56.9%)	26 (53.1%)
Cirrhosis status at randomization		
Presence	24 (47.1%)	23 (46.9%)
Absence	27 (52.9%)	26 (53.1%)
ALT (U/L)		
Mean (SD)	102 (61.9)	108 (62.5)
HDV RNA (log_{10} IU/mL)		
Mean (SD)	5.08 (1.358)	5.10 (1.194)
HBV DNA (log_{10} IU/mL)		
Mean (SD)	0.89 (0.989)	1.30 (1.292)

Body mass index (kg/m^2) = [Weight (kg)/Height $(cm)^2$] X 10,000
Baseline value was the last available value collected on or prior to first dose of HEPCLUDEX for the HEPCLUDEX 2 mg treatment group, and the last available value collected prior to or at randomization for the control group.

Table 6 presents the virologic and biochemical outcomes for Study MYR301 at Week 48.

Table 6. Study MYR301: HDV RNA (Virologic) and ALT (Biochemical) Outcomes at Week 48 in Patients with CHD and Compensated Liver Disease (Full Analysis Set)

	Week 48[a]		
	Delayed Treatment (Control) (N=51)[d]	**HEPCLUDEX 2 mg (N=49)**	**Difference between HEPCLUDEX 2 mg vs. Control**
Combined Response[b] (95% CI)	2% (0.0% to 10.4%)	45%[c] (30.7% to 59.8%)	43% 96% CI: (27.0% to 58.5%) P-value: <0.0001
ALT normalization[be] (95% CI)	12% (4.4% to 23.9%)	51% (36.3% to 65.6%)	--
Undetectable HDV RNA (95% CI)[e]	0% (0.0% to 7.0%)	12% (4.6% to 24.8%)	--

ALT=Alanine aminotransferase; CI=Confidence Interval

a. For missing values, the last observation carrying forward (LOCF) was used if COVID-19 related; otherwise, missing = failure.
b. Combined response was defined as undetectable HDV RNA or decrease in HDV RNA by ≥ 2 $\log_{10}$ IU/mL from baseline and alanine aminotransferase (ALT) normalization. Undetectable is defined as < lower limit of quantification LLOQ (target not detected). Normalization is defined as an ALT value within the normal range: Russian sites, ≤ 31 U/L for females and ≤ 41 U/L for males; all other sites, ≤ 34 U/L for females and ≤ 49 U/L for males.
c. Combined response at Week 48 was consistent across all predefined subgroups with HEPCLUDEX 2 mg, including age (≥45 years vs. <45 years), baseline ALT (1.5 x ULN vs. ≤1.5 x ULN), cirrhosis status at baseline (presence vs. absence). The same was true for viral response and ALT normalization separately.
d. Patients who received delayed treatment in Study MYR301 (HEPCLUDEX 10 mg after 48 weeks).
e. No pre-specified analyses were planned to compare HEPCLUDEX 2 mg to control for the secondary endpoints of undetectable HDV RNA and ALT normalization.

At Week 48, 73.5% (95% CI: 58.9% to 85.1%) of the patients in the HEPCLUDEX 2 mg treatment group (N=49) had virologic response (≥ 2 $\log_{10}$ IU/mL decline in HDV RNA from baseline or undetectable HDV RNA), compared with 3.9% (95% CI: 0.5% to 13.5%) in the control group (N=51). Patients in the HEPCLUDEX 2 mg treatment group also had a decrease in liver stiffness from baseline, with a -3.06 kPA least squares (LS) mean (95% CI: −4.7 to −1.5), compared with 0.87 kPA LS (95% CI: −0.8 to 2.5) in the control group.

For the primary endpoint of combined response as well as for endpoints of undetectable HDV RNA, virologic response, ALT normalization, and change from baseline in liver stiffness, patients in the HEPCLUDEX 2 mg treatment group demonstrated improvements compared with control at Week 48 and continued to improve through Week 144.

Supportive Phase 2 Study (Study MYR203)

Study MYR203 was a Phase 2, randomized, open-label, multicentre, parallel-group trial in which 15 of 90 patients with CHD were randomized to receive once daily HEPCLUDEX 2 mg for 48 weeks with planned follow-up 24 weeks after end of treatment at Week 72. There were 11 males and 4 females, and patients had a mean age (range) or 42 (26 to 62) years. At Week 48, 53% of patients achieved a combined response (when analysed post hoc); 13% achieved

undetectable HDV RNA (defined in this study as HDV RNA value below lower level of detection [<10 IU/mL]).

