ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

HEPCLUDEX 2 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains bulevirtide acetate equivalent to 2 mg bulevirtide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection (powder for injection).

The powder is white to off-white.
After reconstitution, solution with a pH of approximately 9.0 and osmolality of approximately 300 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hepcludex is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult and paediatric patients 3 years of age and older weighing at least 10 kg with compensated liver disease.

4.2 Posology and method of administration

Treatment should be initiated only by a physician experienced in the treatment of patients with HDV infection.

Posology

Bulevirtide should be administered once daily (every 24 hours ± 4 hours) by subcutaneous injection as monotherapy or in co-administration with a nucleoside/nucleotide analogue for treatment of underlying hepatitis B virus (HBV) infection.

The recommended dose of bulevirtide in adult patients is 2 mg once daily.

The recommended dose of bulevirtide in paediatric patients is based on weight as detailed in the Table below.

Dosing for paediatric patients using bulevirtide 2 mg powder for solution for injection

Body Weight (kg)	**Dosing of reconstituted bulevirtide 2 mg powder for solution for injection (ml)**	**Bulevirtide Daily Dose**
10 kg to < 25 kg	0.5 ml	1 mg
25 kg to < 35 kg	0.75 ml	1.5 mg

Body Weight (kg)	Dosing of reconstituted bulevirtide 2 mg powder for solution for injection (ml)	Bulevirtide Daily Dose
35 kg and above	1 ml	2 mg

Concerning co-administration with nucleoside-nucleotide analogues for treatment of HBV infection, refer to section 4.4.

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

Consideration to discontinue the treatment should be given in case of sustained (6 months) HBsAg seroconversion or loss of virological and biochemical response.

Missed doses
If an injection has been omitted and less than 4 hours have elapsed since the scheduled time, the injection must be performed as soon as possible. The time of the next injection will not be calculated from the time of the "rescue" injection, but according to the injection schedule previously established. It is, therefore, necessary to return to the usual pattern of administration, at the appointed time, the following day.

If an injection has been missed and more than 4 hours have elapsed since the scheduled time, the missed dose should not be administered.

The next injection will take place according to the usual schedule (injection of the prescribed dose without doubling), at the appointed time the next day.

If the injection has been made by mistake more than 4 hours after the scheduled time, the next administration must take place in the usual way (i.e. in accordance with the original schedule).

Special populations

Elderly
No data is available in patients > 65 years.

Renal impairment
No studies have been conducted with bulevirtide in patients with renal impairment.
Renal function should be carefully monitored. Elevation of bile salts may occur during treatment. Due to renal excretion of bile salts, elevation of bile salts may be greater in patients with renal impairment.

Hepatic impairment
No dose adjustment is required for patients with mild hepatic impairment (Child-Pugh-Turcotte class A). The safety and efficacy of bulevirtide in patients with decompensated cirrhosis have not been established (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of bulevirtide in patients younger than 18 years of age have not been established in clinical studies. The recommended dosage of bulevirtide for paediatric patients 3 years of age and older weighing at least 10 kg with compensated liver disease is based on population pharmacokinetic/pharmacodynamic modelling and simulation (see section 5.2).

Method of administration

For subcutaneous use only. Bulevirtide may be injected into sites such as the upper thigh, or abdomen.

Appropriate training should be given to the patients self-administering the product or to the caregivers administering the product to minimise the risk of the injection site reactions.

The “Step-by-step injection guide”, provided in the carton, must be followed carefully by the patient or the caregiver.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

HDV and HBV genotype

HDV genotype 1 was predominant in the clinical trials population. It is not known whether HDV or HBV genotype affects the clinical efficacy of bulevirtide.

Decompensated liver disease

The pharmacokinetics, safety and efficacy of bulevirtide in patients with decompensated cirrhosis has not been established. The use in patients with decompensated liver disease is not recommended.

Co-infection with HBV

The underlying HBV infection should be simultaneously managed according to current treatment guidelines. In the clinical study of bulevirtide MYR202, only patients with signs of active hepatitis despite nucleoside/nucleotide analogue treatment were included; tenofovir disoproxil fumarate was co-administered with bulevirtide. Close monitoring of HBV-DNA levels is recommended.

Hepatitis exacerbations after treatment cessation

Discontinuation of treatment with bulevirtide can lead to reactivation of HDV and HBV infections and exacerbation of hepatitis. In case of treatment discontinuation, careful monitoring of liver function tests including transaminase levels, as well as HBV DNA and HDV RNA viral load should be performed.

