swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Hepcludex®

International non-proprietary name:	bulevirtide
Pharmaceutical form:	powder for solution for injection
Dosage strength(s):	2 mg
Route(s) of administration:	subcutaneous injection
Marketing authorisation holder:	Gilead Sciences Switzerland Sàrl
Marketing authorisation no.:	68338
Decision and decision date:	extension of therapeutic indication approved on 16 July 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BLV	Bulevirtide
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HBV	Hepatitis B virus
HDV	Hepatitis D virus
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
NTCP	Sodium taurocholate cotransporting polypeptide
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PEG IFN-α-2a	Pegylated interferon-alpha 2a
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 18 March 2021.

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

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

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose of Hepcludex in paediatric patients is based on weight comprising a daily dosage of 1 mg bulevirtide for paediatric patients weighing 10 kg to < 25 kg, 1.5 mg bulevirtide for paediatric patients weighing 25 kg to < 35 kg, and 2 mg bulevirtide for paediatric patients weighing 35 kg and above.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	6 May 2024
Formal objection	28 May 2024
Response to formal objection	30 May 2024 and 21 June 2024
Formal control completed	25 June 2024
List of Questions (LoQ)	24 October 2024
Response to LoQ	10 January 2025
Preliminary decision	28 March 2025
Response to preliminary decision	27 May 2025
Labelling corrections and/or other aspects	12 June 2025 and 16 June 2025
Response to labelling corrections and/or other aspects	25 June 2025

Final decision	16 July 2025
Decision	approval

3 Medical context

Hepatitis D virus (HDV) is a circular RNA enveloped virus dependent on hepatitis B virus (HBV) for replication and was discovered in 1977. It encodes a single structural protein, the delta antigen (L-HDAg), forming a ribonucleoprotein with the RNA genome. HDV affects 15-20 million people globally, and is most prevalent in the Middle East, Asia, and Africa. In the United States and Europe, seroprevalence is 5-10%. Limited data are available for Switzerland, where a survey estimated the seroprevalence of hepatitis D to be 5.9% among HBV surface antigen-positive patients (Genné D, Rossi I. Hepatitis delta in Switzerland: a silent epidemic. Swiss Med Wkly. 2011 Mar 18;141). No specific data are available for the paediatric population in Switzerland.

HDV infection occurs via coinfection with acute HBV or superinfection in chronic HBV carriers. Transmission occurs very rarely by perinatal transmission from HBV/HDV coinfected mothers. There is some level of intrafamilial spread that mainly occurs through inapparent parenteral transmission, but the vast majority of HDV is acquired through superinfection in HBV-infected patients and is due to sexual transmission and intravenous drug use, which essentially do not happen before adolescence.

In adults, acute coinfection usually presents as a self-limited hepatitis with complete recovery, and only around 5% of patients will progress to the chronic HBV-HDV coinfection stage. Superinfection generally results in acute severe hepatitis, often progressing to chronic HDV infection with a higher mortality than the initial HBV infection. The clinical course is influenced by HDV and HBV genotypes and is accelerated, with a relative risk of cirrhosis and hepatocellular carcinoma about threefold higher than in HBV monoinfection. In children, the clinical course of chronic HBV-HDV coinfection is not as well defined.

Since HDV cannot infect subjects without the presence of an HBV infection, HBV vaccination is the best prevention measure against HDV acquisition. Treatment options are limited. In adults, pegylated interferon-alpha 2a (PEG IFN-α-2a) is used with partial efficacy (20 to 40% sustained virologic response), late relapses and significant side effects. Nucleoside/nucleotide analogues targeting the HBV polymerase are not efficient alone in HDV eradication, as studies showed that, in co-infected patients, HBV viraemia suppression by itself did not change liver-related outcomes (development of cirrhosis and hepatocarcinoma). Literature on the treatment of HDV in children is scarce, and high-quality studies regarding therapeutic options are lacking, in part because of the rarity of the disease.