15 Microbiology

Antiviral Activity in Cell Culture

Bulevirtide inhibited HDV infection in all the combinations of HBV and HDV genotypes tested *in vitro* in a primary human hepatocytes infection assay. The mean bulevirtide EC_{50} values ranged from 0.21 to 0.68 nM for HDV carrying envelopes across HBV genotype (GT) A-H. For 137 clinical isolates, bulevirtide had mean EC_{50} values of 0.40 nM, 0.45 nM, and 0.70 nM against HDV-1 (n=131), HDV-5 (n=5), and HDV-6 (n=1), respectively. The mean EC_{50} values were 0.58 nM, 0.38 nM, and 0.45 nM against HDV clinical isolates carrying the envelopes from HBV GTA (n=10), GTD (n=122), and GTE (n=5), respectively.

Resistance

In clinical studies, patients who experienced virological breakthrough (2 consecutive increases in HDV RNA of ≥ 1 $\log_{10}$ IU/mL from nadir or 2 or more consecutive positive [>Lower limit of quantification; >LLOQ] HDV RNA values if previously HDV RNA was undetectable (<LLOQ) at 2 or more consecutive time points] or HDV RNA decline < 1 $\log_{10}$ IU/mL met the criteria for resistance analysis. In Study MYR301, in the HEPCLUDEX 2 mg group, at Week 24, 7 patients experienced either virological breakthrough (N=1) or HDV RNA decline < 1 $\log_{10}$ IU/mL (N=6);at Week 48, 11 patients experienced either virological breakthrough (N=7) or HDV RNA decline < 1 $\log_{10}$ IU/mL (N=4); and, at Week 144 (end of treatment), 11 patients experienced either virological breakthrough (N=10) or HDV RNA decline < 1 $\log_{10}$ IU/ml (N=1). In Phase 2 Studies MYR202 and MYR204, in the HEPCLUDEX 2 mg with or without peg-IFNα groups, 15 patients experienced either virological breakthrough (N=11) or HDV RNA decline < 1 $\log_{10}$ IU/ml (N=4) at end of treatment (Week 24 for MYR202; Week 96 for MYR204).

Where sequencing of clinical isolates from the resistance population was successful, amino acid substitutions in the HBV bulevirtide sequence or HDV HDAg sequence were not associated with reduced susceptibility to HEPCLUDEX. All substitutions tested remained susceptible to bulevirtide *in vitro*. Four single nucleotide polymorphisms in the NTCP sequence were observed in the resistance analysis population but none were associated with reduced susceptibility to HEPCLUDEX. Therefore, no resistance to HEPCLUDEX was observed.

16 Non-Clinical Toxicology

General toxicology

No special hazard was revealed based on studies of single dose toxicity and repeated dose toxicity.

Genotoxicity

No studies have been performed to evaluate the genotoxic potential of bulevirtide due to the nature and mechanism of action of the product.

Carcinogenicity

No studies have been performed to evaluate the carcinogenic potential of bulevirtide due to the nature and mechanism of action of the product.

Reproductive and Developmental Toxicology

No special hazard was revealed based on studies of reproduction and development.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrHEPCLUDEX®

Bulevirtide for injection

This Patient Medication Information is written for the person who will be taking HEPCLUDEX. 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 HEPCLUDEX, talk to a healthcare professional.

Serious warnings and precautions box

Your hepatitis may get worse after treatment with HEPCLUDEX is stopped:

Stopping treatment with HEPCLUDEX can make hepatitis delta virus (HDV) and hepatitis B virus (HBV) infections worse. Do not stop taking HEPCLUDEX unless your healthcare professional tells you to. Stopping treatment can reactivate the infection and make your disease worse. If your healthcare professional does stop your treatment with HEPCLUDEX they will closely monitor your liver for several months after. They may also resume your treatment.

What HEPCLUDEX is used for:

HEPCLUDEX is used to treat adults with long-term HDV infection with a condition called compensated liver disease.

HEPCLUDEX is not approved for use in children and adolescents since it has not been studied in these patients.

How HEPCLUDEX works:

HEPCLUDEX blocks HDV from getting into liver cells. This reduces the spread of HDV in the liver and reduces inflammation.

