

# Biktarvy<sup>®</sup> (BIC/FTC/TAF)

## Crushing, Dissolving, or Splitting of Tablets

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

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**The full indication, important safety information, and boxed warnings are available at: [www.gilead.com/-/media/files/pdfs/medicines/hiv/biktarvy/biktarvy\\_pi](http://www.gilead.com/-/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi).**

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## Summary

### Product Labeling<sup>1</sup>

In adults and pediatric patients weighing  $\geq 25$  kg with an estimated CrCl  $\geq 30$  mL/min, 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  $\geq 14$  kg to  $< 25$  kg with an estimated CrCl  $\geq 30$  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, TAF and FTC are soluble in water, while BIC is practically insoluble (solubility of 0.1 mg/mL in water at 20°C).

### Available Data on Crushing, Dissolving, or Splitting BIC/FTC/TAF Tablets

A phase 1 crossover study evaluated the bioavailability of crushed or dissolved BIC/FTC/TAF in comparison 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.<sup>2</sup>

- 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 the solid tablet for BIC and FTC, but not TAF. The  $C_{max}$  for the crushed tablet was not equivalent to the solid tablet for FTC or TAF, but was equivalent for BIC.
- Twenty-eight percent of volunteers (5/18) experienced  $\geq 1$  AE, and no AEs led to BIC/FTC/TAF discontinuation.

### Literature Search

Five case reports that involve the use of crushed or dissolved BIC/FTC/TAF tablets are presented below. In three cases, individuals remained virologically suppressed while taking

crushed or dissolved BIC/FTC/TAF for a short period of time. In two cases, individuals were not able to achieve virologic suppression when administered crushed BIC/FTC/TAF.<sup>3-7</sup>

## Available Data on Crushing, Dissolving, or Splitting BIC/FTC/TAF Tablets

### SOLUBIC Study in HIV-Negative Volunteers

#### Study design and demographics

A phase 1, open-label, single-dose, 3-period crossover study ([NCT04244448](#)) evaluated the bioavailability of crushed or dissolved BIC/FTC/TAF in comparison with that of solid BIC/FTC/TAF 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 each. Plasma concentrations were collected before dosing and through 72 hours following the administration of each single dose.<sup>2</sup> The primary endpoints of the study were AUC (AUC<sub>0-∞</sub> for BIC and FTC; AUC<sub>0-last</sub> for TAF, due to its short t<sub>1/2</sub>) and C<sub>max</sub> of each of the three components to determine the bioequivalence of the dissolved or crushed tablets compared with the whole tablet.<sup>2,8</sup> Bioequivalence was met if the 90% CI of the geometric least squares mean ratios of AUC and C<sub>max</sub> 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 Caucasian, and 9 volunteers were female; the median age was 30 years, and the median BMI was 21 kg/m<sup>2</sup>.<sup>2</sup>

#### Results<sup>2</sup>

The AUC for dissolved BIC/FTC/TAF was equivalent to the solid tablet for all individual components (AUC<sub>0-∞</sub> for BIC and FTC; AUC<sub>0-last</sub> for TAF). The C<sub>max</sub> for dissolved BIC/FTC/TAF was considered equivalent to the solid tablet for BIC and FTC, but not for TAF.

The AUC<sub>0-∞</sub> for the crushed tablet showed equivalence to the solid tablet for BIC and FTC, but not for TAF. The C<sub>max</sub> for the crushed tablet showed equivalence to the solid tablet for BIC; however, the crushed FTC and TAF components did not show equivalence (Table 1).