Hepcludex, with the active substance bulevirtide (BLV) is an HBV large envelope protein–derived, synthesised lipopeptide that binds specifically to the sodium taurocholate cotransporting polypeptide (NTCP, a hepatocyte bile salt transporter) and acts as a selective entry inhibitor of HDV into hepatocytes. The de novo infection of liver cells is decreased, viral spread is inhibited, and the life cycle of HDV is disrupted. This event is expected to lead to both reduced necroinflammation and viral load decline. Hepcludex was initially granted a marketing authorisation on 5 February 2024 for the treatment of chronic HDV infection in adults with compensated liver disease.

4 Nonclinical aspects

4.1 Nonclinical conclusions

The applicant did not submit new nonclinical studies to support the requested extension of the indication. This was considered acceptable. There are no concerns with excipients regarding the paediatric population. Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.
From the nonclinical point of view, there are no objections to approval of the proposed extension of indication.

5 Clinical aspects

5.1 Clinical pharmacology

The indication of Hepcludex in children from 3 to less than 18 years of age with a body weight of at least 10 kg was supported by extrapolation of the efficacy and safety established in adult patients based on an exposure-matching approach.

The central clinical pharmacology aspects of the application included:

- a refined adult PopPK/PD BLV-bile salt model
- a justification of the selection of the target exposure bounds associated with safety and efficacy in adult patients
- simulations of expected exposure in paediatric patients to determine dose recommendations in paediatric patients

Refined adult PopPK/PD BLV-bile salt model
The dataset used in this analysis was similar to the dataset used in the previous PopPK analysis (for details on the demographics see Information for healthcare professionals). The model had the following characteristics:

Bulevirtide absorption model: first-order absorption
Bulevirtide disposition model: 1-compartment model with parallel linear and non-linear Michaelis-Menten elimination with inhibitory E_{max} effect of model-predicted bile salt plasma concentrations on V_{max}
Bile salt model: indirect response model with estimated inhibitory E_{max} drug effect of model-predicted bulevirtide plasma concentrations on k_{out}
Covariate model:
- bodyweight on CL/F and on Vc/F using allometric scaling with fixed exponents of 0.75 and 1, bodyweight on k_a using an exponential model,
- log-transformed baseline AST levels on bile salt baseline levels using an exponential model,
- subject in the MYR202 PK sub-study on residual unexplained variability (Frel) using a fractional change model

IIV model: exponential IIV parameters on residual unexplained variability and bile salt baseline levels, box-cox transformed IIV on k_a

Residual unexplained variability (RUV) model: approximate combined additive + proportional RUV model on the log-scale for bile salts, additive RUV on the log-scale for bulevirtide

The new model was a refinement of previous BLV PopPK models as it provided a combined description of BLV and bile acid PK. The model provided a good description of the underlying dataset and was suitable to assess covariate effects within the dataset. Among the demographic covariates assessed, body weight had the largest impact on BLV exposure, but only a small effect on the bile salt exposure. However, the interplay between BLV and bile acids is complex and the mechanistic basis remains poorly understood. The refined model provided a good description of this relationship but cannot provide a deeper mechanistic understanding of the underlying processes. Therefore, predictions of BLV and bile salt exposure and covariate effects beyond the ranges covered in the underlying dataset are associated with a high uncertainty.

PK/PD simulations to support the proposed paediatric dosing
The applicant applied an exposure-matching approach to derive dosing recommendations in paediatric patients. This approach is acceptable, given the similarity of disease between adults and children in terms of HDV as pathogen and the claimed mechanism of action. In contrast, there are uncertainties about similarity between adults and children with regard to PK, disease manifestation and course of disease (as discussed below). However, these points are not considered to be fundamentally prohibitive for an extrapolation approach, but rather increase uncertainty.