Co-infection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV)

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

Excipients

This medicine contains less than 1 mmol of sodium (23 mg) per ml, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

In vitro, it has been shown, that certain medicinal products can inhibit bulevirtide target sodium-taurocholate co-transporting polypeptide (NTCP). The co-administration of such medicinal products (e.g. sulfasalazin, irbesartan, ezetimibe, ritonavir, and ciclosporin A) is not recommended.

As a precautionary measure, close clinical monitoring is warranted when NTCP substrates (e.g. estrone-3-sulfate, fluvastatin, atorvastatin, pitavastatin, pravastatin, rosuvastatin, and thyroid

hormones) are co-administered with bulevirtide. When possible, co-administration of these substrates should be avoided.

In vitro an inhibition of OATP1B1/3 transporters by bulevirtide was observed, albeit only at a concentration ≥ 0.5 µM, which is only reached *in vivo* after administration of high bulevirtide doses (10 mg subcutaneous). The clinical relevance of these findings is unknown. As a precautionary measure, close clinical monitoring is warranted when OATP1B1/3 substrates (e.g. atorvastatin, bosentan, docetaxel, fexofenadine, glecaprevir, glyburide (glibenclamide), grazoprevir, nateglinide, paclitaxel, paritaprevir, pitavastatin, pravastatin, repaglinide, rosuvastatin, simeprevir, simvastatin, olmesartan, telmisartan, valsartan, voxilaprevir) are co-administered. When possible, co-administration of these substrates should be avoided.

In a clinical study in healthy subjects, co-administration of tenofovir and bulevirtide revealed no impact on tenofovir pharmacokinetics.

No CYP inhibition by bulevirtide was observed *in vitro* at clinically relevant concentrations. However, in a clinical study, an approximately 40% increase in geometric mean of partial $AUC_{2\text{-}4h}$ values of co-administered midazolam (CYP3A4 substrate) was observed in combination of high dose bulevirtide (10 mg) and tenofovir (245 mg), whereas no significant influence on midazolam $AUC_{2\text{-}4h}$ was detected for tenofovir alone. As a precautionary measure, close clinical monitoring is warranted for co-administered narrow-therapeutic-index drugs which are sensitive CYP3A4 substrates (e.g. cyclosporine, carbamazepine, simvastatin, sirolimus, and tacrolimus).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of bulevirtide in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

As a precautious measure, it is preferable to avoid the use of bulevirtide during pregnancy and in women of child-bearing potential not using contraception.

Breast-feeding

It is unknown whether bulevirtide is excreted in human milk. Therefore, a decision must be made whether to discontinue breast-feeding or to discontinue / abstain from treatment with bulevirtide, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No human data on the effect of bulevirtide on fertility are available. In animal studies, no effects of bulevirtide on male or female mating and fertility were noted.

4.7 Effects on ability to drive and use machines

The product has minor influence on the ability to drive and use machines. Patients should be informed that dizziness has been reported during treatment with bulevirtide (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions are increase in bile salts (very common), headache (very common), pruritus (very common) and injection site reactions (very common).
Increases in bile salts were usually asymptomatic and reversible upon treatment discontinuation.

The most frequently reported serious adverse reaction is an exacerbation of hepatitis after discontinuation of bulevirtide, possibly related to virologic rebound after discontinuation of treatment (see section 4.4).

Tabulated list of adverse reactions

The following adverse reactions are based on pooled data from clinical studies in adults and post-marketing experience.
Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to, < 1/10), uncommon (≥ 1/1,000 to < 1/100).

Frequency	Adverse reaction
Blood and lymphatic system disorders	
Common	Eosinophilia
Immune system disorders	
Uncommon	Hypersensitivity, including anaphylactic reaction[a]
Nervous system disorders	
Very common	Headache
Common	Dizziness
Gastrointestinal disorders	
Common	Nausea
Hepatobiliary disorders	
Very common	Total bile salts increased
Skin and subcutaneous tissue disorders	
Very common	Pruritus
Musculoskeletal and connective tissue disorders	
Common	Arthralgia
General disorders and administration site conditions	
Very common	Injection site reactions[b]
Common	Fatigue
Common	Influenza like illness

a Adverse reaction identified through post-marketing surveillance
b Includes injection site erythema, injection site reaction, injection site pain, injection site induration, injection site swelling, injection site rash, injection site haematoma, injection site pruritus and injection site dermatitis

Description of selected adverse reactions

Total Bile Salts Increased
Asymptomatic bile salt elevations, associated with the mechanism of action of bulevirtide, were very commonly observed in clinical studies of bulevirtide; the bile salt elevations resolved upon discontinuation of bulevirtide treatment.

Due to renal excretion of bile salts, elevation of bile salts may be greater in patients with renal impairment.

There are no data available on the long-term impact (> 96 weeks) of this bile salt increase induced by bulevirtide.