**Table 1. PK Parameters of BIC, FTC, and TAF According to Administration Modality<sup>2</sup>**

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

Drug	PK Parameter	Solid Tablet	Dissolved Tablet	Crushed Tablet	Dissolved: Solid, % (90% CI)	Crushed: Solid, % (90% CI)
	<b>T<sub>max</sub>, median (range), h</b>	1.5 (1–2.5)	1.5 (0.5–2.5)	2 (1–3)	–	–
	<b>t<sub>1/2</sub>, GM (CV), h</b>	14.2 (46)	14.4 (65)	19.2 (45)	–	–
TAF	<b>AUC<sub>0–last</sub>, GM (CV), h·mg/L</b>	0.053 (98)	0.053 (102)	0.047 (91)	99 (81–120)	84 (69–103)
	<b>C<sub>max</sub>, GM (CV), mg/L</b>	0.065 (130)	0.062 (133)	0.043 (116)	96 (74–124)	66 (51–85)
	<b>T<sub>max</sub>, median (range), h</b>	1 (0.5–2)	0.5 (0.5–1)	0.5 (0.5–2)	–	–
	<b>t<sub>1/2</sub>, GM (CV), h</b>	0.415 (180)	0.383 (55)	0.458 (45)	–	–

Abbreviations: CV=coefficient of variation; GM=geometric mean; T<sub>max</sub>=time at which the maximum concentration is observed.

The authors concluded, 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 (Table 2). No AEs led to BIC/FTC/TAF discontinuation.

**Table 2. Safety, Acceptability, and Preference According to Administration Modality<sup>2</sup>**

Parameter	Solid (N=18)	Dissolved (N=18)	Crushed (N=18)	All Modalities (N=18)
Any AE, n	3	2	1	7 <sup>a</sup>
Possibly related to study drug, n	0	2	1	3 <sup>b</sup>
Taste, <sup>c</sup> median (IQR)	10 (9–10)	3.5 (2–4)	3 (2–4)	–
Ease of swallowing, <sup>c</sup> median (IQR)	10 (10–10)	6.5 (6–9)	9.5 (9–10)	–
Preferred modality, <sup>d</sup> n	1	3	2	–

<sup>a</sup>One AE was reported with the drug not administered yet. All AEs were Grade 1 or 2 and moderate in severity.

<sup>b</sup>All were headaches reported on the day of administration.

<sup>c</sup>Scale: 0=worst taste or most complicated administration; 10=best taste or easiest administration. This was collected after each administration.

<sup>d</sup>Ranking was collected after the third administration period; 1=most preferred and 3=least preferred.

## Literature Search

A literature search was conducted in the Ovid MEDLINE, BIOSIS Previews, and Embase databases for studies published between 1946 and January 9, 2024, using the search terms Biktarvy, bictegravir, emtricitabine, tenofovir alafenamide, and cutting, crushing, splitting tablets, and related search terms. Relevant case reports are summarized below.

## Case Reports

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.<sup>9</sup>

Roa and Bazzi described the case of a 78-year-old African American male with HIV who was newly diagnosed with pancreatic cancer and maintained virologic suppression with crushed BIC/FTC/TAF. The patient was diagnosed with HIV in 2007 and was successfully treated with two different ARV therapies until 2019, when he was switched to BIC/FTC/TAF due to a drug-drug interaction between proton-pump inhibitors and RPV/FTC/TDF. His VL remained undetectable after switching to BIC/FTC/TAF. In 2020, his gastrointestinal symptoms worsened, and he was diagnosed with pancreatic cancer. A PEG tube was placed during the inpatient hospital stay, and chemotherapy was started in the outpatient setting upon hospital discharge. The patient retained the PEG tube due to persistent dysphagia and was advised to crush BIC/FTC/TAF in order to continue the same ARV therapy, as he desired. Crushed BIC/FTC/TAF diluted in 30 to 60 mL of water was administered via the PEG tube separate from self-administered tube feedings throughout chemotherapy to avoid polyvalent cation interactions. The patient's VL remained undetectable after 7 months of crushed BIC/FTC/TAF.<sup>3</sup>

