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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).

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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 HIV-1 infected adult subjects with 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-naïve (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). Rates of discontinuation due to CNS AEs were also similar between groups.[9]

In a retrospective study of an Australian cohort, 22/1265 participants (1.7%) prescribed BIC/FTC/TAF reported neuropsychiatric ADRs; 18 of them discontinued BIC/FTC/TAF.[10]

BIC/FTC/TAF Use and CNS-Related PROs

In Studies 1489 and 1844, BIC/FTC/TAF (as the first initiated ARV or after a switch from DTG/ABC/3TC) was associated with a lower prevalence of neuropsychiatric symptoms, such as dizziness/lightheadedness and difficulty sleeping, than DTG/ABC/3TC.[11,12]

In the DOBINeuro study, VS PWH who were randomly assigned to switch to BIC/FTC/TAF from DTG/ABC/3TC had significant improvements from baseline to Month 3 in sleep disorder (*P*=0.042) and trouble concentrating (*P*=0.04).[13]

In a pilot study, participants who switched from a DTG-based regimen to BIC/FTC/TAF had significantly greater improvements in PROs measuring insomnia, sleepiness, and physical functioning.[14]

BIC/FTC/TAF Use and CNS-Related ADRs

CNS-Related ADRs in ARV-Naïve 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-naïve 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 HIV-1 Infected Adults with 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 three participants: generalized tonic-clonic seizures, suicide, and dizziness. Discontinuation due to CNS-related AEs occurred in three 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, 1 due to suicide that was not considered study drug related.[6,15]

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%.[5,16] 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).[4,17]

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, and suicidal ideation. All were considered to be study drug related except for suicidal ideation. In the DTG/ABC/3TC arm, 1 participant discontinued due to headache, which was considered treatment related.[4]

MIND study[9]

A 1:1 randomized, double-blind study conducted in 80 VS PWH who had a diagnosis of sleep, mood, substance use, or neurocognitive disorders evaluated whether switching from DTG/3TC to BIC/FTC/TAF improved neuropsychiatric safety and tolerability after 24 weeks compared with continuing to receive DTG/3TC. 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 statistically significant 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.

Participants who switched to BIC/FTC/TAF had statistically significant improvements in nausea compared with those who stayed on DTG/3TC (3.9% vs 23.2%, respectively; P=0.03) and abdominal discomfort (16.8% vs 40.2%; P=0.02). There were no statistically significant differences between treatment groups in all other PRO scores and HIV-related symptoms.

Self-reported neuropsychiatric ADRs (Australian cohort)[10]

A retrospective analysis was conducted from records of adult participants dispensed BIC/FTC/TAF who subsequently had a new neuropsychiatric reaction reported between October 2018 and May 2020 in Australia. At least one neuropsychiatric ADR was reported in 1.7% of participants (22/1265); combined total, 50 neuropsychiatric symptoms. More frequently reported neuropsychiatric ADRs included abnormal dreams (n=13), sleep disorders (n=5), and headaches (n=5), with a median (IQR) time from initiation to reaction being 13 (4–94) days. Of the 22 participants who reported neuropsychiatric ADRs, 18 discontinued BIC/FTC/TAF. Discontinuation rates between those with and those without a preexisting psychiatric diagnosis were not statistically significant (*P*=0.58).

BIC/FTC/TAF Use and CNS-Related PROs

Study GS-US-380-1489

PROs from the HIV-SI administered at baseline and at Weeks 4, 12, and 48 further characterized treatment tolerability. Initiation of 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. The PSQI, SF-36, and WPAI tools were also administered at the same time points. No treatment differences were noted.[11,12]

Study GS-US-380-1844

PROs from the HIV-SI, PSQI, SF-36 PCS/MCS, and WPAI administered at baseline and Weeks 4, 12, and 48 further characterized treatment tolerability.[11,12]