Injection Site Reactions
Bulevirtide is intended for subcutaneous injection which is associated with risks for injection site reactions including swelling, redness, irritation, itchiness, infection, haematoma, rash, induration and local pain. These local reactions are more likely to appear if the injection is accidentally misplaced or the solution is accidentally misdirected to the soft tissue.

Eosinophilia
Increases in eosinophil counts were commonly observed in patients receiving bulevirtide treatment; there were no associated clinical sequelae, hepatic adverse reactions, or significant liver-related laboratory abnormalities.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, other antivirals. ATC code: J05AX28

Mechanism of action

Bulevirtide blocks the entry of HBV and HDV into hepatocytes by binding to and inactivating NTCP, a bile salt liver transporter serving as essential HBV/HDV entry receptor.

Clinical efficacy and safety

The clinical efficacy and safety of bulevirtide was investigated in one Phase 3 study and two Phase 2 studies. Patients with chronic HDV infection and active hepatitis were included. The population of these three studies was mainly Caucasian, HDV genotype 1 was predominant.

MYR301 study
In Study 301, 100 of 150 patients with chronic HDV infection were randomised to receive immediate treatment with once daily bulevirtide 2 mg (N=49) or to have treatment delayed for 48 weeks (N=51). Randomisation was stratified by the presence or absence of compensated cirrhosis.

Of the 49 patients in the immediate treatment group, mean age was 44 years; 61% were male, 84% were White, and 16% were Asian. Of the 51 patients in the delayed treatment group, mean age was 41 years; 51% were male, 78% were White and 22% were Asian. All 100 patients had infection with HDV genotype 1.

Baseline characteristics were balanced among the immediate and delayed treatment groups. Of the patients who received 2 mg bulevirtide at baseline, mean plasma HDV RNA was 5.1 $\log_{10}$ IU/mL, mean ALT was 108 U/L, 47% of patients had a history of cirrhosis, and 53% were interferon experienced. 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 tenofovir disoproxil fumarate-containing or tenofovir alafenamide-containing products (49%) and entecavir (14%).

The table below presents the virologic and biochemical outcomes for immediate treatment with bulevirtide 2 mg once daily and delayed treatment at Week 48.

	Week 48[a]	
	Bulevirtide 2 mg (Immediate Treatment) (N=49)	**Delayed Treatment (N=51)**
Undetectable[b] HDV RNA or decrease in HDV RNA by ≥ 2 log_{10} IU/mL and ALT normalisation[c]	45%[d]	2%
Undetectable[b] HDV RNA or decrease in HDV RNA by ≥ 2 log_{10} IU/mL	71%[e]	4%
ALT normalisation[c]	51%[e]	12%

a. For the first endpoint, for missing values, the last observation carrying forward (LOCF) was used if COVID-19 related; otherwise, missing = failure; for the second and third endpoints, missing = failure.
b. < lower limit of quantification LLOQ (target not detected)
c. 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.
d. p-value < 0.0001.
e. Not multiplicity controlled.

MYR202 study
In Study MYR202, 56 of 118 patients with chronic HDV infection and ongoing viral replication who were interferon experienced, had a contraindication to interferon, or were cirrhotic, were randomised to receive bulevirtide 2 mg + TDF (N=28) or TDF alone (N=28) for 24 weeks. At Week 24, 21% of patients in the bulevirtide 2 mg + TDF group achieved a combined response, 54% achieved undetectable HDV RNA (defined as < limit of detection [LOD], where LOD was 14 IU/mL) or decrease by ≥ 2 log_{10} IU/mL, and 43% achieved ALT normalisation. At Week 24, no patients in the TDF group achieved a combined response, 4% achieved undetectable HDV RNA or decrease in HDV RNA by ≥ 2 log_{10} IU/mL, and 7% achieved ALT normalisation (normal ALT was defined as ≤ 31 U/L for females and ≤ 41 U/L for males).

MYR203 study
In Study MYR203, a total of 15 patients were treated with bulevirtide 2 mg daily for 48 weeks. In this limited dataset, the efficacy and safety profiles were not substantially different than for patients treated for 24 weeks. Two patients developed virological breakthrough, possibly related to medication non-adherence.

Immunogenicity

Bulevirtide has the potential to induce antidrug antibodies (ADA), as detected in clinical studies using an enzyme-linked immunosorbent assay (ELISA). In Studies MYR203 and MYR301, a total of 64 patients who were treated with bulevirtide 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 pharmacokinetics, safety, or effectiveness of bulevirtide were altered in these patients.

Paediatric population

See section 4.2 and 5.2 for information on paediatric use.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of bulevirtide were characterised after intravenous and subcutaneous administration. The exposure of bulevirtide increased disproportionally while the apparent clearance and apparent volume of distribution decreased with higher doses.

