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Bixlenvo™ (bictegravir/lenacapavir) Missed Doses

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

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Summary

Product Labeling[1]

Recommended Dosing Schedule for Missed Dose

- Missed Initiation Dose: During the initiation period, if the Day 1 or Day 2 doses of BIC/LEN or LEN are missed, patients should take them as soon as possible (see Table 1). Patients should not take Day 1 and Day 2 doses of LEN on the same day.
- Missed Maintenance Dose: If a maintenance dose of BIC/LEN is missed, patients should take it as soon as possible. If more than 7 days have elapsed since the last maintenance dose, restart the initiation dosage regimen from Day 1, if clinically appropriate to continue BIC/LEN treatment (see Table 1).

Pharmacokinetic and Clinical Data on Missed Maintenance Doses[2]

- PK data indicate that LEN concentrations remain above the IQ1 threshold after up to 7 consecutive missed daily doses of BIC/LEN.
- Participants in the ARTISTRY studies who missed more than 7 doses of BIC/LEN and received LEN reloading maintained viral suppression at Week 48.

Pharmacokinetic Data on Missed Initiation Doses of Oral LEN[3]

- Population PK models predicted that when at least one oral LEN initiation dose is administered alongside taking daily BIC/LEN maintenance dose, mean LEN trough concentrations remain above IQ4 (value of 15 ug/L) with the 5th percentile of the population PK distribution remaining at approximately IQ4 from that day onward.
- If both oral LEN initiation doses are missed alongside taking daily BIC/LEN maintenance dose, model predictions for median trough concentrations of LEN indicated that IQ4 is reached by approximately 5 days under fasted conditions and 8 days under fed conditions; however, substantial PK variability is predicted.
- Because these estimates are based on modeling rather than clinical studies, they should be interpreted cautiously, and no clinical conclusions can be made based on these estimates.

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Product Labeling[1]

Recommended Dosing Schedule for Missed Dose

Missed Initiation Dose
During the initiation period, if the Day 1 or Day 2 doses of BIC/LEN or LEN are missed, patients should take them as soon as possible (see Table 1). Patients should not take Day 1 and Day 2 doses of LEN on the same day.

Missed Maintenance Dose
If a maintenance dose of BIC/LEN is missed, patients should take it as soon as possible. If more than 7 days have elapsed since the last maintenance dose, restart the initiation dosage regimen from Day 1, if clinically appropriate to continue BIC/LEN treatment (see Table 1).

Table 1. Recommended Treatment Regimen for BIC/LEN Initiation and Maintenance

Treatment Time	Dosage: Initiation
Day 1	BIC/LEN 75 mg/50 mg (1 tablet) orally and LEN 600 mg orally (2 × 300 mg tablets)
Day 2	BIC/LEN 75 mg/50 mg (1 tablet) orally and LEN 600 mg orally (2 × 300 mg tablets)
Treatment Time	**Dosage: Maintenance**
Day 3 and thereafter	BIC/LEN 75 mg/50 mg (1 tablet) orally once daily

Patient Counseling Information

Dosing: Initiation Regimen and Missed Dose
Counsel patients that it is important to take both BIC/LEN and LEN tablets during the initiation period which is the first two days of treatment. Counsel patients to take BIC/LEN on a regular dosing schedule with or without food and to avoid missing doses as it can result in development of resistance. Patients should contact their healthcare provider if more than 7 days have elapsed since their last dose of BIC/LEN.

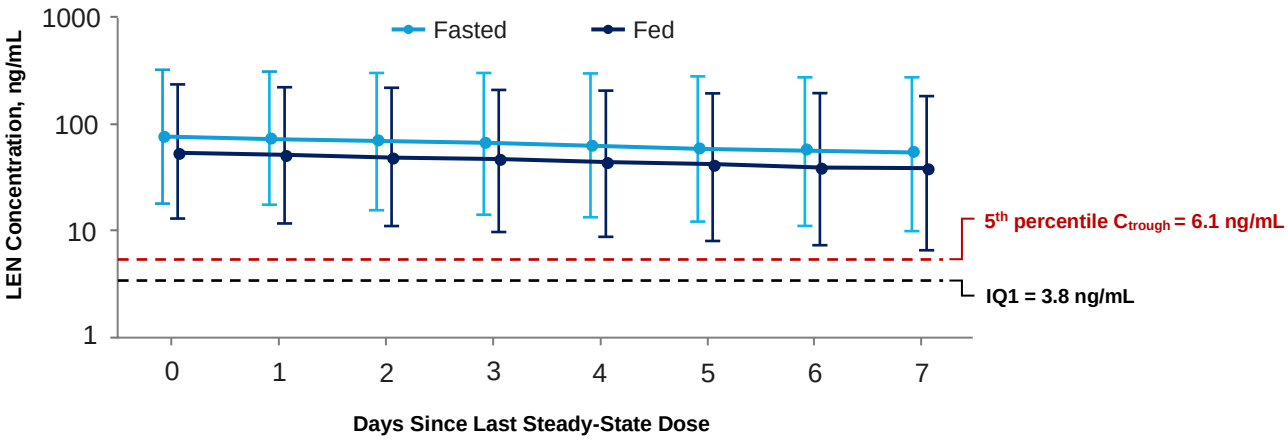
Pharmacokinetic and Clinical Data on Missed Maintenance Doses