The ingredients in HEPCLUDEX are:

Medicinal ingredient: bulevirtide (as bulevirtide acetate)
Non-medicinal ingredients: hydrochloric acid, mannitol, sodium carbonate anhydrous, sodium hydrogen carbonate, sodium hydroxide

HEPCLUDEX comes in the following dosage form:
Powder for solution: 2 mg / vial of bulevirtide (as bulevirtide acetate)

Do not use HEPCLUDEX if:
- you are allergic to bulevirtide

- you are allergic to or any of the other ingredients in HEPCLUDEX or to any part of the container

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

- have decompensated liver disease which is an advanced liver disease where your liver is not working properly.
- have moderate to severe liver problems.
- have kidney problems.
- have human immunodeficiency virus (HIV).
- have hepatitis C virus.

Other warnings you should know about:

Pregnancy
HEPCLUDEX should not be used during pregnancy unless necessary. This is because it is not known how it might affect an unborn baby. Before you are given this medicine, tell your healthcare professional if you are pregnant, think you may be pregnant or are planning to become pregnant. Your healthcare professional will decide if you will be given HEPCLUDEX.

Breastfeeding
Tell your healthcare professional if you are breastfeeding or planning to breastfeed. It is not known if HEPCLUDEX passes into breastmilk. Ask your healthcare professional for advice before breastfeeding your baby.

Driving and using machines
HEPCLUDEX can cause dizziness and tiredness. This might affect your ability to safely drive and use machines.

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 HEPCLUDEX:

- Carbamazepine, phenytoin, fosphenytoin, oxcarbazepine, eslicarbazepine, used to treat seizures
- Cyclosporine, tacrolimus, sirolimus, and everolimus, used to treat immune system disorders
- Ezetimibe, simvastatin, rosuvastatin, used to treat high cholesterol
- Indomethacin, used to treat inflammation and pain
- Irbesartan, used to treat high blood pressure
- Methylprednisolone, used to treat inflammation, allergies, or asthma
- Midazolam, a medicine to treat insomnia (inability to sleep) and for anaesthesia (to avoid pain during surgery)
- Nifedipine, used to treat high blood pressure
- Prochlorperazine, used to treat nausea and vomiting and psychiatric conditions
- Ritonavir, used to treat HIV infection
- Rosiglitazone, used to treat diabetes

- Sulfasalazine, used to treat arthritis, ulcerative colitis, or Crohn's disease
- Warfarin, used to prevent blood clotting

How to take HEPCLUDEX:

- HEPCLUDEX will be prescribed to you and your treatment monitored by a healthcare professional who has experience in managing liver problems caused by viruses.
- Always take this medicine exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Your healthcare professional will show you how to prepare and to inject HEPCLUDEX. Within the HEPCLUDEX carton you will find "Instructions for Use". These instructions are also found at the end of the Patient Medication Information. The "Instructions for Use" is a step-by-step injection guide for patients and caregivers. Read these before you use HEPCLUDEX. Refer to them as needed after that. Especially, please note the following:

- You must store HEPCLUDEX in the refrigerator (2–8 °C) before you prepare it for injection.
- You must mix HEPCLUDEX with Sterile Water for Injection before you inject it.
- The Sterile Water for Injection, syringe and needles you will need to prepare and inject HEPCLUDEX are all provided separately.
- HEPCLUDEX must only be injected subcutaneously, meaning under the skin. It must not be injected by any other route.

Usual adult dose:

The usual dose is 2 mg once a day injected under the skin. Your healthcare professional will decide how long you should keep using HEPCLUDEX for.

Overdose:

If you think you, or a person you are caring for, have taken too much HEPCLUDEX, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

If you miss a dose, take it as soon as possible on the same day. If you were not able to take the missed dose on the same day, then take your next dose at the usual time. Never take a double dose to make up for a missed dose.

Possible side effects from using HEPCLUDEX:

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

Side effects may include:
- Headache
- Itching
- Reactions at the injection site that may include swelling, redness, irritation, bruising, itchiness, rash, or local pain
- Dizziness

- Nausea
- Tiredness
- An increase in the level of bile salts in the blood
- An increase in white blood cells (eosinophils)

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Allergic reaction: shortness of breath or wheezing, difficulty breathing or swallowing, swelling of the face, lips, tongue or throat, skin rash or hives, feeling faint or dizzy, fast heart rate, nausea or vomiting.			✓

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

Storage:

Store in the original package to protect from light. Store in refrigerator between 2°C-8°C.

Once mixed with Sterile Water for Injection, HEPCLUDEX must be used immediately.

Keep out of reach and sight of children.

