Biktarvy® (BIC/FTC/TAF) Coadministration With Polyvalent Cation-Containing Agents

This document is in response to your request for information regarding the coadministration of Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]) with polyvalent cation-containing (PVCC) agents.

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 Labeling[1]

BIC/FTC/TAF can be taken at least 2 hours before or 6 hours after taking antacids containing Al or Mg. BIC/FTC/TAF and supplements or antacids containing Ca or Fe can be taken together with food.

In pregnant individuals, BIC/FTC/TAF can be taken at least 2 hours before or 6 hours after antacids containing Al or Mg regardless of food intake. BIC/FTC/TAF and supplements or antacids containing Ca or Fe can be taken together with food; but when taken on an empty stomach, BIC/FTC/TAF should be taken at least 2 hours before or 6 hours after supplements or antacids containing Ca or Fe.

Coadministration with other supplements has not been studied.

Mechanism of Interaction of PVCC Agents With BIC/FTC/TAF

All INSTIs, including BIC, inhibit strand transfer activity of the HIV integrase enzyme by binding to Mg ions located at the integrase catalytic site, thus preventing the integration of the viral DNA strand into the host genome. When given concomitantly with therapeutic agents containing metal cations, the absorption of INSTIs may be decreased due to chelation, causing a possible decrease in INSTI exposure.[2,3]

Coadministration of PVCC With BIC/FTC/TAF During Phase 3 Clinical Trials

The use of PVCC antacids/supplements was permitted 2 hours before or 6 hours after administration of BIC/FTC/TAF in phase 3 clinical trials. None of the PWH who were receiving PVCC antacids/supplements in the BIC/FTC/TAF ARV-naive phase 3 studies (n=38) experienced virologic failure or had HIV-1 RNA ≥50 copies/mL at Week 48.[3]

PK Data on Coadministration of PVCC With BIC/FTC/TAF

Based on pooled exposure-response analyses for efficacy from BIC/FTC/TAF phase 3 clinical studies, virologic suppression is expected to be maintained at mean BIC exposures

that are 48% of the mean exposure observed in phase 3 clinical studies, a level ensuring continued high mean IQ values (IQ=7.7).[4]

Based on results from a phase 1 PK study and projected IQ changes, a high mean BIC IQ (%CV) of 7.6 (44%) was predicted when all PWH in the phase 3 registrational studies were administered BIC/FTC/TAF 2 hours after Al or Mg antacids.[5]

Product Labeling[1]

The concomitant use of BIC/FTC/TAF with certain drugs may result in known or potentially significant drug interactions. These interactions may lead to loss of therapeutic effect of BIC/FTC/TAF and the possible development of resistance or possible clinically significant adverse reactions from greater exposures of concomitant drugs. Table 1 contains steps to prevent or manage possible and known significant drug interactions with PVCC antacids or supplements, including dosing recommendations.

Table 1. Established and Potentially Significant[a] Drug Interactions[1]

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Oral medications or supplements containing polyvalent cations (eg, Mg, Al, Ca, Fe): • Ca or Fe supplements[c] • Cation-containing antacids or laxatives[c] • Sucralfate • Buffered medications	↓ BIC	Antacids containing Al or Mg: BIC/FTC/TAF can be taken at least 2 hours before or 6 hours after taking antacids containing Al or Mg. Routine administration of BIC/FTC/TAF together with, or 2 hours after, antacids containing Al or Mg is not recommended. Supplements or antacids containing Ca or Fe: BIC/FTC/TAF and supplements or antacids containing Ca or Fe can be taken together with food. Routine administration of BIC/FTC/TAF under fasting conditions together with, or 2 hours after, supplements or antacids containing Ca or Fe is not recommended. *In pregnant individuals:* Antacids containing Al/Mg: BIC/FTC/TAF can be taken at least 2 hours before or 6 hours after antacids containing Al or Mg regardless of food intake. Supplements or Antacids containing Ca or Fe: BIC/FTC/TAF and supplements or antacids containing Ca or Fe can be taken together with food; but when taken on an empty stomach, BIC/FTC/TAF should be taken at least 2 hours before or 6 hours after supplements or antacids containing Ca or Fe.

