Bictegravir (BIC)

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Formulations

Bictegravir is available only in a fixed-dose combination (FDC) tablet.

FDC Tablet

- [Biktarvy]
  - Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg
  - Bictegravir 30 mg/emtricitabine 120 mg/tenofovir alafenamide 15 mg

When using FDC tablets, refer to other sections of Appendix A: Pediatric Antiretroviral Drug Information for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

[Biktarvy] Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF)

Neonate or Child Aged <2 years and Weighing <14 kg

- No data currently are available on the appropriate dose of Biktarvy in children aged <2 years and weighing <14 kg. Studies are being conducted to identify the appropriate dose for this age and weight group.

Child (Aged ≥2 years), Adolescent, and Adult Dose

- One tablet once daily with or without food.

Body Weight	Dose
≥14 to <25 kg	BIC 30 mg/FTC 120 mg/TAF 15 mg
≥25 kg	BIC 50 mg/FTC 200 mg/TAF 25 mg

- The U.S. Food and Drug Administration approved Biktarvy for use in only antiretroviral therapy–naive patients or to replace the current antiretroviral (ARV) regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen and who have no history of treatment failure and no known mutations associated with resistance to the individual components of Biktarvy. Some members on the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommend the use of Biktarvy in patients with prior treatment failure and who have virus containing the M184V mutation (see Efficacy in Clinical Trials in Adults below).

Selected Adverse Events

- Diarrhea, nausea, headache

Special Instructions

- Administer Biktarvy with or without food. See the Drug Interactions section below for guidance when administering Biktarvy with antacids or iron or calcium supplements.
- For children unable to swallow a whole tablet, the tablet can be split and each part taken separately as long as all parts are swallowed within approximately 10 minutes.
- Screen patients for hepatitis B virus (HBV) infection before using FTC or TAF. Severe acute exacerbation of HBV can occur when discontinuing FTC or TAF; therefore, monitor hepatic function for several months after halting therapy with FTC or TAF.

Metabolism/Elimination

- BIC is metabolized by cytochrome P450 3A4 and uridine diphosphate glucuronosyltransferase (UGT1A1).

	Biktarvy Dosing in Patients with Hepatic Impairment • Biktarvy is not recommended for use in patients with severe hepatic impairment. Biktarvy Dosing in Patients with Renal Impairment • Biktarvy is not recommended for use in patients with estimated creatinine clearance <30 mL/min. See the product label for use in patients on dialysis.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* Bictegravir (BIC) is a substrate of cytochrome P450 (CYP) 3A4 and uridine diphosphate glucuronosyltransferase (UGT) 1A1. TAF is a substrate of P-glycoprotein and UGT1A1. Coadministration of the fixed-dose combination (FDC) tablet bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF [Biktarvy]) and rifampin is **contraindicated.**[1,2]
- *Renal effects:* BIC is an inhibitor of organic cation transporter 2 and multidrug and toxin extrusion protein 1, so it decreases tubular secretion of creatinine. This increases serum creatinine and reduces estimated glomerular filtration rate (eGFR) with no change in glomerular function. Drugs that decrease renal function could reduce clearance of FTC.
- *Absorption:* Administering BIC concurrently with antacids lowers the plasma concentrations of BIC. This occurs because of the formation of complexes in the gastrointestinal tract and not because of changes in gastric pH. Chelation by high concentrations of divalent cations—such as iron—decreases absorption of integrase strand transfer inhibitors (INSTIs), including elvitegravir and BIC. For this reason, Biktarvy should be administered at least 2 hours before or 6 hours after antacids and supplements or multivitamins that contain iron, calcium, aluminum, magnesium, and/or zinc[3] when Biktarvy is given on an empty stomach. Biktarvy and antacids or supplements that contain calcium or iron can be taken together with food.

