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Biktarvy® (BIC/FTC/TAF) CNS-Related Adverse Drug Reactions

This document is in response to your request for information regarding Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]) and central nervous system (CNS)–related adverse drug reactions (ADRs). This response was developed according to principles of evidence-based medicine and contains data from Gilead clinical trials and prospective studies (N≥40).

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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]

The primary safety assessment of BIC/FTC/TAF was based on data from two randomized, double-blind, active-controlled trials, Trial 1489 and Trial 1490, that enrolled 1274 adult participants with HIV-1 and no ARV treatment history through Week 144. CNS-related adverse reactions that occurred in ≥2% of participants in the BIC/FTC/TAF arm of either study included headache, abnormal dreams, dizziness, and insomnia. Any-grade depression occurred in <2% of participants in the BIC/FTC/TAF arm in either study. Suicidal ideation, suicide attempt, and depression suicidal occurred in 2% of participants administered BIC/FTC/TAF; these events occurred primarily in subjects with a preexisting history of depression, prior suicide attempt, or psychiatric illness.

BIC/FTC/TAF Use and CNS-Related ADRs

In four BIC/FTC/TAF registrational studies of ARV-naive (Studies 1489 and 1490) or VS (Studies 1878 and 1844) PWH, rates of CNS-related ADRs were low; drug-related headaches were uncommon up to Week 240.[2-5] Overall, 8/1206 participants (0.66%) discontinued BIC/FTC/TAF due to CNS-related AEs.[4-8]

In the MIND study, Grade 2 to 4 CNS AEs occurred at a similar rate between VS PWH who switched from DTG/3TC to BIC/FTC/TAF and those participants who stayed on DTG/3TC (*P*=0.688). Discontinuation rates due to CNS AEs were also similar between groups.[9]

BIC/FTC/TAF Use and CNS-Related PROs

Data on CNS-related PROs reported in PWH on BIC/FTC/TAF are presented below.[10-12]

BIC/FTC/TAF Use and CNS-Related ADRs

CNS-Related ADRs in ARV-Naive PWH

Studies GS-US-380-1489 and GS-US-380-1490

Studies 1489 and 1490 were two phase 3, prospective, randomized, double-blind, active-controlled clinical trials that compared BIC/FTC/TAF (n=314 in Study 1489, n=320 in Study 1490) to DTG/ABC/3TC (n=315) or DTG + FTC/TAF (n=325) in ARV-naive PWH. Baseline demographics and disease characteristics were similar between treatment arms.[2,3]

CNS-related adverse reactions that occurred in ≥2% of participants in the BIC/FTC/TAF arm of either study included headache, abnormal dreams, dizziness, and insomnia. Any-grade depression occurred in <2% of participants in the BIC/FTC/TAF arm in either study. Suicidal ideation, suicide attempt, and depression suicidal occurred in 2% of participants administered BIC/FTC/TAF; these events occurred primarily in subjects with a preexisting history of depression, prior suicide attempt, or psychiatric illness.[1]

Table 1. CNS-Related Adverse Reactions (All Grades) Reported in ≥2% of Adults With HIV-1 and No ARV Treatment History Receiving BIC/FTC/TAF in Studies 1489 or 1490 (Week 144 Analysis)[1a]

ADR, %	Study 1489		Study 1490	
	BIC/FTC/TAF (n=314)	DTG/ABC/3TC (n=315)	BIC/FTC/TAF (n=320)	DTG + FTC/TAF (n=325)
Headache	5	5	4	3
Abnormal dreams	3	3	<1	1
Dizziness	2	3	2	1
Insomnia	2	3	2	<1

[a]Frequencies of ADRs are based on all AEs attributed to study drugs by the investigator. No adverse reactions of Grade 2 or higher occurred in ≥1% of participants treated with BIC/FTC/TAF.

