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Hepcludex® (bulevirtide-gmod) Mechanism of Action

This document is in response to your request for information regarding the mechanism of action (MOA) of Hepcludex® (bulevirtide-gmod [BLV]) for the treatment of chronic HDV.

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Product Labeling[1]

BLV is a synthetic 47-amino acid lipopeptide with a myristoylated N-terminus and an amidated C-terminus derived from amino acids 13 to 59 of the L-HBsAg preS1 domain from an HBV GT-C consensus sequence (corresponding to GT-D preS1 amino acids 2–48). BLV inhibits HDV infection by binding to the HDV receptor NTCP on the plasma membrane of hepatocytes, blocking HDV attachment to NTCP.

Available Data on BLV MOA

NTCP

NTCP is expressed on the basolateral (blood-side) membrane of the hepatocyte; it is not detected in any other tissue. NTCP is a sodium taurocholate/bile acid cotransporter and is responsible for the uptake of bile acids from the portal blood into hepatocytes and is a key component of the enterohepatic recovery of bile acids.[2,3] Its expression is often downregulated in human liver disease.[3]

HBV and HDV bind to NTCP with their respective preS1 domains, which allow the viruses to be internalized into hepatocytes. Therefore, substrates that bind to NTCP reduce the entry of HBV and HDV as well as bile acids.[2]

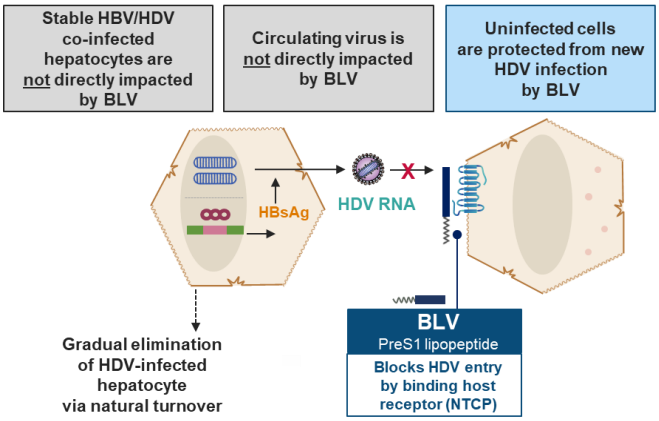
BLV

BLV is a myristoylated lipopeptide that prevents viral infections by competitively binding with NTCP and blocking the entry of HDV into hepatocytes (Figure 1).[2,3]

BLV comprises 47 amino acids of the preS1 domain of the L-HBsAg.[4]

Because the preS1 domain of HBV interacts with NTCP, the blocking of NTCP with BLV is thought to prevent the entry of HDV into hepatocytes.[4] Thus, BLV can prevent de novo infection of uninfected liver cells, leading to a reduction in HDV-infected hepatocytes (Figure 1).[5]

Figure 1. BLV MOA[5]



Abbreviation: HBsAg=hepatitis B surface antigen.

Primary pharmacology studies

In cellular uptake transporter inhibition assays, BLV inhibited human NTCP function in vitro in a dose-dependent manner with a maximum inhibition of 90%.[6]

In HBV and HDV in vitro infection assays, BLV inhibited the infectivity potential of several HBV genotypes and HDV isolates in human hepatic cells.[6]

Due to its mode of action on NTCP, BLV is also expected to impact the uptake of bile acids into the hepatocyte.[2]

HDV RNA and ALT levels are surrogate markers of HDV liver burden: HDV RNA levels reflect the amount of HDV in the periphery, and ALT levels can indicate the extent of liver damage due to viral infection and associated inflammation.[5,7]

References

1. Enclosed. Gilead Sciences Inc. HEPCLUDEX® (bulevirtide-gmod) injection, for subcutaneous use. US Prescribing Information. Foster City, CA.
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3. Appelman MD, Wettengel JM, Protzer U, Oude Elferink RPJ, van de Graaf SFJ. Molecular regulation of the hepatic bile acid uptake transporter and HBV entry receptor NTCP. *Biochim Biophys Acta Mol Cell Biol Lipids.* 2021;1866(8):158960.
4. Urban S, Bartenschlager R, Kubitz R, Zoulim F. Strategies to inhibit entry of HBV and HDV into hepatocytes. *Gastroenterology.* 2014;147(1):48-64.
5. Allweiss L, Volmari A, Suri V, et al. Blocking viral entry with bulevirtide reduces the number of HDV-infected hepatocytes in human liver biopsies. *J Hepatol.* 2024;80(6):882-891.
6. European Medicines Agency (EMA). *Assessment Report: Hepcludex. International non-proprietary name: bulevirtide. Procedure No. EMEA/H/C/004854/0000. 28 May.* 2020.
7. Pawlotsky JM. Virological markers for clinical trials in chronic viral hepatitis. *JHEP Rep.* 2024;6(11):101214.

Abbreviations

BLV=bulevirtide-gmod
GT=genotype
L-HBsAg=large hepatitis B surface antigen
MOA=mechanism of action
NTCP=sodium taurocholate co-transporting polypeptide

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

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