Major Toxicities

- *More common:* Diarrhea, nausea, headache. In two clinical trials, total bilirubin increased by up to 2.5 times the upper limit of normal in 12% of patients who received Biktarvy. In general, however, bilirubin increase was quite mild and did not lead to drug discontinuations in these trials.[2] BIC may cause an increase in creatine kinase concentration. One patient out of 201 in a post-marketing observational study in adults experienced thrombocytopenia,[4] and one participant out of 100 in a prospective cohort study in children and adolescents experienced insomnia/anxiety[5] leading to drug discontinuation. Weight gain has been reported in adults who were receiving Biktarvy (see Table 15h. Lypodystrophies and Weight Gain).
- *Less common (more severe):* Severe immune reconstitution inflammatory syndrome may be more common with INSTIs than with other antiretroviral (ARV) agents.

Resistance

The International Antiviral Society–USA maintains a list of HIV drug resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

BIC, available as part of the FDC tablet Biktarvy, containing BIC 50 mg/FTC 200 mg/TAF 25 mg, was approved by the U.S. Food and Drug Administration (FDA) in 2018 for use in adults and in 2019 for use in children or adolescents weighing ≥25 kg. Biktarvy, containing BIC 30 mg/FTC 120 mg/TAF 15 mg was approved by the FDA in 2021 for use in children aged ≥2 years and weighing ≥14 to <25kg. Biktarvy is FDA approved for patients who have no ARV treatment history or to replace current ARV regimens in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 3 months, with no history of treatment failure and no known mutations associated with resistance to the individual components of the FDC.[2] However, some Panel members recommend the use of Biktarvy in patients with prior treatment failure and who have virus containing the M184V mutation (see Efficacy in Clinical Trials in Adults below).

Efficacy in Clinical Trials in Adults

In a short-term Phase 1 study, BIC monotherapy at doses of BIC 50 mg or BIC 100 mg was well tolerated. Three out of eight participants in both of these dosing groups achieved HIV RNA <50 copies/mL within 11 days.[6] The efficacy (defined as viral load suppression to HIV RNA <50 copies/mL) and safety (as measured by the incidence of study drug discontinuation or death) of Biktarvy were similar to the efficacy and safety of comparator regimens in two Phase 3 randomized trials in treatment-naive adults. Viral load suppression occurred in 89% of participants who received coformulated BIC 50 mg/FTC 200 mg/TAF 25 mg (n = 320) and in 93% of participants who received a regimen of dolutegravir (DTG) 50 mg plus FTC 200 mg plus TAF 25 mg (n = 325). Study drug discontinuation occurred in 1% of participants in both groups.

In a separate trial, viral load suppression occurred in 92% of participants who received BIC/FTC/TAF (n = 314) and in 93% of participants who received coformulated abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg (ABC/DTG/3TC) (n = 315). Study drug discontinuation was not reported for any of the participants who received BIC/FTC/TAF, although it did occur in 1% of participants who received ABC/DTG/3TC.[2,7] Studies that randomized virologically suppressed patients who were on stable ARV regimens to either continue their current regimens or switch to coformulated BIC/FTC/TAF have shown that BIC/FTC/TAF has similar safety and efficacy to existing regimens. Viral load suppression occurred in 94% of participants who were randomized to switch to BIC/FTC/TAF (n = 282) and in 95% of participants who continued taking ABC/DTG/3TC (n = 281). Study drug discontinuation was reported in 2% of participants who received BIC/FTC/TAF and 1% of participants who received ABC/DTG/3TC. Ninety-two percent of participants who were randomized to switch to BIC/FTC/TAF (n = 290) achieved viral load suppression, whereas 89% of participants who continued receiving atazanavir-based or darunavir-based combination ARV regimens (n = 287) achieved viral load suppression. Study drug discontinuation occurred in 1% of participants in both groups.[2]