Participants who completed the 144-week blinded treatment phase were given the option to participate in an additional 96-week open-label extension on BIC/FTC/TAF. Pooled CNS-related ADRs observed through Week 240 that occurred in ≥2% of participants were headache (5%), fatigue (3%), insomnia (2%), and dizziness (2%). CNS-related serious ADRs were reported in 3 participants: generalized tonic-clonic seizures, suicide, and dizziness. Discontinuation due to CNS-related AEs occurred in 3 participants: depression (n=1), paranoia (n=1), and depression, sleep disorder, tension headache, and insomnia (all occurring in 1 participant and considered study drug related). At Week 240, 9 deaths were reported, including 1 due to suicide that was not considered study drug related.[6,13]

CNS-Related ADRs in VS PWH

Study GS-US-380-1878

A phase 3, randomized, open-label clinical study compared outcomes between VS PWH who switched to BIC/FTC/TAF 50/200/25 mg (n=290) and participants who stayed on a baseline regimen of boosted DRV or ATV + 2 NRTIs (n=287).[5] The CNS-related ADR reported in ≥2% of participants in the BIC/FTC/TAF arm was headache (5%). Most cases of headache with BIC/FTC/TAF occurred within the first 4 weeks (incidence: 6.2%); all AEs of headache were Grade 1 or 2 in severity. At Week 48, the incidence of headache was 0.5%,

and the prevalence was 2%.[5,14] In the BIC/FTC/TAF arm, 1 participant discontinued due to schizophrenia, which was considered study drug related by the investigator.[5]

Study GS-US-380-1844

A phase 3, randomized, double-blind study evaluated safety and efficacy outcomes in VS PWH who switched to BIC/FTC/TAF (n=282) compared with those who stayed on a baseline regimen of DTG + ABC/3TC or DTG/ABC/3TC (n=281).[4,15]

Through Week 48, CNS-related ADRs reported in ≥1% of participants in either arm were headache (3%) and abnormal dreams (<1%) in the BIC/FTC/TAF arm and headache (3%), abnormal dreams (2%), and insomnia (1%) in the DTG/ABC/3TC arm. In the BIC/FTC/TAF arm, there were 4 CNS-related AEs leading to discontinuation: headache (n=2), abnormal dreams (n=1), and suicidal ideation (n=1). All except suicidal ideation were considered study drug related. In the DTG/ABC/3TC arm, 1 participant discontinued due to headache, which was considered treatment related.[4]

MIND study[9]

A randomized, double-blind study in VS PWH evaluated whether switching from DTG/3TC to BIC/FTC/TAF improved neuropsychiatric safety and tolerability after 24 weeks compared with continuing DTG/3TC (N=80). Eligible participants had a diagnosis of sleep, mood, substance use, or neurocognitive disorders and were randomly assigned (1:1) to each treatment group. Overall, participants had a high burden of neuropsychiatric comorbidities at baseline, and there were no statistically significant differences in baseline characteristics between groups.

There were no differences in the rates of any-grade AEs between the BIC/FTC/TAF and DTG/3TC groups, including anxiety (14.6% vs 5.1%, respectively), insomnia (7.3% vs 7.7%), depression (7.3% vs 5.1%), headache (4.9% vs 15.4%), and suicidality (4.9% vs 2.6%). Grade 2 to 4 CNS AEs were reported in 6 patients (8 events) in the BIC/FTC/TAF group and in 7 patients (9 events) in the DTG/3TC group (*P*=0.688); 1 serious AE was reported in each group (BIC/FTC/TAF, suicidality; DTG/3TC, unspecific CNS AE). CNS AEs resulted in study drug discontinuation for 3 participants in the BIC/FTC/TAF group and 2 participants in the DTG/3TC group.

There were no significant differences between treatment groups in all other PRO scores and HIV-related symptoms.

BIC/FTC/TAF Use and CNS-Related PROs

Data on CNS-related PROs reported in PWH on BIC/FTC/TAF are presented below (Table 2).

