Hepcludex®
Powder for solution for injection

1. Name of the medicinal product
Hepcludex®

2. Qualitative and quantitative composition
Each vial contains bulevirtide (as acetate) equivalent to 2 mg bulevirtide.
For full list of excipients, see section 6.1.

3. Pharmaceutical form
Sterile, preservative-free, white to off-white lyophilized powder that is to be reconstituted with 1 mL of sterile water for injection prior to administration by subcutaneous injection. Each vial contains 2 mg bulevirtide. Following reconstitution, each vial contains 2 mg/mL of bulevirtide solution.
The administered dose of bulevirtide is 1.7 mg due to the solution hold up in the syringe and the needle.

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 patients with compensated liver disease.

4.2 Posology and method of administration
Therapy should be initiated by a physician experienced in the management of patients with HDV infection.
In all patients, manage the underlying hepatitis B virus (HBV) infection simultaneously as clinically appropriate according to the official guidelines.

Recommended Dosage

Hepcludex should be administered once daily by subcutaneous injection.
The recommended dosage in adults is Hepcludex 2 mg once daily, corresponding to a delivered dose of 1.7 mg.

Duration of treatment

The optimal treatment duration is unknown. Treatment should be continued as long as associated with clinical benefit. Long-term treatment may be considered with the duration of treatment being individualized based on the kinetics of ALT, HDV-RNA and HBsAg, the tolerability of the treatment and the medical assessment by the treating physician. Consideration to discontinue the treatment should be given in case of sustained (6 months) HBsAg seroconversion.

Mode of administration

For subcutaneous use only. Hepcludex may be administered into upper thigh or lower abdomen.

Healthcare professionals should train patients in the proper technique for reconstituting Hepcludex with sterile water for injection and self-administering subcutaneous injections using a syringe.

Please see “Other Information” for instructions on reconstitution of Hepcludex before administration and the package leaflet including Instructions for Use for details on the preparation and administration of Hepcludex.

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.

Special dosage instructions

Patients with hepatic disorders

No dosage adjustment of Hepcludex is required in patients with mild hepatic impairment (Child-Pugh A). The safety and efficacy of Hepcludex in patients with Child-Pugh B or C hepatic impairment or patients with decompensated liver disease have not been evaluated (see section 5.2 “Pharmacokinetic Properties”).

Patients with renal disorders

No dosage adjustment of Hepcludex is required in patients with mild renal impairment (creatinine clearance [CrCl] ≥ 60 and < 90 mL/min). The safety and efficacy of Hepcludex in patients with CrCl < 60 mL/min have not been evaluated (see section 5.2 “Pharmacokinetic Properties”).

Elderly patients

No data are available on which to make a dose recommendation for patients over the age of 65 years (see section 5.2 “Pharmacokinetic Properties”).

Children and adolescents

Hepcludex is indicated for adults 18 years and above.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

Exacerbation of hepatitis after discontinuation of treatment

Severe acute exacerbations of HDV and HBV infection may occur after Hepcludex is discontinued, especially in patients with cirrhosis, who may be at increased risk of more severe flares or progression to hepatic decompensation. Monitor hepatic function closely with both

clinical and laboratory follow-up for several (at least six) months in patients who discontinue Hepcludex. In certain circumstances, resumption of antiviral therapy may be warranted.

HDV and HBV genotype

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

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

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

Decompensated liver disease

The pharmacokinetics, safety and efficacy of Hepcludex in patients with decompensated cirrhosis have 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. Close monitoring of HBV DNA levels is recommended.

Excipients

A 2 mg Hepcludex vial contains less than 1 mmol of sodium (23 mg) per injection, which means it is almost “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other agents on bulevirtide

Concomitant use not recommended

NTCP inhibitors

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

Effect of bulevirtide on other agents

Caution with simultaneous intake

OATP1B1/3 and NTCP substrates

In vitro bulevirtide inhibited the organic anion transporting polypeptides, OATP1B1 and OATP1B3, with IC_{50} values of 0.5 and 8.7 µM, respectively. A clinical drug drug interaction (DDI) study of bulevirtide (administered at 5 mg twice daily) showed a 1.34-fold increase of C_{max} and AUC of the OATP1B1/3 and NTCP substrate, pravastatin (40 mg single dose). Based on bulevirtide exposures at the recommended 2 mg dose, the risk for clinically relevant interactions with OATP1B1/OATP1B3 and/or NTCP substrates is considered to be low.