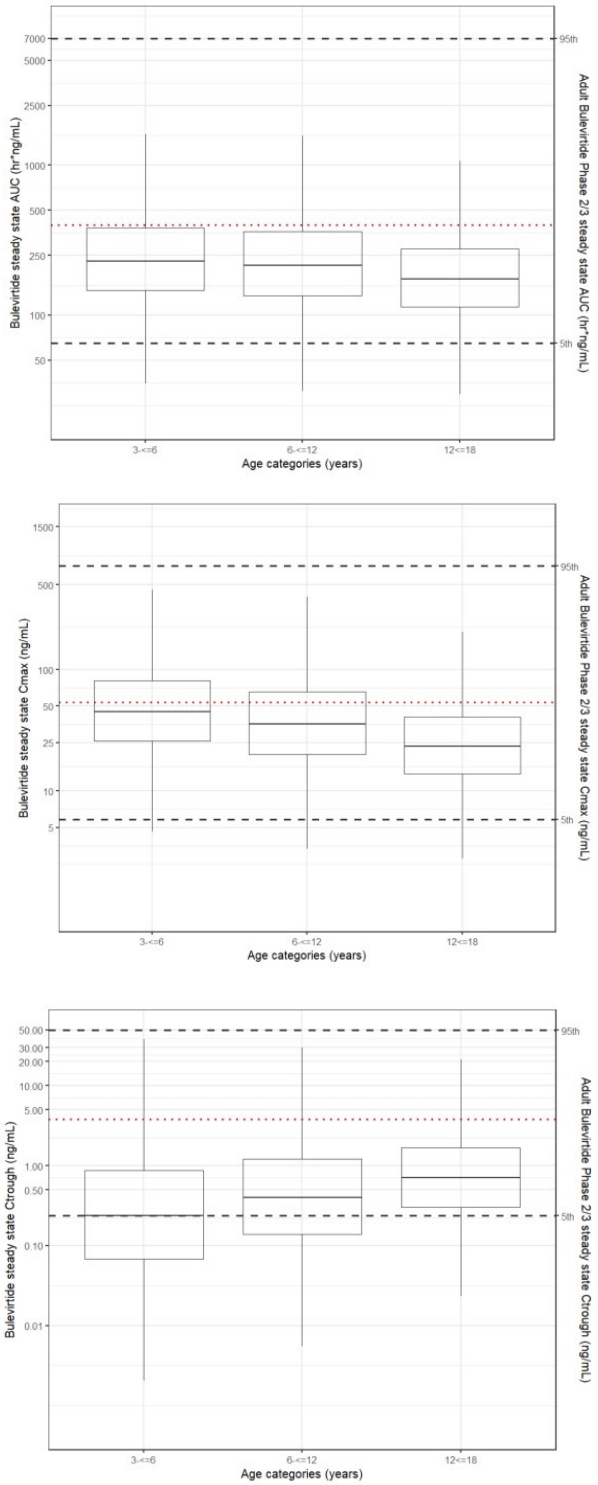
Adult Population Reference Range
The reference exposure window for exposure-matching was selected based on the exposures obtained following the approved daily dose of 2 mg subcutaneously in adult patients.

Simulations of expected exposure in paediatric patients
Using the National Health and Nutrition Examination Survey database, a paediatric dataset of virtual paediatric patients from 3 to less than 18 years of age was generated for simulations. The adult PopPK/PD BLV-bile salt model parameter estimates were used to generate distributions of PK and PD parameters based on the typical values and interindividual variability. Baseline bile salt values and AST levels were assumed to be consistent with adult values. Therefore, the differences in exposures between paediatric and adult patients were solely based on differences in bodyweight.
The assumptions with regard to baseline bile salts and AST level are not supported by any data, and thus are associated with uncertainty. In addition, similar baseline values do not preclude that adults and children might react differently, or to a different extent, to perturbations of the system, as they are caused by BLV. Due to the lack of a full mechanistic understanding of the interplay between BLV and bile-salts, a theoretical assessment of these aspects is difficult.
Steady-state exposures of BLV and steady-state bile salt profiles in paediatric patients were simulated following two different dose regimens: a BLV 2 mg fixed dose or the approved weight band-based regimen (1 mg for patients weighing 10 kg to less than 25 kg, 1.5 mg for patients weighing 25 kg to 35 kg, 2 mg for 35 kg and above).