Table 2. BIC/FTC/TAF Use and CNS-Related PROs[10-12]

Study	Assessments	CNS-Related PROs
BICSTaR multicountry, prospective observational cohort study[10]	SF-36 evaluated QoL in 3004 participants at BL and through Month 12 in the China cohort and through Month 24 in the BICSTaR cohort; HIVTSQs/c assessed treatment satisfaction at BL (n=3029) and Month 12 (n=2109) in all cohorts	• Mean improvements in SF-36 MCS scores from BL to Month 24 in the 321 participants with a neuropsychiatric disorder at BL were +4 (95% CI: 2.5–5.5) vs +1.3 (95% CI: 0.3–2.2) in the reference population • There were small mean changes in SF-36 PCS from BL to Month 24 among participants with any BL comorbidity compared with reference scores (-0.3 and +0.5, respectively) • Median HIVTSQs scores at BL were high among participants with (n=331) and without (n=2698) neuropsychiatric disorder (54 and 56, respectively), and the median change in score improved similarly in participants with (n=263) and without (n=1846) neuropsychiatric disorder (+25 and +27, respectively) at Month 12
GS-US-380-1489[11]	HIV-SI, PSQI, SF-36, and WPAI administered at BL and at Weeks 4, 12, and 48 in participants on BIC/FTC/TAF vs DTG/ABC/3TC	• BIC/FTC/TAF was associated with a lower prevalence of dizziness/lightheadedness and difficulty sleeping than DTG/ABC/3TC • No HIV-SI results favored DTG/ABC/3TC over BIC/FTC/TAF, including difficulty sleeping and dizziness/lightheadedness • No treatment differences were noted between arms in PSQI, SF-36, and WPAI scores
GS-US-380-1844[11]	HIV-SI, PSQI, SF-36, and WPAI administered at BL and Weeks 4, 12, and 48 in participants on BIC/FTC/TAF vs DTG/ABC/3TC	• Switching to BIC/FTC/TAF was associated with a lower prevalence of bothersome symptoms (ie, dizziness/lightheadedness, feeling sad/down/depressed, feeling nervous/anxious, and difficulty sleeping) and poor sleep quality than was continuing DTG/ABC/3TC • No HIV-SI results favored DTG/ABC/3TC over BIC/FTC/TAF • No treatment differences were noted between arms in SF-36 and WPAI scores
DOBINeuro, a phase 3, randomized, multicenter, 12-month study in VS participants[12]	Compared the incidence and severity of neuropsychiatric symptoms among PWH who switched to BIC/FTC/TAF from DTG/ABC/3TC (n=21) or continued DTG/ABC/3TC (n=20)	• In the BIC/FTC/TAF group, the number of participants with sleep disorder decreased from 8 (38%) at BL to 3 (15%) at Month 3; no change occurred in the DTG/ABC/3TC group • After Month 3, significant improvements from baseline in trouble concentrating in the BIC/FTC/TAF group and sadness, fear for health, impact on sex life score, and familiar support score in the DTG/ABC/3TC occurred

Abbreviation: BL=baseline.

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Abbreviations

3TC=lamivudine
ABC=abacavir
ADR=adverse drug reaction
AE=adverse event
ARV=antiretroviral
ATV=atazanavir
BIC=bictegravir
BICSTaR=BICtegravir Single Tablet Regimen
CNS=central nervous system
DRV=darunavir
DTG=dolutegravir
FTC=emtricitabine
HIV-SI=HIV Symptom Index
HIVTSQs/c=HIV Treatment Satisfaction Questionnaire status/change version
MCS=Mental Component Summary
NRTI=nucleos(t)ide reverse transcriptase inhibitor
PCS=Physical Component Summary
PRO=patient-reported outcome
PSQI=Pittsburgh Sleep Quality Index
PWH=people with HIV
QoL=quality of life
SF-36=36-Item Short Form Health Survey
TAF=tenofovir alafenamide
VS=virologically suppressed
WPAI=Work Productivity and Activity Impairment

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:

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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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