Population PK Analysis[2]

In a population PK analysis of 11 studies (N=1295), including single-dose studies and ARTISTRY studies, a stochastic simulation was performed at steady state to characterize the PK of LEN, as a component of BIC/LEN, and to evaluate LEN exposure up to 7 days of missed BIC/LEN maintenance doses.

After 7 consecutive days of missed BIC/LEN doses, simulations showed a median (90% Prediction Interval) LEN C_{trough} of 55.1 (9.86, 273) ng/mL under fasted conditions and 38.9 (6.49, 183) ng/mL under fed conditions, both exceeding the IQ1 of 3.8 ng/mL for LEN (Figure 1 and Table 2). Over the same period, most participants also had projected concentrations above the 5th percentile of the simulated population C_{trough} obtained 26 weeks after subcutaneous LEN administration in treatment-naïve people with HIV. In studies of subcutaneous LEN, efficacy was robust at concentrations above this population 5th percentile of C_{trough}.

Figure 1. Projected Median LEN Concentrations After Missed BIC/LEN Doses



Note: Data points and corresponding error bars have been slightly staggered at each timepoint for clarity. Line markers are median values and error bars are 90% PI. The red dashed line corresponds to the simulated population 5th percentile of C_{trough} (6.1 ng/mL) obtained for subcutaneous LEN administration after 26 weeks in treatment naïve people with HIV. The black dashed line corresponds to IQ1 (3.8 ng/mL).

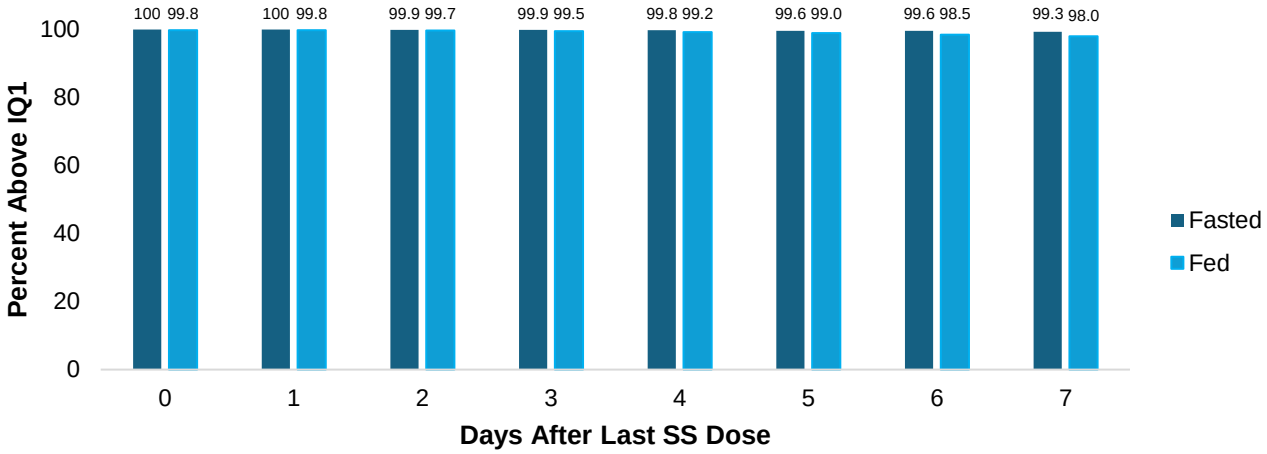
Table 2. Projected Median (90% PI) LEN Concentrations After Missed BIC/LEN Doses