Following BLV 2 mg, the simulated AUC_{tau} and C_{max} exposures in children were above the adult reference exposure in ~75% of children in the 3-6 years age group and ~50% in the 6-12 years age group.
C_{trough} values below the adult reference range were expected in approx. 25 % of paediatric patients for all age categories.

Following the approved weight band-based regimen the simulations indicated comparable C_{max} and AUC_{tau} values across the weight groups and for the majority of subjects within the adult refence range. However, C_{trough} values are expected to fall below the adult reference exposure in approx. 50% of subjects in the 3-6 years age group and a relevant percentage of subjects in the 6-12 years age group (see Figure 1).

Figure 1: Boxplot of Simulated Steady-state PK Parameters by Age Categories in Paediatric Population following the approved dosing regimen



Notes: Black horizontal dashed lines represent distribution of adult exposures, 5th and 95th percentiles based on the 2 and 10 mg doses respectively; the red horizontal dotted lines represent the 95th percentile of adult exposures based on the 2 mg dose.

Abbreviations: AUCtau=area under the concentration-time curve over one dosing interval; Cmax=maximum concentration; Ctrough=trough concentration; Source: Applicant`s documentation

Simulation results for bile salts
The simulated bile salt concentrations in paediatric patients fell within the adult refence range following both dose regimens, implying that the differences in exposure expected with the 2 mg flat dose regimen versus the weight band-based regimen have only limited impact on bile salts. However, this conclusion is dependent on the assumption that the interdependency between BLV and bile salts can be extrapolated from adults to paediatric patients. Although there remained uncertainty regarding this assumption, it was considered acceptable, as the applicant provided evidence of minimal clinical sequelae associated with bile salt elevations in children as well as adults with NTCP deficiency.

5.2 Efficacy

No clinical efficacy data of BLV in the paediatric population were submitted with the present application.

Results from adult studies indicate that after 48 weeks of treatment, in approximately 50% of patients BLV resulted in a ≥ 2 $\log_{10}$ decrease in HDV viral load associated with ALT normalisation. This so-called combined response was a surrogate endpoint reasonably likely to predict clinical benefit. When treatment was stopped, there was a rebound in HDV levels in the vast majority of patients.

It is currently unknown if, even with similar plasma exposure rates to BLV, the response to treatment and long-term outcomes in children would be the same as in adults. Indeed, paediatric and adult hepatic physiology can differ, for example with a differential evolution of fibrosis. Nevertheless, the applicant provided data indicating that HBV-HDV coinfection can also lead to cirrhosis in adolescents. Further, it is acknowledged that a paediatric efficacy study would be difficult to conduct. Finally, the efficacy of BLV treatment can be easily assessed by measuring hepatic parameters (ALT) and viral load evolution (HDV RNA). In that context, the lack of clinical efficacy data is considered not prohibitive to approval.

5.3 Safety

No clinical safety data of BLV in the paediatric population were submitted with the present application.

In adults, BLV has been well tolerated in clinical trials and the safety profile is reassuring. There was a clear dose-related increase in bile acids, which returned to baseline values when BLV was stopped. Bile salt increases were asymptomatic, not related to any clinical sequelae, and did not result in treatment discontinuations or interruption.

The potential clinical sequelae of bile salt elevations in the paediatric population were discussed with the applicant in relation to the adult data and literature on patients with NTCP deficiencies (and hence high bile salt levels). Some patients with NTCP deficiencies presented deficits in liposoluble vitamins. Indeed, while bile salts are crucial for the proper absorption of fat-soluble vitamins, elevated bile salt levels can actually hinder their absorption. Further, vitamin D deficiency is more frequent in patients with chronic HDV infection. The applicant provided data showing that BLV treatment was not associated with a greater decline in vitamin D levels than anticipated in adult patients with underlying chronic hepatitis D. However, this cannot be extrapolated to the paediatric population. As vitamin D deficiency can affect important physiological aspects of bone growth, which is particularly significant in the paediatric population, this aspect has been addressed in the warning section of the Information for healthcare professionals to ensure proper monitoring and/or substitution.

