

Biktarvy[®] (BIC/FTC/TAF)

Crushing, Dissolving, or Splitting of Tablets

This document is in response to your request for information regarding Biktarvy[®] (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]) and the crushing, dissolving, or splitting of tablets.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

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

Summary

Product Labeling¹

In adults and pediatric patients weighing ≥ 25 kg with an estimated CrCl ≥ 30 mL/min, or virologically suppressed adults with an estimated CrCl < 15 mL/min who are receiving chronic hemodialysis, the recommended dosage of BIC/FTC/TAF is one tablet containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF taken orally once daily with or without food.

In pediatric patients weighing ≥ 14 kg to < 25 kg with an estimated CrCl ≥ 30 mL/min, the recommended dosage of BIC/FTC/TAF is one tablet containing 30 mg of BIC, 120 mg of FTC, and 15 mg of TAF taken orally once daily with or without food. For children unable to swallow a whole tablet, the tablet can be split and each part taken separately as long as all parts are ingested within approximately 10 minutes.

For the individual components of BIC/FTC/TAF, BIC, FTC, and TAF are soluble in water, with solubility of 0.1 mg/mL in water at 20°C, approximately 112 mg/mL in water at 25°C, and 4.7 mg/mL in water at 20°C, respectively.

Real-World Data on Crushing or Dissolving BIC/FTC/TAF

A retrospective, multicenter study assessed whether crushed or dissolved BIC/FTC/TAF was effective at maintaining or achieving virologic suppression in hospitalized PWH who required an enteral route of medication administration (N=19). Within 1 year of receiving ≥ 1 week of crushed or dissolved BIC/FTC/TAF, 17 patients (89%) were virologically suppressed, and no patients developed resistance.²

PK Data on Crushing or Dissolving BIC/FTC/TAF

A phase 1 crossover study evaluated the bioavailability of crushed or dissolved BIC/FTC/TAF compared with solid BIC/FTC/TAF in HIV-negative, healthy adult volunteers (N=18). After fasting, volunteers received BIC/FTC/TAF dissolved in water, crushed in applesauce, and as a solid tablet in random sequence.³

- Dissolved BIC/FTC/TAF was considered equivalent to the solid tablet for all PK parameters evaluated, with the exception of the C_{max} for TAF.
- The $AUC_{0-\infty}$ for the crushed tablet was equivalent to that of the solid tablet for BIC and FTC, but not TAF. The C_{max} for the crushed tablet was not equivalent to that of the solid tablet for FTC or TAF but was equivalent for BIC.
- Twenty-eight percent of volunteers (5/18) experienced ≥ 1 AE, and no AEs led to BIC/FTC/TAF discontinuation.

Case Reports on Crushing or Dissolving BIC/FTC/TAF

Case reports involving the use of crushed or dissolved BIC/FTC/TAF are summarized below.⁴⁻⁸

Real-World Data on Crushing or Dissolving BIC/FTC/TAF

Retrospective Study in PWH²

Study design and demographics

A retrospective, multicenter study assessed whether crushed or dissolved BIC/FTC/TAF was effective at maintaining or achieving virologic suppression in hospitalized PWH who required an enteral route of medication administration (N=19). The analysis included patients who had received crushed or dissolved BIC/FTC/TAF between December 2016 and December 2023 for ≥ 1 week and had a VL assessment within 1 year of treatment. The primary endpoint was confirmed virologic suppression (VL <200 copies/mL) within 1 year of treatment. Secondary endpoints included the development of resistance during the 1-year follow-up period.

Table 1. Baseline Demographics and Disease Characteristics (Mercure et al)²

Key Demographics and Characteristics	BIC/FTC/TAF (N=19)
Age, median (IQR), years	54 (47.5–66.5)
Male, n (%)	16 (84)
Virologically suppressed or had an undetectable VL, n (%)	11 (58)
Resistance at baseline, ^a n (%)	8 (42)
Administered crushed/dissolved BIC/FTC/TAF, n (%)	8 (42)/ 2 (11)

Abbreviations: INSTI=integrase strand transfer inhibitor; NNRTI=non-nucleos(t)ide reverse transcriptase inhibitor; NRTI=nucleos(t)ide reverse transcriptase inhibitor; PI=protease inhibitor.

^aNRTI, n=5 (26%); NNRTI, n=4 (21%); PI, n=4 (21%); INSTI, n=0.

Results

The median (IQR) duration of treatment with crushed or dissolved BIC/FTC/TAF was 19 (7.5–64) days. At least one dose was missed in 6 patients (32%). Within 1 year of receiving crushed or dissolved BIC/FTC/TAF, 17 patients (89%) were virologically suppressed; of these, 11 patients (58%) maintained undetectable VLs, and 6 patients (31%) achieved virologic suppression. Patients who did not achieve the primary endpoint were either lost to follow-up or did not survive. No patients developed resistance, and 3 patients (16%) continued to receive crushed or dissolved BIC/FTC/TAF after discharge.

Eight deaths were reported (causes related to infection, n=5; causes related to HIV, n=2; and unknown cause, n=1); 6 patients (75%) had comorbid conditions that contributed to death in critical care settings.