Do not reuse the vials, syringe, needles, or any remaining Sterile Water for Injection.

If you want more information about HEPCLUDEX:

- 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: (Drug Product Database: Access the database); the manufacturer's website [www.gilead.ca], or by calling 1-866-207-4267.

This leaflet was prepared by Gilead Sciences Canada, Inc.

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Foster City, CA 94404
USA

Gilead Sciences Canada, Inc.
Mississauga, ON L5N 7K2

e259704-GS-000

Instructions for Use: Step-by-step injection guide for patients / caregivers

Read the **Patient Medication Information** before you use HEPCLUDEX.

Before you begin treatment at home, your healthcare professional will show you how to prepare and inject HEPCLUDEX. This guide shows how to prepare and inject HEPCLUDEX. Talk to your healthcare professional if you have questions, or if you need more information or help. Take your time to carefully prepare and inject HEPCLUDEX.

If you have been prescribed HEPCLUDEX, but are unable to administer it yourself, these instructions for use are for your caregiver. They will prepare and inject HEPCLUDEX for you.

You will need the following items which are obtained separately from HEPCLUDEX:

- Vials with Sterile Water for Injection (referred to below as “sterile water”)
- Disposable syringes
- Longer needles (for HEPCLUDEX preparation)
- Shorter needles (for HEPCLUDEX injection)

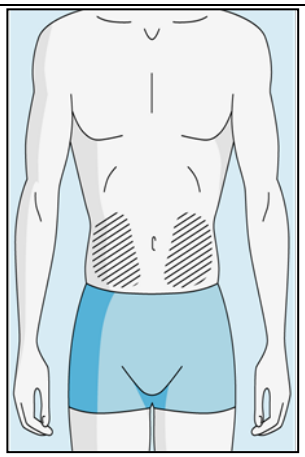
Important! Do not reuse the HEPCLUDEX vial, syringe, needles or any remaining sterile water for injection.

Injection sites

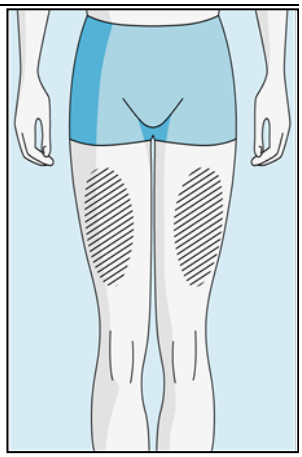
The best places to inject are the abdomen and upper thighs, as shown in the pictures. If administered by a healthcare professional or caregiver only, it can also be injected in the back of the upper arm. In order to reduce injection site reactions, you should change the site of HEPCLUDEX injection regularly.

Do not inject HEPCLUDEX into the following areas: knee, groin, the lower or inner buttocks, directly over a blood vessel, around the navel (belly button), on scar tissue, a bruise, a mole, a surgical scar, tattoo or burn site, or where there is an injection site reaction.

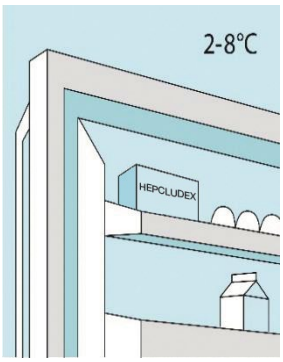
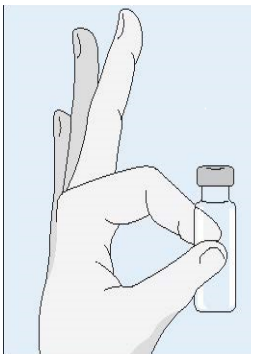
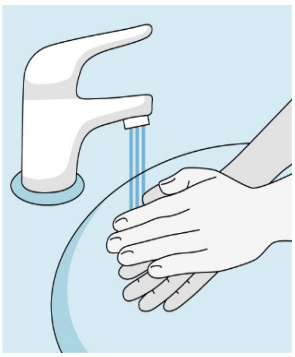
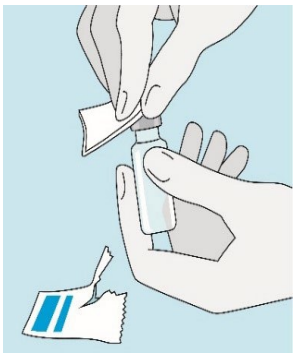
Abdomen



Upper thighs



1. Before you inject

			
1A **Storage**	**1B** **Preparing doses**	**1C** **Wash hands**	**1D** **Clean vial**
HEPCLUDEX vials must be stored in the original packaging in the refrigerator (2–8 °C) in order to protect HEPCLUDEX from light.	The following instructions are for dissolving a single dose.	Wash your hands well using soap and warm water and dry them with a clean towel. Once your hands are clean, **do not** touch anything else other than the medicine, supplies and the area around the injection site.	Wipe the vial top with a new alcohol pad and let the top air-dry. If you touch the rubber top after cleaning it, clean it again with a new alcohol pad.