Since BLV is administered by daily subcutaneous injections, there might be concerns regarding safety, tolerability and long-term treatment adherence in the younger age group. With the weight-band based BLV dosing, injectable volumes are smaller as compared to the 2 mg-fixed dose, particularly in children weighing under 35 kg, providing a more favourable tolerability profile.

5.4 Final clinical benefit risk assessment

Medical and regulatory context
Hepcludex was approved in Switzerland in February 2024 for the treatment of chronic HDV infection in adult patients with compensated liver disease. In the target population, in comparison to HBV monoinfection, chronic HDV hepatitis induced by an HDV-HBV co-infection presents an accelerated clinical course with a relative risk of cirrhosis, liver decompensation and hepatocellular carcinoma about threefold higher than in HBV monoinfection.

In children, the clinical course of chronic HBV-HDV coinfection is not as well defined and high-quality studies regarding therapeutic options are lacking, in part because of the rarity of the disease. In adults, PEG IFN-α-2a is used with partial efficacy (20 to 40% sustained virologic response), late relapses and significant side effects. Since PEG IFN-α is often poorly tolerated and can interfere with growth, it is rarely used until puberty.

Beneficial and unfavourable effects and respective uncertainties
A refined adult PopPK/PD model, which described well the BLV and bile salt PK in the available adult dataset, was available. In accordance with previous models, body weight was the covariate with the greatest impact on exposure. However, the mechanistic basis of the complex PK of BLV and the interplay between BLV and bile acids remain poorly understood. However, this point is not considered to be fundamentally prohibitive for an extrapolation approach, but rather increases uncertainty.

Simulations of exposure in paediatric patients in the age groups of 3-6 years, 6-12 years and 12-<18 years following a fixed dose of 2 mg once daily indicated that only in the age group of 12-<18 years are the majority of patients expected to have exposures within the adult reference range, while exposures above the adult reference range are expected in ~75% of children in the 3-6 years age group and in ~50% of children in the 6-12 years age group. The elevated exposure does not raise concerns with regard to efficacy, but is associated with a risk of elevated bile salt concentrations and potentially other unknown safety risks. The resulting risk in paediatric patients, especially in the long term, is unknown. C_{trough} values below the adult reference range are expected in approx. 25 % of paediatric patients for all age categories, which might pose a risk of reduced efficacy.
With the approved weight band-based dosing regimen, the risks resulting from an elevated exposure in terms of AUC and C_{max} were reduced, but 50% of subjects in the age group of 3-6 years and approx. 25% of subjects in the other age groups are expected to have $C_{troughs}$ below the adult reference range, which might pose a risk of reduced efficacy. However, as the efficacy of BLV treatment can partially be assessed by measuring hepatic parameters and viral load evolution, the risk of reduced efficacy can be monitored in clinically practice, in contrast to the unknown potential safety risk arising from an exposure above the reference range with the 2 mg fixed dose regimen.

No clinical data are available that allow Hepcludex efficacy to be evaluated in the paediatric population. Results from adult studies indicate that after 48 weeks of treatment, in approximately 50% of patients BLV resulted in a ≥ 2 $\log_{10}$ decrease in HDV viral load associated with ALT normalisation (the so-called combined response, a surrogate endpoint reasonably likely to predict clinical benefit). It is currently unknown if, even with similar plasma exposure rates to BLV, the response to treatment and long-term outcomes in children would be the same as in adults. Efficacy of BLV treatment can partially be assessed by measuring hepatic parameters and HDV viral load evolution. As for adults, in the paediatric population there would also be a number of unknowns regarding the optimal place of BLV in the therapeutic arsenal. These relate to treatment duration, potential BLV + PEG-IFNα combination treatment and long-term clinical outcomes.

No clinical safety data of BLV in the paediatric population are available. Hepcludex has a reassuring safety profile in the adult clinical trials. There was a clear dose-related asymptomatic increase in bile salts, which returned to baseline values when BLV was stopped, an outcome that is also anticipated in the paediatric population. Data indicated that in patients with liver injury due to HDV or with

elevated bile salt levels due to NTCP deficiencies presented deficits in liposoluble vitamins and usually needed supplementation. Since BLV is administered daily by subcutaneous injection, there might be concerns regarding long-term treatment adherence in the younger age groups. Safety aspects, including consequences of elevated bile salts, tolerability of daily subcutaneous injections, risk of hepatitis flares after therapy interruption, will be addressed in periodic safety update reports (PSURs).