[a]Table is not all-inclusive.
[b]↓ = decrease.
[c]Drug-drug interaction study was conducted with either BIC/FTC/TAF or its components as individual agents.

Mechanism of Interaction of PVCC Agents With BIC/FTC/TAF

All INSTI agents, including BIC, inhibit the strand transfer activity of the HIV integrase enzyme by binding to Mg ions located at the integrase catalytic site, thus preventing the integration of the viral DNA strand into the host genome. When given concomitantly with therapeutic agents containing metal cations, the absorption of INSTIs may be decreased due to chelation, causing a possible decrease in INSTI exposure.[2,3] A covariate analysis of a population-based PK model determined that concomitant proton pump inhibitor use had no clinically relevant impact on BIC or TAF exposure in PWH.[6]

Coadministration of PVCC With BIC/FTC/TAF During Phase 3 Clinical Trials

The efficacy and safety of BIC/FTC/TAF was evaluated in four phase 3, randomized, active controlled clinical trials in ARV-naive (N=634) and virologically suppressed (N=572) PWH.[7-10] The use of PVCC antacids/supplements was permitted 2 hours before or 6 hours after administration of BIC/FTC/TAF. None of the PWH who were receiving PVCC antacids/supplements (n=38) experienced virologic failure or had HIV-1 RNA ≥50 copies/mL at Week 48.[3]

PK Data on Coadministration of PVCC With BIC/FTC/TAF

Background PK Data From Phase 3 Studies

IQ is defined as C_T (BIC C_T=2.61 mcg/mL from phase 3 clinical trials) divided by $paEC_{95}$ of wild-type HIV-1 virus activity (BIC $paEC_{95}$=0.162 mcg/mL). This is a measure of minimum *in vivo* exposure relative to *in vitro* potency. A high mean IQ of 16.1 was observed for BIC in the BIC/FTC/TAF registrational phase 3 studies (n=584).[3-5]

Based on pooled exposure-response analyses for efficacy from BIC/FTC/TAF phase 3 clinical studies, virologic suppression is expected to be maintained at mean BIC exposures that are 48% of the mean exposure observed in phase 3 clinical studies, a level ensuring continued high mean IQ values (IQ=7.7).[4]

Phase 1 Study

Study design[1,3,5]

A phase 1, open-label, single-dose, fixed-sequence, multiple-cohort, multiple-period study of 42 healthy individuals was conducted to determine the effect on BIC PK when administering Al or Mg antacids and Ca or Fe supplements simultaneously with BIC/FTC/TAF under fasted or fed conditions or staggered 2 hours apart. Further analyses were conducted to assess the potential impact of PVCC antacid/supplement coadministration on pharmacodynamics (as IQ) of BIC in PWH administered once-daily BIC/FTC/TAF.