Distribution

The estimated volume of distribution is smaller than total body water. *In vitro* plasma protein binding is high with > 99% of bulevirtide bound to plasma proteins.

Biotransformation

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

Based on the results of *in vitro* interaction studies, bulevirtide did not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4.

No *in vitro* induction of CYP1A2, CYP2B6 or CYP3A4 by bulevirtide was observed.

Based on the *in vitro* studies, no clinically relevant interaction is expected for most common efflux transporters (MDR1, BCRP, BSEP, MATE1 and MATE2K) and uptake transporters (OATP2B1, OAT1, OAT3, OCT1 and OCT2). A specific *in vitro* interaction was identified with the organic anion transporting polypeptides, OATP1B1 and OATP1B3 with IC_{50} values of 0.5 and 8.7 μM, respectively.

Elimination

No bulevirtide excretion into urine was detected in healthy volunteers. Elimination via target (NTCP) binding is assumed to be the main route. Both distribution and elimination after multiple dosing were reduced compared to values estimated after the first dose. Accumulation ratios for 2 mg dose for C_{max} and AUC were approximately 2-fold. Steady state is assumed to be achieved within the first weeks of administration. After reaching peak concentrations, plasma levels declined with $t_{1/2}$ of 4-7 hours.

Other special populations

Renal impairment
No studies have been conducted with bulevirtide in patients with renal impairment.

Hepatic impairment
No studies have been conducted with bulevirtide in patients with moderate and severe hepatic impairment.

Elderly
No data is available in patients older than 65 years of age.

Paediatric population
The pharmacokinetics of bulevirtide in paediatric patients have not been evaluated in a clinical study. Dosing recommendations for paediatric patients 3 years of age and older weighing at least 10 kg are based on exposure matching the paediatric bulevirtide concentration to concentrations observed in adults with HDV infection treated with bulevirtide 2 mg once daily. Simulated steady-state plasma exposures of bulevirtide weight-based dosing (see section 4.2) once daily by subcutaneous injection in paediatric patients are predicted to be within the safe and efficacious exposures associated with 2 mg bulevirtide once daily by subcutaneous injection in adults.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, and toxicity to reproduction and development.

No genotoxicity and carcinogenicity studies were conducted due to the nature and mechanism of action of the product.

A pre and post-natal development study (PPND) has been completed in rats and did not show any bulevirtide-related toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate anhydrous
Sodium hydrogen carbonate
Mannitol
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, except those mentioned in section 6.6.

6.3 Shelf life

2 years

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.

6.4 Special precautions for storage

Store in a refrigerator (2°C -8°C). In order to protect from light, keep the vials in the outer carton.

6.5 Nature and contents of container

Colourless glass vial with bromobutyl or chlorobutyl rubber stopper, sealed with a flip off cap (aluminium with plastic disc).

Pack-size of 30 vials.

6.6 Special precautions for disposal and other handling

Each vial is intended for single use only and the excess of unused product must be properly disposed of. Sterile water for injections, syringes (with necessary graduations according to the dose to be administered), needle tips and alcohol wipes should be provided to the patient.

Instructions for use

The bulevirtide vial should be taken from the refrigerator shortly before the injection and the blue flip-off cap has to be removed. A single-use syringe should be taken and a needle tip attached to the syringe head in order to extract 1 ml of sterile water for injection into the syringe. The syringe needle with the syringe containing the sterile water for injection should then be inserted into the bulevirtide vial through the rubber stopper. The sterile water for injection inside the syringe will then be injected into the bulevirtide vial and the bulevirtide vial has to be carefully swayed until a clear solution is obtained. The required content for the dose to be administered from the bulevirtide vial has to be extracted back into the same syringe with the same needle tip (See Table below).

Required dose volumes to be extracted for administration of bulevirtide

Bulevirtide Dose	Required volume of reconstituted bulevirtide to be extracted
1 mg	0.5 ml
1.5 mg	0.75 ml
2 mg	1 ml

The needle tip has then to be detached from the syringe. To this syringe, a needle tip for subcutaneous injection has to be attached and any remaining air bubbles have to be removed from the syringe prior to injection. The content of the bulevirtide vial will then be administered subcutaneously.

Disposal of medicinal product and auxiliary components

All used components/ waste should be handled according to the current regulation.

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

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1446/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 July 2020
Date of latest renewal: 17 July 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Gilead Sciences Ireland UC
IDA Business and Technology Park
Carrigtohill
Co. Cork
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4. 2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

1. Periodic safety update reports (PSURs)

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

2. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
1. At the request of the European Medicines Agency;
2. Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

HEPCLUDEX 2 mg powder for solution for injection
bulevirtide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 2 mg bulevirtide (as acetate).