However, use with caution if OATP1B1/OATP1B3 and/or NTCP substrates (e.g. estrone-3-sulfate, fluvastatin, atorvastatin, pitavastatin, pravastatin, rosuvastatin, thyroid hormones, bosentan, docetaxel, fexofenadine, glecaprevir, glyburide (glibenclamide), grazoprevir, nateglinide, paclitaxel, repaglinide, simvastatin, olmesartan, telmisartan, valsartan and voxilaprevir) are administered in combination with bulevirtide.

CYP3A4 substrates

In clinical DDI studies, no strongly pronounced interaction effects of bulevirtide on the clearance of the CYP3A4 substrate midazolam were observed; however, weak interaction effects of bulevirtide on CYP3A4 substrates cannot be ruled out. As such, close monitoring is recommended as a precautionary measure if sensitive CYP3A4 substrates with a narrow therapeutic index (e.g. cyclosporine, carbamazepine, sirolimus and tacrolimus) are administered in combination with bulevirtide.

Other 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 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.
In a clinical pharmacokinetic drug interaction study in healthy volunteers, there was no significant effect of bulevirtide on the pharmacokinetics of tenofovir disoproxil fumarate (TDF), a potential concomitant medication for the treatment of HBV infection.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/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 (see section 5.3 “Preclinical safety data”).
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.

Lactation

It is unknown whether bulevirtide is excreted in human milk. However, due to its high protein binding, bulevirtide is not likely to be secreted in milk. A decision must be made whether to breastfeed/discontinue breastfeeding or to discontinue / abstain from treatment with bulevirtide, taking into account the benefit of breastfeeding 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 (see section 5.3 “Preclinical safety data”).

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Summary of the safety profile

Assessment of adverse reactions is based on pooled data from 64 patients with HDV who received 48 weeks of treatment with Hepcludex 2 mg in a Phase 2 study (MYR203) and a Phase 3 study (MYR301), 28 patients with HDV who received 24 weeks of treatment with Hepcludex 2 mg in a Phase 2 study (MYR202), and from post-marketing experience.

List of adverse reactions

A tabulated list of adverse reactions is presented in Table 1. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and not known (frequency cannot be estimated from the available data).

Table 1: Tabulated list of adverse reactions

Frequency[a]	Adverse reaction
Blood and lymphatic system disorders	
Common	eosinophilia
Immune system disorders	
Not known	hypersensitivity, including anaphylactic reaction[b]
Nervous system disorders	
Very Common	headache (15,6%)
Common	dizziness
Gastrointestinal disorders	
Common	nausea
Hepatobiliary disorders	
Very Common	total bile salts increased (20,3%)
Skin and subcutaneous tissue disorders	
Very common	pruritus (10,9%)
General disorders and administration site conditions	
Very Common	injection site reactions (15,6%)[c]
Common	fatigue

a Frequency based on all patients receiving bulevirtide 2 mg (with or without a nucleoside/nucleotide analog for HBV treatment) through Week 48 in the MYR203 and MYR301 clinical studies.

b Adverse reaction identified through post-marketing surveillance.

c Includes injection site erythema, injection site reaction, injection site pruritus, injection site hematoma, injection site swelling, injection site pain, injection site induration and injection site rash.

Description of specific adverse reactions and additional information

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.

Total Bile Salts Increased

Asymptomatic bile salt elevations, associated with the mechanism of action of Hepcludex, were reported as adverse events very commonly in 20.3% of patients in clinical studies of Hepcludex 2 mg; the bile salt elevations resolved upon discontinuation of Hepcludex.
Due to renal excretion of bile salts, elevation of bile salts may be greater in patients with renal impairment.
As there are only limited data available on the long-term use of Hepcludex, the long-term consequences of bile salt elevations induced by Hepcludex in humans are unknown.

Immunogenicity

Hepcludex 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 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 safety or effectiveness of Hepcludex were altered in these patients.