Days After Last SS BIC/LEN Dose	Median (90% PI) LEN Concentration, ng/mL		Mean (90% CI) LEN Concentration, ng/mL	
	Fasted	Fed	Fasted	Fed
0	77.4 (18.0, 324)	55.4 (13.0, 236)	113 (110, 115)	80.5 (78.4, 82.5)
1	72.7 (17.5, 310)	52.4 (11.7, 221)	109 (106, 111)	76.8 (74.9, 78.6)
2	70.2 (15.5, 301)	48.9 (11.0, 219)	104 (101, 107)	74.4 (72.4, 76.3)
3	66.8 (14.1, 301)	48.1 (9.67, 209)	101 (97.9, 103)	70.9 (69.0, 72.7)
4	63.6 (13.3, 298)	44.8 (8.77, 205)	96.2 (93.7, 98.7)	67.9 (66.1, 69.7)
5	59.4 (12.1, 280)	42.3 (8.04, 193)	92.4 (89.9, 94.9)	65.3 (63.5, 67.0)
6	57.1 (11.0, 273)	39.9 (7.29, 194)	89.7 (87.2, 92.1)	62.5 (60.8, 64.1)
7	55.1 (9.86, 273)	38.9 (6.49, 183)	86.4 (84.0, 88.8)	61.1 (59.3, 62.8)

Abbreviation: PI=prediction interval; SS=steady state.

Projected LEN concentrations remained above IQ1 in most participants for up to 7 days after the last steady-state dose of BIC/LEN (Figure 2).

Figure 2. Percentage of People on BIC/LEN With Projected LEN Plasma Concentrations Above IQ1



Clinical Data from ARTISTRY Studies

ARTISTRY-1 (NCT05502341) is an ongoing, randomized, multicenter, open-label, phase 2/3 study designed to evaluate the efficacy and safety of switching to oral BIC/LEN (75mg/50 mg) vs continuing a complex ART regimen in VS PWH.[4]

ARTISTRY-2 (NCT06333808) is an ongoing, randomized, multicenter, double-blind, active-controlled phase 3 study designed to evaluate the efficacy and safety of switching from BIC/FTC/TAF to oral BIC/LEN (75 mg/50 mg) vs continuing BIC/FTC/TAF in VS PWH.[5]

In ARTISTRY-1 and ARTISTRY-2, participants who switched to BIC/LEN received a 2-day oral loading dose regimen of LEN 600 mg (2 x 300 mg LEN on Day 1 and 2), in addition to the daily dose of BIC/LEN starting on Day 1. If a participant missed the scheduled daily dose(s) of BIC/LEN, recommendations for restarting treatment were provided based on number of days since missed scheduled daily dose (Table 3).[6,7]

Table 3. Missed Daily Dose(s) Recommendation for BIC/LEN Treatment Groups[6,7]

Number of Days Since Missed Scheduled Daily Dose	Recommendation
1 to 7 days (1 to 7 days missed daily doses)	Take study drug orally as soon as possible. Then resume normal schedule by taking study drug(s) the next day and daily thereafter.
More than 7 days (more than 7 missed daily doses)	Reload by dosing the 2-day oral loading regimen of LEN (2 x 300 mg on Day 1 and 2 of treatment reinitiation) in addition to restarting the normal schedule of dosing by taking study drug(s) on Day 1 of treatment reinitiation and thereafter.

Seven participants across both studies missed more than 7 consecutive doses and underwent LEN reloading with BIC/LEN reinitiation per protocol (Table 4). All seven participants maintained HIV-1 RNA suppression at Week 48, at their last available measurement, or at the measurement after reloading.[2]

Table 4. Clinical Data From BIC/LEN Participants Receiving LEN Reloading (After Missing >7 Consecutive Daily Doses) During the ARTISTRY Studies[2]

Participant	Study	Study Days of LEN Reloading	HIV-1 RNA at LEN Reloading	HIV-1 RNA at Week 48	Study Drug Discontinued
1	ARTISTRY-1	153 and 154	Not assessed	Undetectable	No
2	ARTISTRY-1	176 and 177	Not assessed	Undetectable	No
3	ARTISTRY-1	258 and 259 439 and 440[a]	Undetectable Undetectable	<20 c/mL	No
4	ARTISTRY-2	43 and 44	Undetectable	Undetectable	Yes[b]
5	ARTISTRY-2	54 and 55	Not assessed	Undetectable	No
6	ARTISTRY-2	111 and 112	Undetectable	No data[c]	Yes[c]
7	ARTISTRY-2	343 and 344[d]	Not assessed	<20 c/mL	No

[a]Occurred after Week 48; HIV-1 RNA was undetectable at Week 72 (Study Day 502).
[b]Participant decided to discontinue study drug.
[c]HIV-1 RNA was undetectable at the last available viral load assessment at Week 24 (Study Day 174). The participant discontinued study drug per investigator's decision before Week 48.
[d]Occurred after Week 48; HIV-1 RNA was <20 c/mL at Week 60 (Study Day 427).