3. LIST OF EXCIPIENTS

Excipients: sodium carbonate anhydrous, sodium hydrogen carbonate, mannitol, hydrochloric acid, and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
30 single-use vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use after reconstitution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. In order to protect from light, keep the vials in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1446/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

HEPCLUDEX

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

HEPCLUDEX 2 mg powder for injection
bulevirtide
Subcutaneous use after reconstitution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 mg

6. OTHER

Store in a refrigerator

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Hepcludex 2 mg powder for solution for injection
bulevirtide

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

If Hepcludex has been prescribed for your child, please note that all the information in this leaflet is addressed to your child (in this case please read "your child" instead of "you").

1. What Hepcludex is and what it is used for

What Hepcludex is
Hepcludex contains the active substance bulevirtide, which is an antiviral medicine.

What Hepcludex is used for
Hepcludex is used to treat long-term (chronic) hepatitis delta virus (HDV) infection in adults and children 3 years of age and older weighing at least 10 kg with compensated liver disease (when the liver is still working well enough).

Infection with hepatitis delta virus causes inflammation of the liver.

How Hepcludex works
HDV uses a particular protein in liver cells to enter the cells. Bulevirtide, the active substance in this medicine blocks the protein and so prevents the HDV from getting into liver cells. This reduces the spread of HDV in the liver and reduces inflammation.

2. What you need to know before you use Hepcludex

Do not use Hepcludex:
1. if you are allergic to bulevirtide or any of the other ingredients of this medicine (listed in section 6).

If you are not sure, speak to your doctor before using this medicine.

Warnings and precautions
Do not stop your treatment with Hepcludex unless your doctor advises you to do so. Stopping the treatment can reactivate the infection and worsen your disease.

Talk to your doctor or pharmacist before using Hepcludex:

1. if your liver is not working well enough – it is not known how well Hepcludex works in these circumstances; if your liver is not functioning well, using Hepcludex is not recommended.

2. if you have had kidney disease or if tests have shown problems with your kidneys. Before and during treatment, your doctor may order blood tests to check how well your kidneys are working;

3. if you have HIV infection or hepatitis C - it is not known how well Hepcludex works in these circumstances; your doctor may order blood tests to check the status of your HIV or hepatitis C infection

Children and adolescents
Children under 3 years of age or weighing less than 10 kg should not be treated with Hepcludex.

Other medicines and Hepcludex
Please tell your doctor if you are using, have recently used, or might use any other medicines.

Some medicines can increase side effects of Hepcludex and you should not use them at the same time. This is why you should tell your doctor if you are using any of these medicines:

1. ciclosporin, a medicine that supresses the immune system;
2. ezetimibe, used for treating high blood cholesterol;
3. irbesartan, used for treating high blood pressure and heart disease;
4. ritonavir, used to treat HIV infection;
5. sulfasalazine, (used for treating rheumatoid arthritis, ulcerative colitis, and Crohn's disease.

Some medicines can increase or decrease the effects of Hepcludex when used together. In some cases, you may need to have certain tests or your doctor may change the dose or monitor you regularly:
1. cancer treatments (e.g. dasatinib, docetaxel, ibrutinib, paclitaxel);
2. antihistamine medicines used for allergies (e.g. ebastine, fexofenadine);
3. immune system medicines (e.g. everolimus, sirolimus, tacrolimus);
4. medicines for hepatitis C and HIV treatment (e.g. darunavir, glecaprevir, grazoprevir, indinavir, maraviroc, paritaprevir, saquinavir, simeprevir, tipranavir, voxilaprevir);
5. medicines for diabetes (e.g. glibenclamide, nateglinide, repaglinide);
6. medicines for erectile dysfunction (e.g., avanafil, sildenafil, vardenafil);
7. medicines for treating high blood pressure and heart disease (e.g. olmesartan, telmisartan, valsartan);
8. statin, medicines used for high blood cholesterol (e.g. atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin);
9. thyroid hormones used to treat thyroid problems;
10. alfentanil, an opioid medicine used to treat severe pain;
11. bosentan, used for pulmonary arterial hypertension;
12. buspirone, an anxiety medicine;
13. budesonide, used for asthma and chronic obstructive pulmonary disease;
14. conivaptan and tolvaptan, used to treat hyponatraemia (low sodium levels);
15. darifenacin, used to treat urinary incontinence;
16. dronedarone, heart medicine for cardiac arrhythmias;
17. eletriptan, used for migraine headaches;
18. eplerenone, used for high blood pressure;
19. estrone-3-sulfate a menopausal hormone medicine;
20. felodipine and nisoldipine (heart medicines);

21. lomitapide, used for high blood cholesterol;
22. lurasidone and quetiapine, antipsychotic medicines for psychiatric disorders;
23. midazolam and triazolam, medicines to treat insomnia (inability to sleep) and for anaesthesia (to avoid pain during surgery);
24. naloxegol, used to treat dependence on opioid medicines for severe pain;
25. ticagrelor, anticoagulant to prevent blood clotting.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. You should not use this medicine unless specifically told to by your doctor.