Switching to BIC/FTC/TAF was associated with a significantly lower prevalence of select patient-reported bothersome symptoms and poor sleep quality than was continuing DTG/ABC/3TC. Bothersome symptoms included dizziness/lightheadedness, feeling sad/down/depressed, feeling nervous/anxious, and difficulty sleeping. No HIV-SI results favored DTG/ABC/3TC over BIC/FTC/TAF. No treatment differences were noted between arms using the SF-36 PCS/MCS and WPAI tools.[11,12]

DOBINeuro Study[13]

A phase 3, randomized, multicenter, 12-month study in Italy 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). Eligible participants were VS for >12 months and had received DTG/ABC/3TC for >6 months. Participants with major psychiatric disorders or those who received antidepressant or antipsychotic medications were excluded. Enrollment was prematurely stopped due to a delayed recruitment process; therefore, the study was not fully powered for the primary endpoint (ie, differences in neuropsychiatric symptoms using the SCL-90-R at Month 3). Baseline demographics and disease characteristics were generally similar between arms, and there were no differences between groups in the proportion of cognitively impaired participants in global scores or any individual dimension.

In the BIC/FTC/TAF group, the number of participants with sleep disorder decreased from 8 (38%) at baseline to 3 (15%) at Month 3 (*P*=0.042); no significant change occurred in the

DTG/ABC/3TC group. After Month 3, significant improvements from baseline in trouble concentrating (*P*=0.04) in the BIC/FTC/TAF group and sadness (*P*=0.01), fear for health (*P*=0.03), impact on sex life score (*P*=0.03), and familiar support score (*P*=0.03) in the DTG/ABC/3TC occurred. There were no significant changes from baseline to after Month 3 in either group in other dimensions of the SCL-90-R. Within arms and between the BIC/FTC/TAF and DTG/ABC/3TC groups, there were no significant differences in secondary endpoint assessments of health-related quality of life or suicide risk at baseline and after Month 3. No CNS AEs were reported.

Therapeutic Switch Pilot Study[14]

A randomized pilot study (N=19) assessed PRO results of VS PWH who had been receiving a DTG-based regimen for ≥4 months, were naive to BIC therapy, had insomnia (severity index score of ≥8), and either switched to BIC/FTC/TAF (n=7) or continued a DTG-based regimen (n=12). Participants had received the baseline DTG-based regimen for a median (range) of 41 (13–91) months.

Median scores on the Insomnia Severity Index, Epworth Sleepiness Scale, and the SF-36 Physical Functioning domain improved significantly more in those who switched to BIC/FTC/TAF than in those who continued a DTG-based regimen (Table 2).

Table 2. PROs That Improved Significantly More With BIC/FTC/TAF Than With a DTG-Based Regimen (Henderson et al)[14]

PRO, Median (Range)	Baseline (N=19)	Change From Baseline		*P*-Value
		BIC/FTC/TAF (n=7)	DTG-Based ART (n=12)	
Insomnia Severity Index	17 (8–26)	-9 (-14 to -2)[a]	-1 (-10 to +4)	0.025
Epworth Sleepiness Scale	5 (0–15)	-3 (-6 to +1)	2 (-3 to +6)	0.005
SF-36 Physical Functioning	NR[b]	-5 (-40 to 5)	0 (-5 to +15)	0.025

Abbreviation: NR=not reported.
[a]n=5. [b]Median (range) SF-36 score at baseline across 8 domains, 81 (57–100).

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Abbreviations

3TC=lamivudine
ABC=abacavir
ADR=adverse drug reaction
AE=adverse event
ARV=antiretroviral
ATV=atazanavir
BIC=bictegravir
CNS=central nervous system
DRV=darunavir
DTG=dolutegravir
FTC=emtricitabine
HIV-SI=HIV Symptom Index
MCS=Mental Component Summary
NRTI=nucleos(t)ide reverse transcriptase inhibitor
OLE=open-label extension
PCS=Physical Component Summary
PRO=patient-reported outcome
PSQI=Pittsburgh Sleep Quality Index
PWH=people with HIV
SCL-90-R=Symptom Checklist-90-R
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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