GILEAD | Medical Information

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.

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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.

Summary

Product Labeling[1]

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.

Clinical 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.[2]

- 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 ≥1 AE, and no AEs led to BIC/FTC/TAF discontinuation.

Case Reports on Crushing, Dissolving, or Splitting BIC/FTC/TAF Tablets

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.[3-7]

Clinical 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 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.[2] The primary endpoints of the study were AUC ($AUC0_{-\infty}$ for BIC and FTC; $AUC_{0\text{-last}}$ 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 compared with the whole tablet.[2,8] 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/m^2.[2]

Results[2]

The AUC for dissolved BIC/FTC/TAF was equivalent to the solid tablet for all individual components ($AUC_{0-\infty}$ for BIC and FTC; $AUC_{0\text{-last}}$ for TAF). The C_{max} for dissolved BIC/FTC/TAF was considered equivalent to the solid tablet for BIC and FTC, but not for TAF.

The $AUC_{0-\infty}$ 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; 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[2]

Drug	PK Parameter	Solid Tablet	Dissolved Tablet	Crushed Tablet	Dissolved: Solid, % (90% CI)	Crushed: Solid, % (90% CI)
BIC	$AUC_{0-\infty}$, 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)	–	–

Drug	PK Parameter	Solid Tablet	Dissolved Tablet	Crushed Tablet	Dissolved: Solid, % (90% CI)	Crushed: Solid, % (90% CI)
FTC	$AUC_{0-\infty}$, 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)	–	–
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, 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[2]

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

[a]One AE was reported with the drug not administered yet. All AEs were Grade 1 or 2 and moderate in severity.
[b]All were headaches reported on the day of administration.
[c]Scale: 0=worst taste or most complicated administration; 10=best taste or easiest administration. These data were collected after each administration.
[d]Ranking was collected after the third administration period; 1=most preferred and 3=least preferred.

Case Reports on Crushing, Dissolving, or Splitting BIC/FTC/TAF Tablets

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.[9]

A 78-year-old African American male with HIV was newly diagnosed with pancreatic cancer. The patient had been 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, which was his wish. 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.[3]

A 64-year-old male patient with HIV (virologically suppressed on an ARV regimen that included DTG/ABC/3TC) presented to the clinic and was newly diagnosed with esophageal adenocarcinoma with metastases to the liver; symptoms included 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.[4]

A 52-year-old female patient with HIV who was virologically suppressed (VL <20 c/mL) 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/mcL; after 12 months: 370 cells/mcL). 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.[5]

A 43-year-old male with newly diagnosed HIV was hospitalized due to changes in his neurological state, failure to thrive, and low blood pressure. His initial VL was 769,704 c/mL, and his CD4 count was 36 cells/mcL. 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 VL 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 VL 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.[6]

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) presented to the hospital with cerebral toxoplasmosis. No resistance information was available during the time the patient was treated with these ARV regimens. 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/mcL). After the initial 4 weeks of treatment, her VL was 1084 c/mL, and her CD4 cell count was 134 cells/mcL. 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 NG 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 + 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.[7]

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Abbreviations

3TC=lamivudine
ABC=abacavir
AE=adverse event
ARV=antiretroviral
AUC=area under the concentration-time curve
$AUC_{0-\infty}$=area under the curve from time 0 extrapolated to infinite time
AUC_{0-last}=area under the curve from time 0 to the time of the last quantifiable concentration after dosing
BIC=bictegravir
CD4=cluster of differentiation 4
C_{max}=maximum concentration
COBI=cobicistat
DRV=darunavir
DRV/r=darunavir/ritonavir
DTG=dolutegravir
EVG=elvitegravir
FTC=emtricitabine
LPV/r=lopinavir/ritonavir
NG=nasogastric
PEG=percutaneous endoscopic gastrostomy
PK=pharmacokinetics
RAL=raltegravir
RPV=rilpivirine
$t_{1/2}$=elimination half-life
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
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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