If you are a woman of childbearing potential, you should not use this medicine without using an effective method of contraception.

Talk to your doctor to decide whether you should breastfeed while using Hepcludex.
It is not known whether Hepcludex can pass into breast milk. Therefore, a decision must be made whether to discontinue breast-feeding or to discontinue Hepcludex.

Driving and using machines
Dizziness and tiredness are side effects which may impair your ability to drive and use machines. If you have any concerns consult your doctor.

Hepcludex contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially "sodium-free".

3. How to use Hepcludex

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Dosage
Hepcludex is to be given once a day, as an injection just under the skin (subcutaneous injection).
Your doctor and nurse will show you how to prepare and inject Hepcludex. This package leaflet contains a step-by-step injection guide to help you inject the medicine (see section 7).

Recommended dose
The recommended dose of Hepcludex in adults is 2 mg once daily.

The recommended dose of Hepcludex in patients aged 3 to less than 18 years depends on weight, as outlined in the table below.

Age/ weight	Dose	Amount to inject
Children aged 3 years or more who weigh 35 kg or more	2 mg, once a day	1.0 ml
Children aged 3 and over, who weigh at least 25 kg but less than 35 kg	1.5 mg, once a day	0.75 ml
Children aged 3 and over, who weigh at least 10 kg but less than 25 kg	1 mg, once a day	0.5 ml

Your doctor will say how long you need to use the medicine for.

If you use more Hepcludex than you should
If you think you may have used more than you should, tell your doctor immediately.

If you forget to use Hepcludex
If less than 4 hours have passed since your missed dose of Hepcludex, take the missing dose as soon as possible and take your next scheduled dose at the usual time.

If more than 4 hours have passed since your missed dose of Hepcludex, **do not** take the missed dose. Take the next dose the following day at the usual time. Do not take a double dose to make up for the missed dose. Tell your doctor if you have missed a dose of Hepcludex.

If you stop using Hepcludex
If you do not want to use Hepcludex anymore, talk to your doctor before stopping the treatment. Stopping the treatment can reactivate the infection and worsen your disease. Tell your doctor immediately about any changes in symptoms after stopping treatment.

If you have any further questions on the use of Hepcludex, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Please tell your doctor if any of the side effects occur, or if you notice any side effects not listed in this leaflet.

The following side effect is **very common** (this may affect more than 1 in 10 people):
- headache
- itching
- reactions at the injection site that may include swelling, redness, irritation, bruising, itchiness, rash, hardening, infection or local pain

The following side effects are **common** (these may affect up to 1 in 10 people):
- dizziness
- nausea
- tiredness
- flu-like illness
- joint pain

The following side effects are **uncommon** (these may affect up to 1 in 100 people):
- allergic reactions, including anaphylactic reaction (sudden life-threatening allergic reaction).

Symptoms of allergic reactions can include:
- shortness of breath or wheezing
- swelling of the face, lips, tongue or throat (angioedema)
- skin rashes
- changes to blood pressure or heart rate.

Symptoms of anaphylactic reaction are like those of allergic reaction, but more severe and require immediate medical care.

Blood tests may also show:
- an increase in the level of bile acids in the blood (very common)
- an increase in white blood cells (eosinophils) (common).

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help to provide more information on the safety of this medicine.

5. How to store Hepcludex

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C -8°C). In order to protect from light, keep the vials in the outer carton.

The reconstituted solution should be used immediately. However, if this is not possible it can be stored for up to 2 hours at a temperature of up to 25°C.

Do not throw away any medicines or used needles via wastewater or household waste. Ask your pharmacist how to safely dispose medicines and used needles.

6. Contents of the pack and other information

What Hepcludex contains
The active substance is bulevirtide 2 mg. Each vial contains bulevirtide acetate equivalent to 2 mg bulevirtide.

The other ingredients are: sodium carbonate anhydrous, sodium hydrogen carbonate, mannitol, hydrochloric acid, sodium hydroxide.

What Hepcludex looks like and contents of the pack
Bulevirtide is a powder for solution for injection and comes as a white to off-white powder.
Each carton contains 30 single doses.

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County Cork, T45 DP77
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Manufacturer
Gilead Sciences Ireland UC
IDA Business and Technology Park
Carrigtohill
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in <{MM/YYYY}><{month YYYY}>.