2. Mix the injection

2A

Draw up sterile water

Pick up the syringe. Put the longer needle (with cap) on the syringe.

Important! Be sure the capped needle is tight by pushing it down slightly while twisting it clockwise.

Pull off the plastic cap.

Open the vial of sterile water for injection. Insert the needle in the vial and gently turn the water vial upside down. Make sure the tip of the needle is always below the surface of the water to help keep air bubbles from entering the syringe.

Slowly pull the plunger back to get 1 mL of sterile water into the syringe. Carefully remove the needle and syringe from the vial.

2B

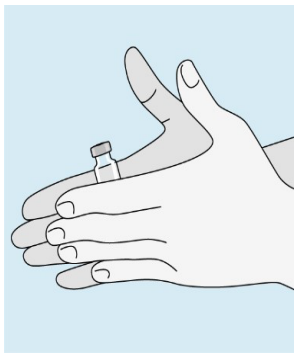
Inject sterile water into the powder

Gently tap the HEPCLUDEX vial to loosen the powder.

Insert the needle with sterile water into the vial at an angle.

Inject the sterile water slowly, so it can drip down the side of the vial into the powder.

Remove the needle from the vial, and put the syringe and needle somewhere safe.



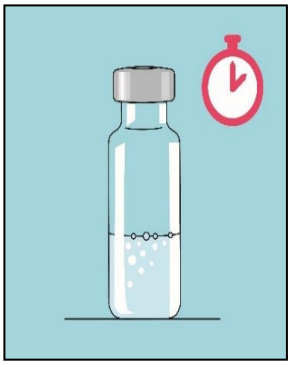
2C

Gently mix HEPCLUDEX solution

Gently tap the HEPCLUDEX vial with your fingertip for 10 seconds to start dissolving the powder.

Then gently swirl or roll the vial between your hands to ensure thorough mixing. Make sure no powder is stuck to the vial wall.

Important! Do not shake the vial. Shaking will make the medicine foam and it will take much longer to dissolve.

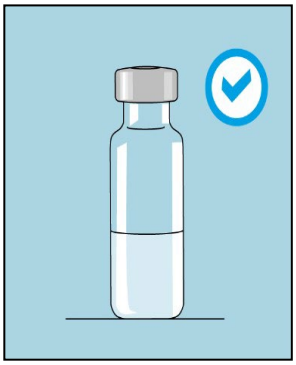


2D

Wait for HEPCLUDEX to fully dissolve

Once the powder starts to dissolve, set it aside and it will completely dissolve.

After tapping, it could take up to 3 minutes to dissolve.



2E

HEPCLUDEX ready for injection

When mixed completely, the HEPCLUDEX solution should be clear.

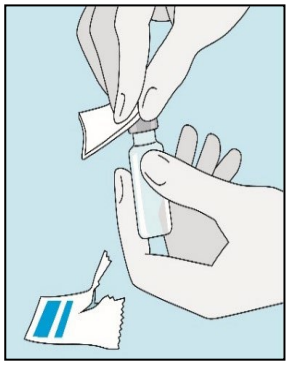
Important! Completely dissolved HEPCLUDEX should be clear and without foam.

If the solution appears foamy or yellowish, allow more time for it to dissolve.

If you see bubbles, gently tap the vial until they disappear.

If you see any particles in the solution once it is completely dissolved, do not use that vial. Contact your healthcare professional that provided it.

Dissolved HEPCLUDEX must be used right away.