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

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

ATC code

J05AX28

Mechanism of action

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

Pharmacodynamics

Antiviral activity in cell culture

Bulevirtide potently inhibited HDV infection in all the combinations of HBV and HDV genotypes tested in a primary human hepatocytes infectious system. The mean bulevirtide EC_{50} values ranged from 0.26 to 0.64 nM across HDV-1 to HDV-8 and from 0.21 to 0.68 nM for HDV carrying envelopes across HBV genotype A-H. Similarly, the mean bulevirtide EC_{50} values against HDV-1 viruses pseudotyped with multiple strains of HBV genotype A-D were 0.57 nM (genotype A), 0.59 nM (genotype B), 0.43 nM (genotype C), and 0.33 nM (genotype D). For 137 clinical isolates, bulevirtide had mean EC_{50} values of 0.40 nM, 0.45 nM, and 0.70 nM against HDV-1, HDV-5 and HDV-6, 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 genotype A, genotype D and genotype E, respectively.

Resistance

In Clinical Studies

In Study MYR301, resistance analysis was performed on 6 patients at Week 24 and 9 patients at Week 48 in the bulevirtide 2 mg group who experienced virologic breakthrough (2 consecutive increases in HDV RNA of ≥ 1 $\log_{10}$ IU/mL from nadir or 2 or more consecutive positive (target detected) HDV RNA values if previously HDV RNA was undetectable (target not detected) at 2 or more consecutive time points; 4 patients at Week 48) or HDV RNA decline < 1 $\log_{10}$ IU/mL (6 patients at Week 24 and 5 patients at Week 48). In Study MYR202, resistance analysis was performed on 5 patients in the bulevirtide 2 mg group who experienced virologic breakthrough (a single patient) or HDV RNA decline < 1 $\log_{10}$ IU/mL (4 patients) at Week 24. No amino acid substitutions tested at HBV bulevirtide sequence positions or HDV HDAg associated with reduced susceptibility to Hepcludex were identified in these isolates from any of these patients at baseline, Week 24 and Week 48. All substitutions tested remained susceptible to bulevirtide *in vitro*. No resistance to Hepcludex was observed.

Clinical efficacy

The efficacy and safety of Hepcludex 2 mg once daily in the treatment of adults with chronic hepatitis D and compensated liver disease is based on data through 48 weeks of treatment from one randomised, open-label Phase 3 study, Study MYR301 (N=150) and from data through 24 weeks and 48 weeks of treatment from two randomised open-label Phase 2 studies, Study MYR202 (N=118) and Study MYR203 (N=90), respectively. Additional data at 24 weeks of follow up (corresponding to Week 72) are provided for Study MYR203. A total of 92 patients in Studies MYR301, MYR202 and MYR203 received Hepcludex 2 mg once daily.

Across Studies MYR301, MYR202 and MYR203, combined response was defined as undetectable HDV RNA or decrease in HDV RNA by ≥ 2 $\log_{10}$ IU/mL from baseline and ALT normalisation. Undetectable HDV RNA was defined as < lower limit of quantification [LLOQ] (target not detected) in Study MYR301; and < limit of detection [LOD], where LOD was 14 and 10 IU/mL in Studies MYR202 and MYR203, respectively.

Study MYR301

In Study MYR301, 100 of 150 patients with chronic HDV infection were randomised to receive immediate treatment with once daily Hepcludex 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 patients had infection with HDV genotype 1. Baseline characteristics were balanced among the immediate and delayed treatment groups. Of the patients in the immediate treatment group, 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. Patients were treated 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%).

Table 2 presents the virologic and biochemical outcomes for immediate treatment with Hepcludex 2 mg once daily and delayed treatment at Week 24 and Week 48.

Table 2: Study MYR301: HDV RNA (virologic) and ALT (biochemical) outcomes at Week 24[a,b] and Week 48[b] in patients with chronic HDV infection and compensated liver disease (Full Analysis Set)

	Week 24		Week 48	
	Hepcludex 2 mg (Immediate Treatment) (N=49)	**Delayed Treatment (N=51)**	**Hepcludex 2 mg (Immediate Treatment) (N=49)**	**Delayed Treatment (N=51)**
Undetectable[c] HDV RNA or decrease in HDV RNA by ≥ 2 $\log_{10}$ IU/mL and ALT normalisation[d]	37%[e]	0%	45%[e]	2%
Undetectable[c] HDV RNA or decrease in HDV RNA by ≥ 2 $\log_{10}$ IU/mL	55%[f]	4%	71%[f]	4%
ALT normalisation[d]	53%[f]	6%	51%[f]	12%

a Interim results.
b 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.
c < lower limit of quantification [LLOQ], target not detected.
d 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.
e p-value < 0.0001.
f Nominal p-value < 0.0001.