Initial studies in participants switching to BIC/FTC/TAF from stable antiretroviral therapy (ART) required undetectable viral load for 3 or 6 months and no proven or presumed preexisting resistance to any of the components of BIC/FTC/TAF.[2,8,9] Further analysis of data from these studies used proviral genotyping and showed presence of M184V/I mutation in 54 (10%) of 543 BIC/FTC/TAF-treated participants. Presence of this mutation did not affect viral load suppression, with Week 48 HIV RNA <50 copies/mL in 52 (96%) of 54 participants with archived M184V/I mutations compared with Week 48 HIV RNA <50 copies/mL in 561 (98%) of 570 participants without the mutation.[10] A study to measure the effect of preexisting nucleoside reverse transcriptase inhibitor (NRTI) mutations on virologic outcome in participants switching from a stable regimen to BIC/FTC/TAF showed Week 48 HIV RNA <50 copies/mL in 223 (94%) of 237 participants without M184V/I resistance and in 42 (89%) of 47 participants with M184V/I mutations at baseline.[11,12] At Week 48, HIV RNA <50 copies/mL was maintained in 199 (93%) of 213 participants with no NRTI resistance mutation and in 66 (93%) of 71 participants with any NRTI resistance mutation, including K65R/E/N, any number of thymidine analogue mutations (M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/R/N), T69 insertions, T69D, K70E/G/M/Q/S/T, L74I/V, V75A/S/M/T, Y115F, Q151M, or M184V/I.[11] That study required preenrollment virologic suppression for 6 months in those with suspected NRTI resistance and 3 months for those without suspected NRTI resistance.[11] In practice, Panel members have used BIC/FTC/TAF even in patients with detectable viral load, prior ARV failure, or preexisting NRTI mutations; this is based on the premise that the ability to simplify multi-pill or multi-dose regimens to a single small pill, once daily, can overcome potential resistance barriers with definite adherence benefits.[13]

Pharmacokinetics

Pharmacokinetic (PK) studies of Biktarvy containing BIC 50 mg, have been performed in adults, adolescents aged 12 years to <18 years who weigh ≥35 kg, and children aged 6 years to <12 years who weigh ≥25 kg. PK studies of "low-dose" Biktarvy, which contains BIC 30 mg, have been performed in children aged ≥2 years weighing 14 to <25 kg.[14] These studies show a higher BIC maximum serum concentration (C_{max}) in the younger cohorts than in the older cohorts, perhaps because the administered dose is higher on a mg/kg basis (see Table A below). The lower trough serum concentration (C_{tau}) and higher C_{max} in the younger age/lower body weight cohorts suggest more rapid clearance in children and adolescents than in adults. In the cohorts with body weight[14] ≥14 to <25 kg and body weight[5] ≥35 kg, there is a lower geometric mean ratio when C_{tau} is compared to adult values, and the lower 90% confidence interval suggests that some patients have quite rapid clearance (see Table B below). These PK observations raise the concern that some of the patients in the youngest age/lowest body weight cohorts may experience suboptimal trough concentrations, which may lead to less "pharmacologic forgiveness" in persons with lower adherence (see Table B below).[15]

Table A. Bictegravir Pharmacokinetics in Children, Adolescents, and Adults with HIV

PK Parameters	Children Aged ≥2 Years and Weighing ≥14 to <25 kg[14]	Children Aged 6 Years to <12 Years and Weighing ≥25 kg[5]	Adolescents Aged 12 Years to <18 Years and Weighing ≥35 kg[5]	Adults[2]
Dose (mg)	30	50	50	50
Dose for Lowest Weight in the Cohort (mg/kg)	2.14	2	1.43	1.25[a]
AUC_{tau} ng•h/mL Mean (CV%)	109,000 (24)	128,000 (28)	89,100 (31)	102,000 (26.9)
C_{max} ng/mL Mean (CV%)	10,100 (21)	9,460 (24)	6,240 (27)	6,150 (22.9)
C_{tau} ng/mL Mean (CV%)	2,000 (78)	2,360 (39)	1780 (44)	2,610 (35)

[a] This dose was calculated using 40 kg as the lowest weight for adults.