Benefit-risk balance

The benefit/risk of Hepcludex in the paediatric population with the approved weight band-based dosing regimen is considered positive based on extrapolation from adult data and because simulations indicate bulevirtide exposures (Cmax and AUC) within the adult reference range, with the caveat that Ctroughs below the adult reference range are expected which might pose a risk of reduced efficacy. Further, as therapeutic options are very limited in the paediatric population, uncertainties related to the extrapolation approach are acceptable as treatment response can be monitored in the clinical setting.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Hepcludex was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

HEPCLUDEX®

Composition

Active substances

Bulevirtide as bulevirtide acetate

Excipients

Sodium carbonate anhydrous, sodium hydrogen carbonate, mannitol, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment).

One 2.0 mg single-dose vial of Hepcludex contains 0.63 mg sodium.

Pharmaceutical form and active substance quantity per unit

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.

Indications/Uses

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

Dosage/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 dose in adults is Hepcludex 2 mg.
The recommended dose of Hepcludex in paediatric patients is based on weight as detailed in Table 1 below.

Table 1: Dosing for paediatric patients using Hepcludex 2 mg powder for solution for injection

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

The subcutaneous injection of 1 ml of the reconstituted Hepcludex 2 mg powder corresponds 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 or the caregiver 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 “Pharmacokinetics”).

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 “Pharmacokinetics”).

Elderly patients

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

Children and adolescents

The safety and efficacy of Hepcludex in patients under 18 years of age have not been evaluated in clinical studies. The recommended dosage of Hepcludex 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 “Pharmacokinetics”).

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

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

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.

Hypovitaminose

Paediatric patients with elevated bile salt concentrations may be at increased risk for low levels of fat-soluble vitamins (including vitamin D deficiency). These should be monitored regularly and appropriate nutritional supplementation should be provided.

Excipients

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

Interactions

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 und 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 (eg. 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 (eg. 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.

Pregnancy, 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 “Preclinical 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 “Preclinical data”).

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.

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 2. 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 2: 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 very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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.

Properties/Effects

ATC code

J05AX28

Mechanism of action

Bulevirtide is a 47-amino acid, N-terminally myristoylated, HBV-L-protein derived, syntheticlipopeptide. 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 3 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 3: 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.

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.

Pharmacokinetics

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 $AUC_{0\text{-}24h}$ 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 4.

Table 4: 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 “Posology/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 “Posology/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

The pharmacokinetics of bulevirtide in paediatric patients have not been evaluated in a clinical study. The dosing recommendations for children 3 years of age and older weighing at least 10 kg are based on an extrapolation approach aiming for a bulevirtide exposure in children matching the bulevirtide exposure in adults with HDV infection using bulevirtide 2 mg once daily. Population pharmacokinetic/pharmacodynamic modelling and simulations predict that the steady-state bulevirtide exposures in children with the recommended weight-based dosing of bulevirtide (see “Dosage/Administration”) are similar to the exposure range established as safe and efficacious with the subcutaneous injection of 2 mg bulevirtide once daily in adults.

Preclinical 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.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicinal product after the expiry date ("EXP") stated on the pack.

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 at room temperature (up to 25°C). 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.

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.

Instructions for handling

Dose preparation and administration

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 (with necessary graduations according to the dose to be administered). 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” 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 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.

<u>Reconstitution Instructions</u>

- 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 required 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 (See Table 5).

Table 5: Required dose volumes to be extracted for administration of Hepcludex

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

- 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.

Do not reuse the vials, syringe, needles or any remaining 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

68338 (Swissmedic)

Packs

Hepcludex, powder for solution for injection: 30 single-dose vials [A]

Marketing authorisation holder

Gilead Sciences Switzerland Sàrl, Zug

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March 2025