Exacerbation of hepatitis after discontinuation of treatment

In Study MYR301, 46 patients who received 144 weeks of treatment with Hepcludex 2 mg were followed in the posttreatment period for up to 96 weeks. In this posttreatment period, hepatic adverse events (AEs) and ALT elevations were observed, consistent with hepatitis exacerbation following discontinuation of antiviral treatment for HBV and HDV and/or progression of liver disease while off-treatment.

Hepatic AEs were observed in 50% (23/46) of patients in the 96-week posttreatment period; the most frequent posttreatment AEs involved laboratory elevations of transaminases, gamma glutamyl transferase (GGT) and bilirubin, or reported hepatitis D. Grade 3 or higher posttreatment hepatic AEs were observed in 20% (9/46) of patients.

Posttreatment ALT elevations to > 5 x upper limit of normal (ULN) were observed in 18 of 46 (39%) patients, while posttreatment ALT elevations to > 10 x ULN were observed in 5 of 46 (11%) patients. Patients with cirrhosis at baseline were more likely to experience more severe posttreatment ALT elevations: 10 of 18 (56%) patients with posttreatment ALT > 5 x ULN and 4 of 5 (80%) patients with posttreatment ALT > 10 x ULN had cirrhosis at baseline, respectively. The majority of the posttreatment ALT elevations were associated with HDV RNA increases and most occurred within the first 24 weeks posttreatment. None of the 18 patients

with posttreatment ALT elevations experienced liver-related clinical events. At least 8 of the 18 patients with posttreatment ALT > 5 x ULN restarted commercial Hepcludex 2 mg in the 96-week posttreatment period.

Study MYR202

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 Hepcludex 2 mg + TDF (N=28) or TDF alone (N=28) for 24 weeks. At Week 24, 21% of patients in the Hepcludex 2 mg + TDF group achieved a combined response, 54% achieved undetectable HDV RNA or decrease by ≥ 2 $\log_{10}$ IU/mL, and 43% achieved ALT normalization. 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).

Study MYR203

In Study MYR203, 15 of 90 patients with chronic HDV infection were randomised to receive once daily Hepcludex 2 mg for 48 weeks. The primary efficacy endpoint was defined as the proportion of patients with undetectable HDV RNA at Week 72 (end of the 24-week treatment-free follow-up period). At Weeks 24 and 48, respectively, 33% and 53% of patients achieved a combined response; 47% and 60% achieved undetectable HDV RNA or decrease in HDV RNA by ≥ 2 $\log_{10}$ IU/mL; and 64% and 73% achieved ALT normalisation (normal ALT was defined as ≤ 31 U/L for females and ≤ 41 U/L for males). At Week 72, one patient (7%) who had received Hepcludex 2 mg achieved the primary endpoint of undetectable HDV RNA; an additional 4 patients (27%) achieved decrease in HDV RNA by ≥ 2 $\log_{10}$ IU/mL. Three patients who had received Hepcludex 2 mg achieved ALT normalization and combined response at Week 72.

5.2 Pharmacokinetic Properties

The pharmacokinetic (PK) properties of bulevirtide were characterised after intravenous and subcutaneous administration. The exposure of bulevirtide increased in a more than proportional manner with increasing doses (dose range: 100 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 population 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 analysis) are provided in Table 3.

Table 3: Steady state pharmacokinetic parameters of bulevirtide following subcutaneous administration of Hepcludex 2 mg in HDV-Infected Adults[a]

Parameter[b]	Bulevirtide
Cmax (ng/mL)	24 (20-30)
AUC0-24h (ng•h/mL)	261 (216-315)

a From Population PK analysis exposure estimates of MYR301 study participants, N = 49.

b Values refer to geometric mean (90% confidence interval).

Absorption

After subcutaneous injection, bulevirtide reached maximum plasma concentrations between 0.5 and 3 hours.
The absolute bioavailability of 2 mg bulevirtide after subcutaneous injection has not been estimated. Bioavailability following subcutaneous doses of 5 mg and 10 mg is estimated to be 48% and 57%, respectively. As bulevirtide demonstrates non-linear PK, extrapolation of bioavailability at other dose levels should be done with caution.