Fulco et al described the case of a 64-year-old male patient with HIV who was virologically suppressed on an ARV regimen that included DTG/ABC/3TC. Upon presentation to the clinic, the patient was diagnosed with esophageal adenocarcinoma with metastases to the liver; dysphagia; and difficulty ingesting oral medications. He was then switched to BIC/FTC/TAF for a smaller tablet size. For 6 weeks, the patient remained off medication and experienced an increase in VL to 501 c/mL without immunologic decline. The patient had a PEG tube placed for enteral nutrition and chemotherapy. After 4 months, the patient returned to the clinic and reported crushing the BIC/FTC/TAF tablet with a pulverizer, diluting the powder with 30 to 60 mL of water, and administering the medication via his PEG tube. After this daily routine, 240 mL of enteral nutrition was given. After 4 months of crushed BIC/FTC/TAF administration, the patient's VL was undetectable. The patient continued with this crushed regimen and maintained an undetectable VL for an additional 6 months. Eventually, esophageal dilation was successfully performed, which led to a return to oral tablet administration and nutrition.<sup>4</sup>

Ferrandez et al reported the case of a 52-year-old female patient with HIV who was virologically suppressed (VL <20 c/mL) and switched to BIC/FTC/TAF from EVG/COBI/FTC/TAF due to drug interaction considerations. The patient dissolved the BIC/FTC/TAF tablet in a tablespoonful of orange juice (with no manipulation), which was subsequently swallowed after 10 minutes. The patient did not consult her treating pharmacist or physician before starting this method of administration. The patient later reported swallowing issues from globus sensation to the pharmacist. BIC/FTC/TAF treatment continued for 12 months, and no tolerance issues or AEs were reported. The patient maintained a VL <20 c/mL after 12 months of treatment, and her CD4 count increased (baseline: 282 cells/ $\mu$ L; after 12 months: 370 cells/ $\mu$ L). The authors visually observed that the film coating completely dissolved after 4 minutes, and the tablet disintegrated in orange juice (pH 4) after 14 minutes without agitation.<sup>5</sup>

Rowe et al reported the case of a 43-year-old male with newly diagnosed HIV who was hospitalized due to changes in his neurological state, failure to thrive, and low blood pressure. His initial HIV RNA level was 769,704 c/mL, and his CD4 count was 36 cells/ $\mu$ L. On Day 8 in the hospital, he was started on daily oral BIC/FTC/TAF. On Day 28, after receiving 14 of the 20 scheduled doses of BIC/FTC/TAF, his HIV RNA level was 5887 c/mL. The next day, the patient was reintubated with a diagnosis of bilateral pneumothorax and began receiving BIC/FTC/TAF via NG tube until a PEG tube was placed on Day 38. He then started receiving crushed BIC/FTC/TAF diluted in 30 mL of water administered via the PEG tube with continuous tube feeds. On Day 65, the patient had received 37 consecutive doses

of BIC/FTC/TAF, and his HIV RNA level was 8047 c/mL. On Day 67, his ARV regimen was switched to DTG twice daily + DRV/r + FTC/TDF, and tube feedings were changed from continuous to intermittent boluses to avoid potential drug-drug interactions. DTG and FTC/TDF were crushed while DRV and ritonavir were given as liquid formulations. A resistance panel showed E157Q and V118I mutations. On Day 92, his HIV RNA level was 1071 c/mL; DRV/r was discontinued, and the DTG dose was decreased to once daily. He was discharged on Day 161, and oral BIC/FTC/TAF was restarted once the PEG tube was removed 2 months later, at which point his VL was 429 c/mL. The patient achieved virological suppression and remained suppressed at the 1-year follow-up.<sup>6</sup>

A case report from Lozano et al described the case of a 39-year-old female patient with HIV who was ARV-experienced and had been lost to follow-up several times on previous ARV regimens (TDF + FTC + LPV/r, ABC + FTC + RAL). No resistance information was available during the time the patient was treated with these ARV regimens. The patient was admitted to the hospital with cerebral toxoplasmosis. Next generation sequencing with a 1% cutoff determined wild-type virus, and BIC/FTC/TAF was initiated (VL: 1023,292 c/mL; CD4 cell count: 37 cells/ $\mu$ L). After the initial 4 weeks of treatment, her VL was 1084 c/mL, and her CD4 cell count was 134 cells/ $\mu$ L. After 2 months of treatment, acute neurologic deterioration with epilepsy, right hemiparesis, and dysphagia were reported due to the development of progressive multifocal leukoencephalopathy immune reconstitution syndrome. Subsequently, BIC/FTC/TAF was crushed and administered via a nasogastric tube. Twelve weeks after starting BIC/FTC/TAF, the patient's VL was 10,232 c/mL, and M184V, L74I, and R263K mutations emerged. Treatment was changed to FTC/TAF once daily plus DRV/r twice daily. After 1 month, the patient's VL was 204 c/mL, and the same mutations were present. Two months after switching treatment, the patient's VL remained at 204 c/mL, and the R263K mutation was cleared, while the M184V mutation remained stable.<sup>7</sup>