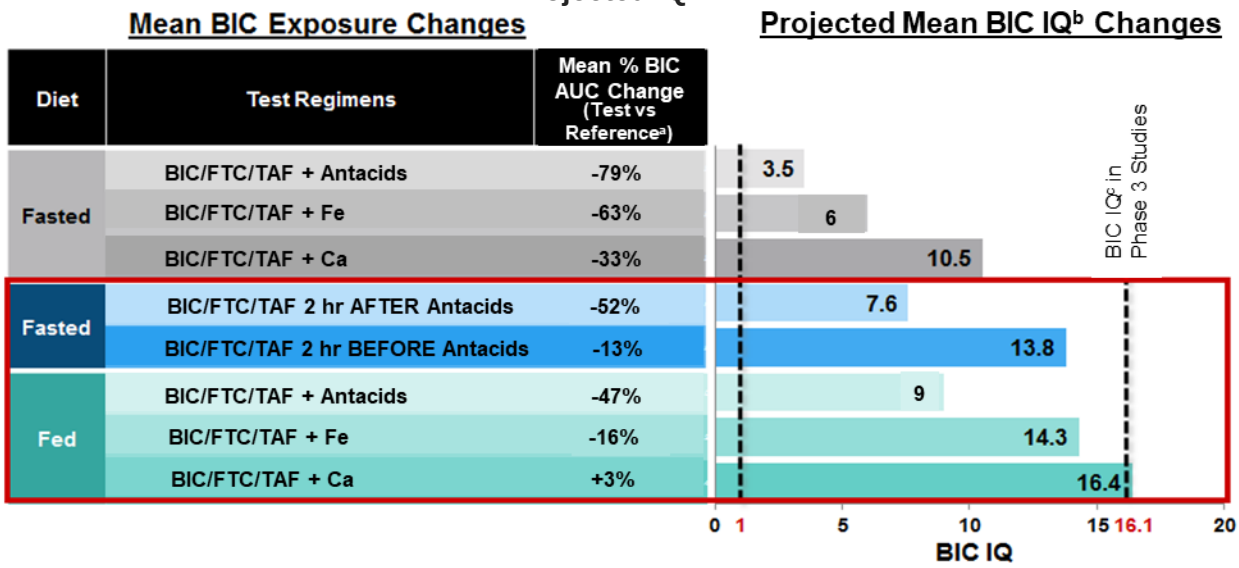
In order to predict BIC exposure with PVCC antacid/supplement coadministration, the mean BIC IQ from BIC/FTC/TAF phase 3 registrational studies was multiplied by the observed C_{24} GLSM ratio for each PVCC antacid/supplement regimen studied. Additionally, individual BIC IQ values in the BIC/FTC/TAF phase 3 registrational studies were predicted assuming all patients took their daily dose of BIC/FTC/TAF under fasted conditions, 2 hours after administering an Al or Mg antacid.

Results

Figure 1 shows that coadministration of BIC/FTC/TAF with PVCC antacids/supplements (Mg, Al, Ca, or Fe) decreased BIC exposure in most instances, particularly when administered simultaneously under fasted conditions. Decreased BIC exposure due to chelation with polyvalent cations was attenuated with staggered administration of PVCC antacid/supplements by ±2 hours and/or administering with food (test treatments outlined in red in Figure 1).[1,3,5]

Figure 1 also displays the projected BIC IQ which corresponded with each PVCC antacid/supplement regimen. BIC/FTC/TAF and PVCC antacids/supplements administered with a 2-hour stagger or simultaneously with food were projected to result in mean BIC IQ changes ≥7.6. Although the lower bound of the BIC therapeutic window is unknown, BIC exposures that are 48% of the mean observed in phase 3 clinical studies are expected to maintain virologic suppression, ensuring continued high mean IQ values (IQ=7.7).[3,4] A high mean BIC IQ (%CV) of 7.6 (44%) was predicted when all PWH in the phase 3 registrational studies were administered BIC/FTC/TAF 2 hours after Al or Mg antacids.[5]

Figure 1. Effect of Coadministered PVCC Antacids/Supplements on BIC PK and Projected IQ[1,3,5]



[a]Reference treatment was BIC/FTC/TAF alone.
[b]Mean BIC IQ from BIC/FTC/TAF phase 3 registrational studies was multiplied by the observed C_{24} GLSM ratio for each PVCC antacid/supplement regimen studied.
[c]IQ is defined as C_T divided by $paEC_{95}$ of wild-type HIV-1 virus activity.
Note: Antacids included Al hydroxide 1600 mg, Mg hydroxide 1600 mg, and simethicone 160 mg. Supplements included Ca carbonate 1200 mg or ferrous fumarate 324 mg.

Administering BIC/FTC/TAF and PVCC antacids/supplements with a 2-hour stagger or with food can mitigate decreased BIC exposures due to polyvalent cations and is projected to result in high BIC IQ values.

References

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Abbreviations

Al=aluminum
ARV=antiretroviral
BIC=bictegravir
C_{24}=concentration 24 hours post-dose
Ca=calcium
C_T=concentration at the end of the dosing interval
CV=coefficient of variation
Fe=iron
FTC=emtricitabine
GLSM=geometric least-squares mean
INSTI=integrase strand transfer inhibitor
IQ=inhibitory quotient
Mg=magnesium
$paEC_{95}$=protein-adjusted 95% effective concentration
PK=pharmacokinetic(s)
PVCC=polyvalent cation-containing
PWH=people with HIV
TAF=tenofovir alafenamide

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

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