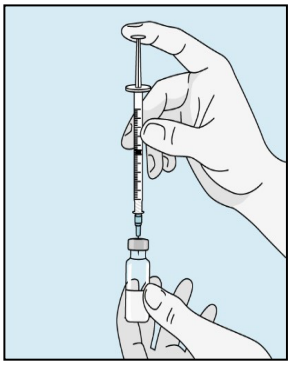
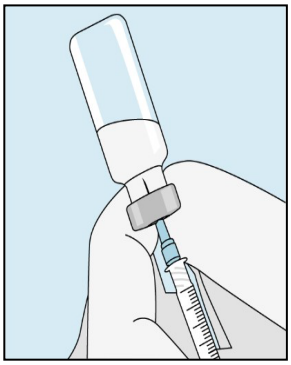
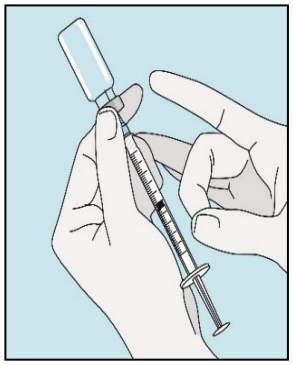
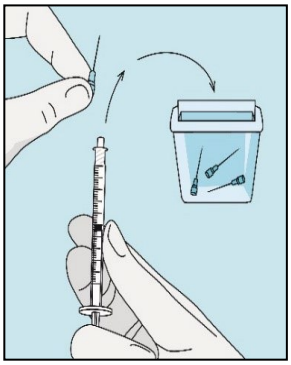
2F

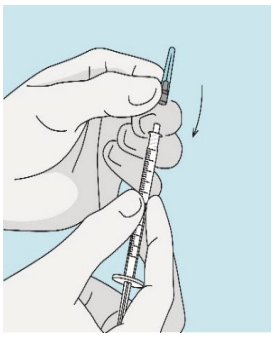
Clean vial

Clean the HEPCLUDEX vial top again, using a new alcohol pad.

Allow it to air dry.

3. Inject a dose

			
3A **Insert needle into vial**	**3B** **Draw up HEPCLUDEX**	**3C** **Finishing preparation**	**3D** **Change and discard the needle**
Pick up the syringe with the long needle attached. Insert the needle into the vial of dissolved HEPCLUDEX.	Gently turn the vial upside down. Make sure the tip of the needle is always below the surface of the HEPCLUDEX solution to help keep air bubbles from entering the syringe. Slowly pull the plunger to get 1 mL of HEPCLUDEX. To be sure you end up with 1 mL of HEPCLUDEX in the syringe, you may need to pull the plunger past the 1 mL mark on the syringe.	Gently tap or flick the syringe and push / pull the plunger to remove extra air and bubbles. Carefully remove the needle and syringe from the vial. **Important!** Discard the vial after use, including any unused excess liquid.	Remove the longer needle from the syringe and dispose of it properly so that nobody can be injured. **Important!** Do not put the plastic cap back on the needle.



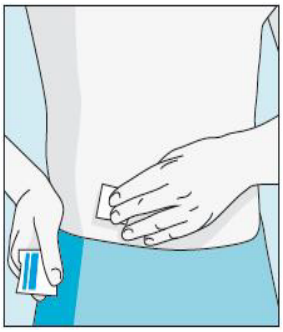
3E

Attach needle for injection

Place the shorter needle with cap on the syringe.

Important! Be sure the capped needle is tightly attached to the syringe by pushing it down slightly while twisting it clockwise.

Pull off the plastic cap.



3F

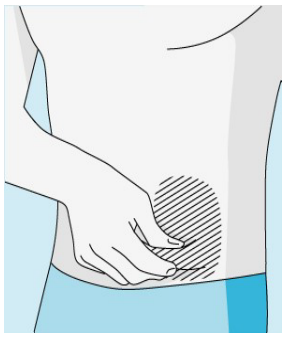
Choose the injection site

Choose a site different from the one you used for your last injection.

Clean the injection site with a new alcohol pad.

Start in the centre, apply pressure and clean in a circular motion, working outward.

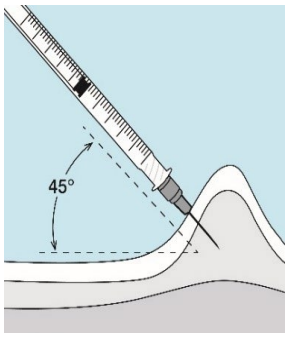
Important! Allow site to air-dry.



3G

Prepare injection site

Pinch and hold a fold of skin around the injection site.



3H

Inject HEPCLUDEX

Pierce the skin with the needle at a 45-degree angle. The needle should be inserted most of the way in.

Slowly push the plunger all the way to inject HEPCLUDEX.

Remove the needle from skin.

Remove the needle from the syringe and dispose of both properly so that nobody can be injured.