Key: AUC_{tau} = area under the concentration time curve over the dosing interval; C_{max} = maximum serum concentration; C_{tau} = trough serum concentration at the end of the dosing interval; CV = coefficient of variation; PK = pharmacokinetic

Table B. Bictegravir Pharmacokinetics in Children and Adolescents with HIV

Cohort Characteristics	Dose (mg)	Dose for Lowest Weight in Cohort (mg/kg)	GMR% (90% CI) Compared to Adult Values[a]		
			AUC_{tau}	C_{max}	C_{tau}
Aged ≥2 Years and Weighing **≥14** to <25 kg[14]	30	2.14	109 (96.7, 122)	166 (149, 184)	67.7 (49.6, 92.4)
Aged 6 **Years to <12 Years** and Weighing ≥25 kg[5]	50	2	125 (117–134)	153 (143–163)	88.9 (80.6-98.0)
Aged 12 Years to <18 Years and Weighing ≥35 kg[5]	50	1.43	86 (80–93)	100 (94–107)	65.4 (58.3–73.3)

[a] In this table, child and adolescent pharmacokinetic (PK) values are compared to the PK values of adults who received bictegravir 50 mg. The dose for the lowest weight in the adult cohort was 1.25 mg/kg; this was calculated using 40 kg as the lowest weight for adults.

Key: AUC_{tau} = area under the concentration time curve over the dosing interval; C_{max} = maximum serum concentration; C_{tau} = trough serum concentration at the end of the dosing interval; CI = confidence interval; GMR = geometric mean ratio

Use of Biktarvy in Children and Adolescents Weighing ≥25 kg

BIC 50 mg/FTC 200 mg/TAF 25 mg (Biktarvy) was administered to adolescents aged 12 years to <18 years who weighed ≥35 kg (maximum body weight 56.1 kg) and who had had viral loads of <50 copies/mL for ≥6 months on their previous ARV regimens. The drug was well tolerated, and was associated with a fall in eGFR similar to that seen in adults. This decrease in eGFR was considered to be from changes in tubular secretion of creatinine and was not a true change in glomerular function. In comparing cohorts of children (body weight ≥14 kg to <25 kg) and adolescents (body weight ≥35 kg) to adult cohorts the geometric mean ratio of C_{tau} was noted to be lower (see Tables A and B above). All 50 participants in the study had viral loads <50 copies/mL at Week 24, and 49 of 50 had viral loads <50 copies/mL at week 48.[5]

BIC 50 mg/FTC 200 mg/TAF 25 mg was administered to children aged 6 years to <12 years who weighed ≥25 kg and who had had viral loads <50 copies/mL for ≥6 months on their current ARV regimens.[5] Despite a high AUC and C_{max} (see Table A above), the drug combination was well tolerated, with a fall in eGFR similar to that seen in adult studies. One participant stopped the study drug because of insomnia and anxiety. The geometric mean ratio of C_{tau} compared with adult values (see Table B above) showed trough concentrations similar to those seen in adults.[5] All 50 participants in the study had viral loads <50 copies/mL at Week 24 and 49 of 50 had viral loads <50 copies/mL at Week 48.[5]

Use of Biktarvy in Children Weighing ≥14 to <25 kg

Biktarvy tablets consisting of BIC 30 mg/FTC 120 mg/TAF15 mg were administered to children aged ≥2 years weighing ≥14 to <25 kg and who had viral load <50 copies/mL on stable ART. PK evaluation showed high AUC and C_{max}, similar to those in patients aged 6 years to <12 years who weighed ≥25 kg, a similarly low C_{tau} (see Table A above), and a lower geometric mean ratio when C_{tau} was compared with adult values (see Table B above).[14] In general, the low-dose tablet was well tolerated over 55 weeks in the 22 children studied.[16] Adverse events considered related to the study drug included transient neutropenia (n = 2) and abdominal pain (n = 3).[16] At 24 weeks, the median change in CD4 cell count was −100 cells/μL, and the change in CD4 percentage was +0.5%. HIV RNA at <50 copies/mL was maintained in 20 of 22 participants at 24 weeks.[16]

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