7. Step-by-step injection guide for patients/caregivers

Before using Hepcludex, you must first read sections 1 – 6 of this package leaflet.

Before you begin treatment with this medicine at home, your doctor or nurse will show you how to prepare and inject Hepcludex. This guide shows how to prepare and inject Hepcludex. Speak with your doctor or nurse if you are unclear about anything or you have questions or need more information or help. Take your time to carefully prepare and inject Hepcludex.

If your child has been prescribed Hepcludex , but is unable to administer it themselves, please note that all the information in this step-by-step injection guide for administration of Hepcludex is addressed to you, as the child's caregiver.

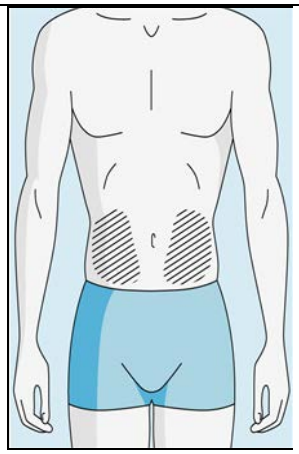
Children or adolescents should only inject themselves following training from a healthcare professional and under supervision of an adult caregiver.

Injection sites

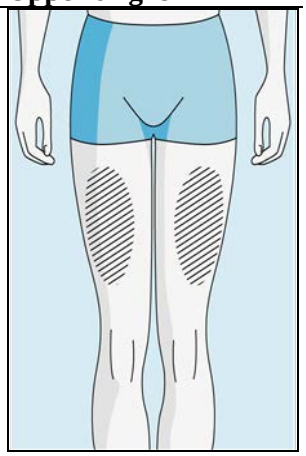
The best places to inject are the abdomen and upper thighs, shown in the pictures. In order to reduce injection site reactions, you may change the site of Hepcludex injection regularly.

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.

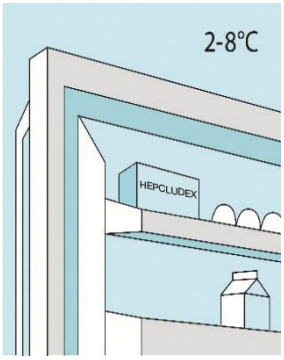
Abdomen



Upper thighs

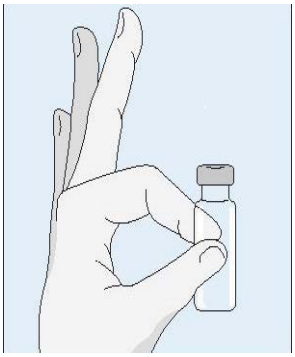


1. Before you inject



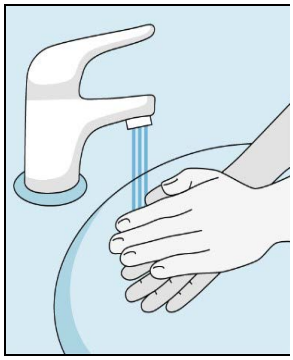
1A
Storage

Hepcludex vials must be stored in the original packaging in the refrigerator (2–8 °C) in order to protect Hepcludex from light.



1B
Preparing doses

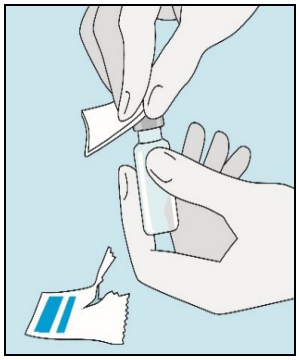
The following instructions are for dissolving a single dose.



1C
Wash hands

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.

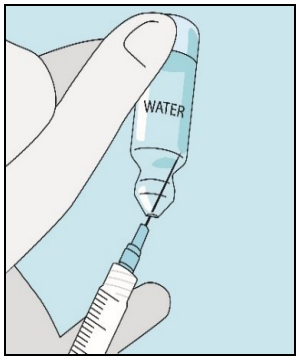


1D
Clean vial

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 on.

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 1.0 ml of sterile water into the syringe. Carefully remove the needle and syringe from the vial.

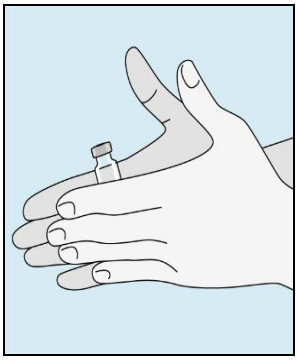
2B
Inject sterile water into the powder

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.

