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Hepcludex® (bulevirtide-gmod) Pregnancy and Breastfeeding

This document is in response to your request for information regarding the use of Hepcludex® (bulevirtide-gmod [BLV]) for the treatment of chronic HDV infection in pregnant or breastfeeding individuals.

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/hdv/hepcludex/hepcludex_pi.

Product Labeling[1]

Indications and Usage

BLV is indicated for the treatment of chronic HDV infection in adults without cirrhosis or with compensated cirrhosis.

This indication is approved under accelerated approval based on a decrease in HDV RNA and ALT normalization. An improvement in disease-related clinical outcomes has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Dosage and Administration

Recommended dosage in adults

The recommended dosage in adults is BLV 8.5 mg once daily administered by subcutaneous injection.

Use in Specific Populations

Pregnancy

Risk summary

There are insufficient human data on the use of BLV during pregnancy to inform a drug-associated risk of birth defects and miscarriage. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the US general population, the background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

In nonclinical reproductive toxicity studies, BLV demonstrated no adverse effect on embryofetal development when administered to pregnant rats and rabbits at systemic

exposures (area under the concentration-time curve) 4- and 37-fold relative to exposure in humans at the recommended human dose (RHD).

Data: animal data

BLV was administered via subcutaneous injection to pregnant rats and rabbits (2.5 mg/kg/day) on Gestation Days 6 through 17 and 6 through 20, respectively, and also to rats from Gestation Day 6 to Lactation/Postpartum Day 20. There were no adverse effects on embryofetal development in rats and rabbits. During organogenesis, exposure in rats and rabbits was 4 and 37 times higher, respectively, than the exposure in humans at the RHD. In a pre/postnatal development study in rats, BLV (2.5 mg/kg/day) was administered via subcutaneous injection from Gestation Day 6 to Lactation Day 21. No effects were observed in the offspring at maternal exposures 3 times the exposure at the RHD.

Lactation

Risk summary

It is not known whether BLV is present in human breast milk, affects human milk production, or has effects on the breastfed infant. In nonclinical pre- and postnatal developmental rat studies, BLV was not measured in the plasma of pups or in the milk of nursing animals. However, due to its high protein binding, liver tropism, and high specificity for sodium taurocholate co-transporting polypeptide, BLV is not likely to be secreted in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BLV and any potential adverse effects on the breastfed child from BLV or from the underlying maternal condition.

Clinical Studies

Clinical trials in adults with chronic HDV infection without cirrhosis or with compensated cirrhosis

Trial MYR301

The efficacy of BLV once daily in the treatment of adults with chronic HDV infection without cirrhosis or with compensated cirrhosis is based on data through Week 144 from a multicenter, randomized, open-label, parallel-arm phase 3 trial, Trial MYR301 (NCT03852719), in which 100 participants received BLV 8.5 mg once daily. The MYR301 protocol specified the BLV dose as 10 mg; however, a dose recovery study later showed that the delivered dose was 8.5 mg.

Clinical Data on BLV Use During Pregnancy and Breastfeeding

In phase 2/2b clinical studies (MYR202, MYR203, and MYR204), pregnant or breastfeeding female individuals were excluded.[2-4]

MYR301 Study

MYR301 was an open-label, multicenter, randomized, phase 3 study that evaluated the safety and efficacy of immediate treatment with BLV 2 mg or 10 mg compared with delayed

treatment with BLV 10 mg beginning at Week 48 in participants with chronic HDV (N=150). Data through treatment Week 144 and 96 weeks of posttreatment follow-up have been published.[5]

Pregnant or breastfeeding individuals were excluded from enrolling in the study. During the study, 3 pregnancies were reported. One participant in the BLV 2 mg arm had a pregnancy that was confirmed on Day 746; BLV treatment was discontinued, and the infant was delivered at term after an uncomplicated delivery and was deemed to be healthy. Another participant was enrolled in the delayed treatment arm and became pregnant several months after the last dose of BLV 10 mg. The infant was delivered at term and was deemed healthy. The third participant in the delayed BLV 10 mg treatment arm had a positive pregnancy test at their first study visit and withdrew from the study without ever receiving a dose of BLV; no outcomes for the pregnant participant or infant were available.[6]

Case Report

There are limitations in the interpretation of case reports. Case reports cannot be generalized. Unlike controlled clinical trials, causality cannot be inferred based on uncontrolled observational data. In addition, incidence or prevalence cannot be estimated due to the lack of a representative population sample. Other limitations of case reports include the retrospective design and publication bias.[7]

HDV-associated glomerulonephritis[8]

A 42-year-old South Asian woman presented at 14 weeks' gestation with acute kidney injury. Her Cr level was elevated from a baseline of 0.92 mg/dL to 1.3 mg/dL, and she exhibited new nephrotic syndrome, with a urine protein-to-creatinine ratio of 3.5 g/g and albumin level of 2.8 g/dL. The initial kidney biopsy was deferred due to pregnancy. The patient developed severe pre-eclampsia and required emergent cesarean delivery.
A postpartum kidney biopsy showed evidence of immune-complex glomerulonephritis with segmental sclerosis; autoimmune serologies and HBV viral load were negative, but her HDV viral load was elevated to 270,000 IU/mL. It was determined that the glomerular disease was due to chronic HBV and active HDV co-infection. Immunosuppressive therapy was deferred, and the patient initiated an experimental regimen of BLV and tenofovir. Her HDV viral load and proteinuria improved (peak of 5.7 g/g to 1.2 g/g).

References

1. Enclosed. Gilead Sciences Inc. HEPCLUDEX® (bulevirtide-gmod) injection, for subcutaneous use. US Prescribing Information. Foster City, CA.
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3. ClinicalTrials.gov. Myrcludex B in Combination With Peginterferon Alfa-2a Versus PeginterferonAlfa-2a Alone in Patients With Chronic Viral Hepatitis B With Delta-agent. ClinicalTrials.gov Identifier: NCT02888106. Available at https://clinicaltrials.gov/ct2/show/record/NCT02888106. Accessed: 23 November 2021. Last Updated: 30 April. 2021.
4. Asselah T, Chulanov V, Lampertico P, et al. Bulevirtide Combined with Pegylated Interferon for Chronic Hepatitis D [Supplementary Appendix]. *N Engl J Med.* 2024;391(2):133-143.

5. Wedemeyer H, Aleman S, Blank A, et al. 144 Weeks of bulevirtide monotherapy for chronic hepatitis D: Final and post-treatment results from a phase III randomized trial. *J Hepatol.* 2026;85(3):493-503.
6. Wedemeyer H, Aleman S, Blank A, et al. 144 Weeks of bulevirtide monotherapy for chronic hepatitis D: Final and post-treatment results from a phase III randomized trial [Supplement]. *J Hepatol.* 2026;85(3):493-503.
7. Nissen T, Wynn R. The Clinical Case Report: A Review of Its Merits and Limitations. *BMC Res Notes.* 2014;7:264. https://www.ncbi.nlm.nih.gov/pubmed/24758689
8. Vaddadi SM, Wiegley N, Ananthakrishnan S, Madan N. A Viral Conundrum: Hepatitis D and Immune-Complex Glomerulonephritis [Abstract-FR-PO954]. *J Am Soc Nephrol.* 2024;35(10S).

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Hepcludex US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/hdv/hepcludex/hepcludex_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or www.accessdata.fda.gov/scripts/medwatch

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