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## References

1. Enclosed, Gilead Sciences Inc. BIKTARVY® (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, for oral use. US Prescribing Information. Foster City, CA.
2. Hocqueloux L, Lefeuvre S, Bois J, et al. Bioavailability of dissolved and crushed single tablets of bictegravir, emtricitabine, tenofovir alafenamide in healthy adults: the SOLUBIC randomized crossover study. *J Antimicrob Chemother.* 2022;78(1):161-168.
3. Roa PE, Bazzi R. Crushed bictegravir/emtricitabine/tenofovir alafenamide in a human immunodeficiency virus-positive patient with pancreatic cancer. *Int J STD AIDS.* 2022;33(1):97-98.
4. Fulco PP. Crushed bictegravir/emtricitabine/tenofovir alafenamide in a human immunodeficiency virus-positive patient with esophageal cancer. *Am J Health Syst Pharm.* 2020;77(7):509-510.
5. Ferrandez JS, Garcia AL, Alonso-Vega GG, Gonzalez AO, Garcia TM. Successful Bictegravir/Emtricitabine/Tenofovir Alafenamide Treatment in a HIV Patient With Swallowing Difficulties. *Ann Pharmacother.* 2020;55(4):556-557.
6. Rowe SM, Clary JC, Drummond M, Derrick C, Sanasi K, Bookstaver PB. Increased viral load in a hospitalized patient on treatment with crushed bictegravir/emtricitabine/tenofovir alafenamide: A case report and review of the literature. *Am J Health Syst Pharm.* 2022;79(16):1330-1336.
7. Lozano AB, Chueca N, de Salazar A, et al. Failure to Biktarvy® and Development of Resistance Mutations in an Antiretroviral Experienced Patient [Journal Pre-Proof]. *Antiviral Res.* 2020.
8. Hocqueloux L, Lefeuvre S, Bois J, et al. Bioavailability of Solid vs. Dissolved vs. Crushed Single-Tablet of Bictegravir / Emtricitabine / Tenofovir Alafenamide in HIV Negative Volunteers: the SOLUBIC Study [Poster]. Paper presented at: 18th European AIDS Conference; 27-30 October, 2021; Online & London, United Kingdom.
9. Nissen T, Wynn R. The Clinical Case Report: A Review of Its Merits and Limitations. *BMC Res Notes.* 2014;7:264.

## Abbreviations

3TC=lamivudine

ABC=abacavir

AE=adverse event

ARV=antiretroviral

AUC<sub>0-∞</sub>=area under the curve from

time 0 extrapolated to infinite time

AUC<sub>0-last</sub>=area under the curve from time 0 to the

time of the last quantifiable concentration

after dosing

BIC=bictegravir

C<sub>max</sub>=maximum concentration

COBI=cobicistat

DRV=darunavir

DRV/r=darunavir plus ritonavir

DTG=dolutegravir

EVG=elvitegravir

FTC=emtricitabine

LPV/r=lopinavir plus ritonavir

PEG=percutaneous

endoscopic gastrostomy

PK=pharmacokinetics

RAL=raltegravir

RPV=rilpivirine

t<sub>1/2</sub>=elimination half-life

TAF=tenofovir

alafenamide

TDF=tenofovir disoproxil fumarate

VL=viral load

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## 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](http://www.gilead.com/-/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi).

## Follow-Up

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Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or

🌐 [www.gilead.com/utility/contact/report-an-adverse-event](http://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](http://www.accessdata.fda.gov/scripts/medwatch)

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