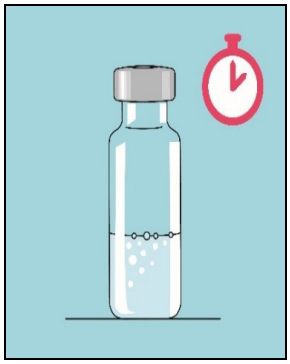


2C
Gently mix Hepcludex

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

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

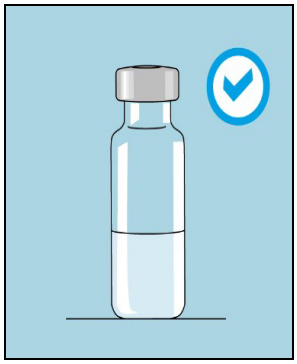
Important! Do not shake the vial. Shaking will make the medicine foam and it will take much longer to dissolve.



2D
Inspect Hepcludex

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

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



2E
Hepcludex ready for injection

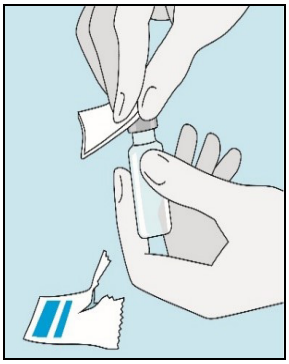
When mixed completely, the Hepcludex solution should be clear.

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 doctor or pharmacist that provided it.

Reconstituted Hepcludex must be used immediately.

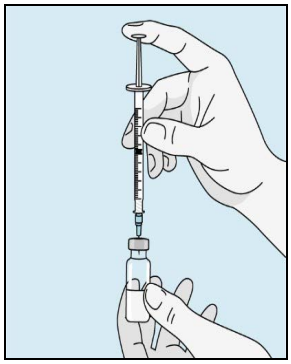


2F
Clean vial

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

Allow it to air dry.

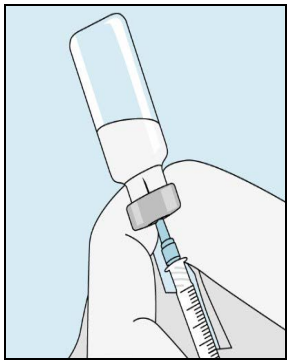
3. Inject a dose



3A
Insert needle into vial

Pick up the syringe.

Insert the needle into the vial of liquid Hepcludex .



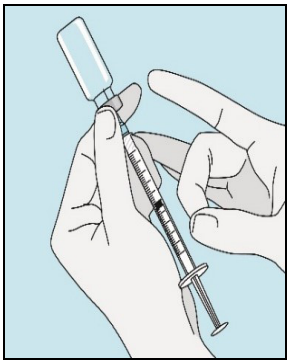
3B
Draw up Hepcludex

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.

Double check the amount to inject, using the table called *Recommended dose* in section 3 of the package leaflet.

Slowly pull the plunger to get the amount of liquid you need.



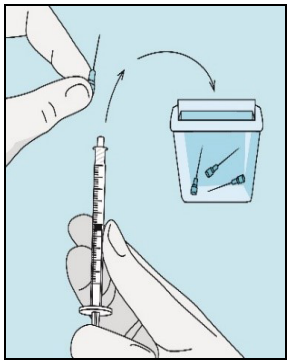
3C
Finishing preparation

Gently tap or flick the syringe and push/pull the plunger to remove extra air and bubbles.

To be sure you end up with the right amount of Hepcludex in the syringe, you may need to pull the plunger past the mark on the syringe.

Carefully remove the needle and syringe from the vial.

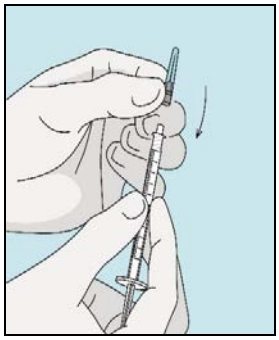
Important! Discard the vial after use, including any unused excess liquid.



3D Change and discard the needle

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 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.

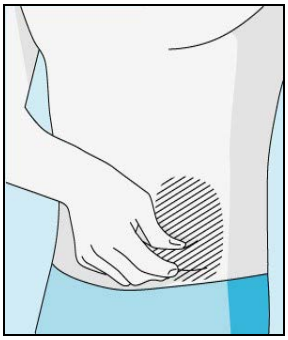
3F
Choose the injection site

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

Clean the injection site with a new alcohol pad.

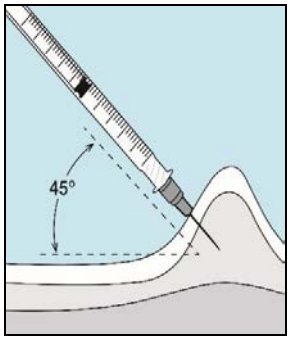
Start in the centre, apply pressure and clean in a circular motion, working outward.

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 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 (see 3D).