Pharmacokinetic Data on Missed Initiation Doses of Oral LEN

No clinical data are available evaluating missed LEN initiation-dose scenarios. Available information is based on population PK modeling:[3]

<u>If at least one oral LEN initiation dose is administered (Day 1, Day 2, or both):</u>

Population PK models predicted that when at least one LEN initiation dose is administered alongside taking daily BIC/LEN maintenance dose, mean LEN trough concentrations remain above IQ4 (value of 15 ug/L) with the 5th percentile of the population PK distribution remaining at approximately IQ4 from that day onward.

<u>If both oral LEN initiation doses are missed:</u>

If both LEN initiation doses are missed alongside taking daily BIC/LEN maintenance dose, model predictions for median trough concentrations of LEN indicated that IQ4 is reached by approximately 5 days under fasted conditions and 8 days under fed conditions; however, substantial PK variability is predicted. By Week 4, modeled LEN exposure under fed and fasted conditions supported continuation without additional loading in most individuals. LEN exhibits considerable PK variability, resulting in a broad range around the median estimates of the time for LEN trough concentration to reach IQ4. Individuals in the lower percentiles could take longer than 4 weeks to attain IQ4 under fed conditions.

Because these estimates are based on modeling rather than clinical studies, they should be interpreted cautiously, and no clinical conclusions can be made based on these estimates.

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References

1. Enclosed, Gilead Sciences Inc. BIXLENVO™ (bictegravir and lenacapavir) tablets, for oral use. U.S. Prescribing Information. Foster City, CA.
2. Arora P, Saqr A, Sklar P, Marathe DD, Johnston C. Pharmacokinetic and Clinical Data Supporting the LEN Reloading Strategy for BIC/LEN Single-Tablet Regimen Dosing in the ARTISTRY Studies [Poster P-1019]. Paper presented at: IDWeek; October 21-24, 2026; Washington, DC.
3. Gilead Sciences Inc. Data on File.
4. Orkin C, Ruane PJ, Hedgcock M, et al. Switch to single-tablet bictegravir-lenacapavir from a complex HIV regimen (ARTISTRY-1): a randomised, open-label, phase 3 clinical trial. *Lancet.* 2026;407(10535):1249-1258.
5. Meissner EG, Ramgopal M, Ruane PJ, et al. Safety and efficacy of switching to bictegravir-lenacapavir versus continuing bictegravir-emtricitabine-tenofovir alafenamide in virologically suppressed people with HIV-1 (ARTISTRY-2): a double-blind, multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet HIV.* 2026;13(8):e538-e547.
6. Orkin C, Ruane PJ, Hedgcock M, et al. Switch to single-tablet bictegravir-lenacapavir from a complex HIV regimen (ARTISTRY-1): a randomised, open-label, phase 3 clinical trial [Supplementary appendix]. *Lancet.* 2026;407(10535):1249-1258.
7. Meissner EG, Ramgopal M, Ruane PJ, et al. Safety and efficacy of switching to bictegravir-lenacapavir versus continuing bictegravir-emtricitabine-tenofovir alafenamide in virologically suppressed people with HIV-1 (ARTISTRY-2): a double-blind, multicentre, randomised, controlled, phase 3, non-inferiority trial [Supplementary appendix]. *Lancet HIV.* 2026;13(8):e538-e547.

Abbreviations

ART=antiretroviral therapy
BIC=bictegravir
C_{trough}=lowest observed drug concentration
FTC=emtricitabine
IQ1=inhibitory quotient 1
IQ4=inhibitory quotient 4
LEN=lenacapavir
PK=pharmacokinetics
PWH=people with HIV
TAF=tenofovir alafenamide
VS=virologically suppressed

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Bixlenvo and Sunlenca US Prescribing Information available at:
www.gilead.com/-/media/files/pdfs/medicines/hiv/bixlenvo/bixlenvo_pi.
www.gilead.com/-/media/files/pdfs/medicines/hiv/sunlenca/sunlenca_pi.

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