PK Data on Crushing or Dissolving BIC/FTC/TAF

SOLUBIC Study in HIV-Negative Volunteers

Study design and demographics

A phase 1, open-label, single-dose, three-period crossover study evaluated the bioavailability of crushed or dissolved BIC/FTC/TAF compared with that of a solid tablet in HIV-negative, healthy adult volunteers (N=18). After fasting, all healthy volunteers received BIC/FTC/TAF dissolved in water, crushed in applesauce, and as a solid tablet in random sequence separated by a washout period of 14 to 28 days. Plasma concentrations were collected before dosing and through 72 hours following the administration of each dose.³ The primary endpoints of the study were AUC (AUC_{0-∞} for BIC and FTC; AUC_{0-last} for TAF, due to its short t_{1/2}) and C_{max} of each of the three components to determine the bioequivalence of the dissolved or crushed tablets with the whole tablet.^{3,9} Bioequivalence was met if the 90% CI of the geometric least squares mean ratios of AUC and C_{max} for the dissolved or crushed tablets were within 80% to 125% of the whole tablet. Secondary endpoints included assessments of safety and tolerability. All volunteers were White, and 9 volunteers were female; the median age was 30 years, and the median BMI was 21 kg/m².³

Results³

The AUC for dissolved BIC/FTC/TAF was equivalent to that of the solid tablet for all individual components (AUC_{0-∞} for BIC and FTC; AUC_{0-last} for TAF). The C_{max} for dissolved BIC/FTC/TAF was considered equivalent to that of the solid tablet for BIC and FTC, but not for TAF. The AUC_{0-∞} for the crushed tablet showed equivalence to the solid tablet for BIC and FTC, but not for TAF. The C_{max} for the crushed tablet showed equivalence to the solid tablet for BIC, but not for FTC and TAF (Table 2).

**Table 2. PK Parameters of BIC, FTC, and TAF
According to Administration Modality (Hocqueloux et al)³**

Drug	PK Parameter	Solid Tablet	Dissolved Tablet	Crushed Tablet	Dissolved: Solid, % (90% CI)	Crushed: Solid, % (90% CI)
BIC	AUC _{0-∞} , GM (CV), h·mg/L	107.9 (39)	119.4 (31)	115 (36)	111 (100–122)	107 (96–118)
	C _{max} , GM (CV), mg/L	5 (42)	5.2 (62)	5.5 (84)	105 (93–119)	110 (97–124)
	T _{max} , median (range), h	2.3 (0.5–4)	2.5 (0.5–4)	2 (0.5–8)	–	–
	t _{1/2} , GM (CV), h	19.1 (20)	18.2 (18)	19.1 (25)	–	–
FTC	AUC _{0-∞} , GM (CV), h·mg/L	10.5 (18)	10.5 (20)	9.1 (19)	100 (94–105)	86 (82–91)
	C _{max} , GM (CV), mg/L	2 (24)	2 (38)	1.4 (27)	97 (87–108)	70 (63–78)
	T _{max} , median (range), h	1.5 (1–2.5)	1.5 (0.5–2.5)	2 (1–3)	–	–
	t _{1/2} , GM (CV), h	14.2 (46)	14.4 (65)	19.2 (45)	–	–

Drug	PK Parameter	Solid Tablet	Dissolved Tablet	Crushed Tablet	Dissolved: Solid, % (90% CI)	Crushed: Solid, % (90% CI)
TAF	AUC _{0-last} , GM (CV), h·mg/L	0.053 (98)	0.053 (102)	0.047 (91)	99 (81–120)	84 (69–103)
	C _{max} , GM (CV), mg/L	0.065 (130)	0.062 (133)	0.043 (116)	96 (74–124)	66 (51–85)
	T _{max} , median (range), h	1 (0.5–2)	0.5 (0.5–1)	0.5 (0.5–2)	–	–
	t _{1/2} , GM (CV), h	0.415 (180)	0.383 (55)	0.458 (45)	–	–

Abbreviations: CV=coefficient of variation; GM=geometric mean; T_{max}=time at which the maximum concentration is observed.

The authors concluded that in cases where the BIC/FTC/TAF tablet cannot be swallowed in solid form, the tablet should be dissolved in water and taken immediately, rather than crushed. Overall, 28% of volunteers (5/18) experienced ≥1 AE. No AEs led to BIC/FTC/TAF discontinuation. Solid and crushed tablets were rated significantly easier to swallow compared with dissolved tablets ($P<0.005$), and crushed and dissolved tablets were rated significantly worse than whole tablets in terms of taste ($P<0.001$).

Case Reports on Crushing or Dissolving BIC/FTC/TAF

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. Additionally, 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.¹⁰

Several case reports have described the administration of crushed or dissolved BIC/FTC/TAF, with durations ranging from 1 to 12 months. In three patients, HIV-1 VLs remained undetectable after receiving a course of crushed or dissolved tablets. Two other patients with high initial VLs and complex comorbidities achieved virologic suppression after switching from BIC/FTC/TAF to another antiretroviral regimen.⁴⁻⁸

References

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Abbreviations

AE=adverse event
AUC=area under the concentration-time curve
AUC_{0-∞}=area under the concentration-time curve from time 0 extrapolated to infinite time

AUC_{0-last}=area under the concentration-time curve from time 0 to the time of the last quantifiable concentration after dosing
BIC=bictegravir
C_{max}=maximum concentration

FTC=emtricitabine
PK=pharmacokinetic(s)
PWH=people with HIV
t_{1/2}=elimination half-life
TAF=tenofovir alafenamide
VL=viral load

Product Label

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

www.gilead.com/-/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_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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