Distribution

In vitro protein binding is high with > 99.9% of bulevirtide bound to plasma proteins.
Following multiple dosing with bulevirtide 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 bulevirtide 2 mg subcutaneous injection, total mean apparent systemic clearance 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.

Kinetics in specific patient groups

Age, gender, and race

Based on population PK modelling, age (years; median [min, max]: 39.0 [18.0, 65.0]), gender (n, male=277; female=137, race (n; White=367; Black or African American=9, Asian=37; other=1) or body weight (kg; median [min, max]: 74.3 [39.7, 110]) did not have a clinically relevant impact on the systemic exposure of bulevirtide.

Hepatic impairment

Population PK modeling characterised a 41.5% increase in AUC_{tau} and 38.3% increase in C_{max} in patients with mild hepatic impairment (Child-Pugh A) (n=154) compared to patients with normal liver function (n=230). The pharmacokinetics of bulevirtide have not been evaluated in patients with moderate and severe hepatic impairment (Child-Pugh B and C, respectively) (see section 4.2 “Posology and method of administration”).

Renal impairment

In a population PK analysis, mild renal impairment (CrCL ≥ 60 and < 90 mL/min, n = 60) did not significantly affect the pharmacokinetics of bulevirtide. The pharmacokinetics 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 (see section 4.2

“Posology and method of administration”). As bulevirtide is > 99.9% protein bound, dialysis is not expected to alter exposures of bulevirtide.

Elderly patients

The pharmacokinetics of bulevirtide have not been evaluated in the elderly (65 years of age and older).

Children and adolescents

Hepcludex is indicated for adults 18 years and above.

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. Carcinogenicity and genotoxicity studies have not been conducted with bulevirtide.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, sodium bicarbonate, sodium carbonate, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment).
One 2.0 mg single-dose vial of Hepcludex contains 0.63 mg sodium.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Do not use this medicinal product after the expiry date ("EXP") stated on the pack.
The expiry date of the product is indicated on the packaging materials.

Shelf life after opening

The reconstituted injection preparation is not preserved. After reconstitution, chemical and physical in-use stability has been demonstrated for 2 hours up to 25°C. Do not store in a refrigerator. From a microbiological point of view, it is recommended that the product be used immediately.
Do not reuse or save reconstituted Hepcludex for future use.

6.4 Special precautions for storage

Keep out of reach of children.
Store in a refrigerator (2–8°C).
Store in the original packaging in order to protect from light.

6.5 Special precautions for disposal and other handling

Dose preparation and administration

Healthcare professionals should train patients 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 to read the “Instructions For Use” at the time they receive a prescription for Hepcludex and as needed for ongoing administration of Hepcludex.

Emphasize the following instructions to the patient:

- 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 and syringe and needles for preparation and injection are provided separately from Hepcludex; they should be stored out of the reach of children.
- Hepcludex must be administered by subcutaneous injection. Do not administer by any other route.

Reconstitution Instructions

- Aseptically reconstitute Hepcludex lyophilized powder by adding 1 mL of sterile water for injection to the Hepcludex vial.
- Carefully tap and then 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, do not use that vial of solution.
- Use reconstituted product 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 refrigerate.
- The volume for the dose to be administered has to be extracted from the Hepcludex vial back into the same syringe with the same needle tip used beforehand for injecting the sterile water into the Hepcludex vial.
- Then remove the needle tip from the syringe. Attach a needle tip for subcutaneous injection to this syringe and remove all remaining air bubbles from the syringe prior to injection.

Administration Instructions

- Administer by subcutaneous injection into the upper thigh or lower abdomen.
- 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.
- Change the injection site with each injection.

Important: Remind patients that it is important that they do not reuse the vials, syringe, needles or any remaining sterile water for injection. Hepcludex and auxiliary supplies are for **single use only**. Dispose of all components after use, including unused sterile water for injection.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Full instructions for use and handling of Hepcludex are provided in the package leaflet (see “Instructions for Use”).

Authorisation number
38439

Packs
Hepcludex, powder for solution for injection: 30 single-dose vials

Manufacturer

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