



Bixlenvo™ (bictegravir/lenacapavir)

Mechanism of Action

This document is in response to your request for information regarding Bixlenvo™ (bictegravir/lenacapavir [BIC/LEN]) and its mechanism of action.

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Product Labeling¹

Bictegravir: BIC inhibits the strand-transfer activity of HIV-1 integrase (integrase strand-transfer inhibitor; INSTI), with a 50% inhibitory concentration (IC₅₀) value of 7.5 nM. Inhibition of integrase prevents the integration of linear HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the virus.

Lenacapavir: LEN is a multistage, selective inhibitor of HIV-1 capsid function that directly binds to the interface between capsid protein (p24) subunits in hexamers. Surface plasmon resonance sensorgrams showed dose-dependent and saturable binding of LEN to cross-linked wild-type capsid hexamer with an equilibrium binding constant (K_D) of 1.4 nM. LEN inhibits HIV-1 replication by interfering with multiple essential steps of the viral lifecycle, including capsid-mediated nuclear uptake of HIV-1 proviral DNA (by blocking nuclear import proteins binding to capsid), virus assembly and release (by interfering with Gag/Gag-Pol functioning, reducing production of capsid protein subunits), and capsid core formation (by disrupting the rate of capsid subunit association, leading to malformed capsids).

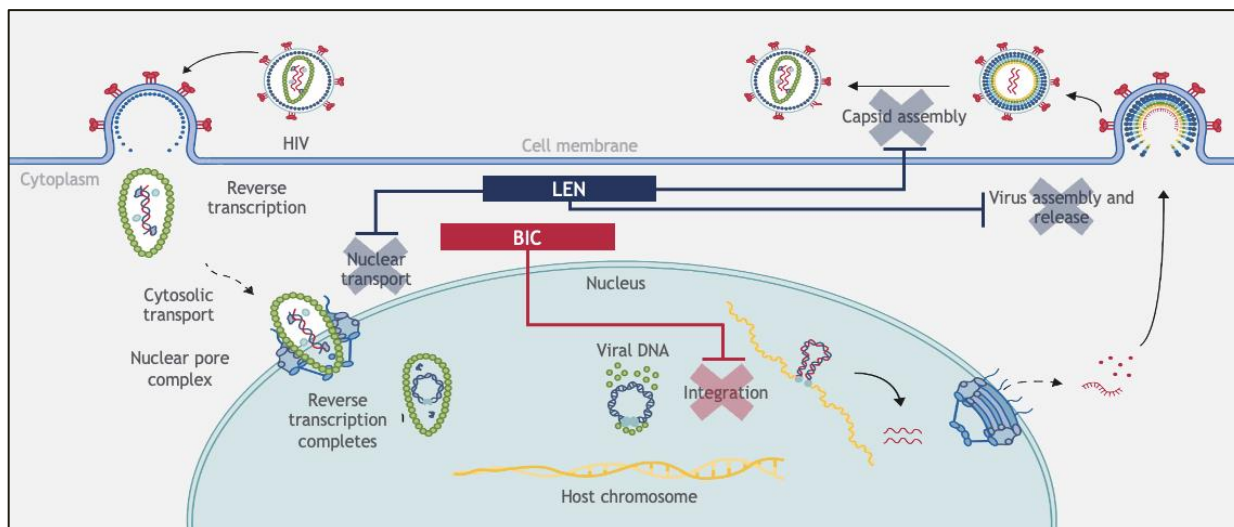
Available Data on the Mechanism of Action of LEN

BIC is a novel, potent, unboosted second-generation INSTI. Integrase strand transfer inhibitors block the strand transfer step of viral DNA integration into the host genome to inhibit HIV-1 replication (Figure 1). BIC maintained antiviral activity against HIV-1 variants resistance to other classes of antiretrovirals in vitro, with an improved resistance profile compared to first-generation INSTIs including RAL and EVG.² Additionally, BIC demonstrated synergistic antiviral activity against HIV-1 when combined with LEN.³

LEN is a novel, first-in-class, HIV-1 capsid inhibitor with a multistage mechanism of action and a desirable in vitro profile. The HIV capsid protein is part of the group -specific antigen (gag) region of the HIV-1 gene and plays multiple roles in the HIV replication cycle. LEN binds to the viral capsid protein and prevents nuclear transport, virus assembly and release,

and capsid assembly in new virions (Figure 1).^{4,5} LEN remained fully active against a broad spectrum of HIV-1 variants resistance to other ARV classes, demonstrating a non-overlapping resistance profile.⁶

Figure 1. Mechanism of Action of BIC/LEN^{1,6-11}



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Abbreviations

BIC=bictegravir

DNA=deoxyribonucleic acid

EVG=elvitegravir

HIV=human

immunodeficiency virus

INSTI=integrase-strand
transfer inhibitor

LEN=lenacapavir

RAL=raltegravir

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Bixlenvo US Prescribing Information available at:

www.gilead.com/-/media/files/pdfs/medicines/hiv/BIXLENVO/BIXLENVO_pi

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