Brand Name	Biktarvy
Active Ingredient(s)	bictegravir, emtricitabine, tenofovir alafenamide
Strength	50-200-25 mg
Dosage Form	tablet
Inactive Ingredients	croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. coating contains iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.
NDC	61958-2501-1
DIN	02478579
Canadian Distributor	Gilead Sciences Canada Inc. 600 6711 Mississauga Road, Mississauga, Ontario, Canada L5N 2W3
NDA Number	NDA210251
US Distributor (NDA Holder)	Gilead Sciences, Inc 333 Lakeside Drive, Foster City, CA 94404
Manufacturer (Final Packager)	Not available
API Manufacturer	Not available
Relationship to Sponsor	The Sponsor may have or have had agreements with the U.S. manufacturer for rebates. The Sponsor has no relationship with the foreign manufacturer.

Current FDA-approved Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BIKTARVY safely and effectively. See full prescribing information for BIKTARVY.

BIKTARVY® (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, for oral use
Initial U.S. Approval: 2018

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B
See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of BIKTARVY. Closely monitor hepatic function in these patients. If appropriate, anti-hepatitis B therapy may be warranted. (5.1)

----------INDICATIONS AND USAGE----------
BIKTARVY is a three-drug combination of bictegravir (BIC), a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI), and emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV-1 nucleoside analog reverse transcriptase inhibitors (NRTIs), and is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 14 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY. (1)

----------DOSAGE AND ADMINISTRATION----------
- Testing: Prior to or when initiating BIKTARVY test for hepatitis B virus infection. Prior to or when initiating BIKTARVY, and during treatment, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus. (2.1)
- Recommended dosage in adults and pediatric patients weighing at least 25 kg: One tablet containing 50 mg BIC, 200 mg FTC, and 25 mg TAF taken once daily with or without food. (2.2)
- Recommended dosage in pediatric patients weighing at least 14 kg to less than 25 kg: One tablet containing 30 mg BIC, 120 mg FTC, and 15 mg TAF taken once daily with or without food. (2.3)
- Renal impairment: BIKTARVY is not recommended in patients with estimated creatinine clearance of 15 to below 30 mL/min, or below 15 mL/min who are not receiving chronic hemodialysis, or below 15 mL/min who have no antiretroviral treatment history. (2.4)
- Hepatic impairment: BIKTARVY is not recommended in patients with severe hepatic impairment. (2.5)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF. (3)
Tablets: 30 mg of BIC, 120 mg of FTC, and 15 mg of TAF. (3)

----------CONTRAINDICATIONS----------
BIKTARVY is contraindicated to be co-administered with:
- dofetilide. (4)
- rifampin. (4)

----------WARNINGS AND PRECAUTIONS----------
- Immune reconstitution syndrome: May necessitate further evaluation and treatment. (5.3)
- New onset or worsening renal impairment: Assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein when initiating BIKTARVY and during therapy as clinically appropriate in all patients. Also assess serum phosphorus in patients with chronic kidney disease. (5.4)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.5)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence greater than or equal to 5%, all grades) are diarrhea, nausea, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Because BIKTARVY is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended. (7.1)
- Consult the Full Prescribing Information prior to and during treatment for important drug interactions. (4, 5.2, 7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission. (8.2)
- Pediatrics: Not recommended for patients weighing less than 14 kg. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of BIKTARVY.

Closely monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue BIKTARVY. If appropriate, anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

BIKTARVY is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing at least 14 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY.

2 DOSAGE AND ADMINISTRATION

2.1 Testing When Initiating and During Treatment with BIKTARVY

Prior to or when initiating BIKTARVY, test patients for hepatitis B virus infection *[see Warnings and Precautions (5.1)]*.

Prior to or when initiating BIKTARVY, and during treatment with BIKTARVY, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus *[see Warnings and Precautions (5.4)].*

2.2 Recommended Dosage in Adults and Pediatric Patients Weighing at Least 25 kg

BIKTARVY is a three-drug fixed dose combination product containing bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF). The recommended dosage of BIKTARVY 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:

- adults and pediatric patients weighing at least 25 kg with an estimated creatinine clearance greater than or equal to 30 mL/min; or
- virologically-suppressed adults with an estimated creatinine clearance below 15 mL/min who are receiving chronic hemodialysis. On days of hemodialysis, administer the daily dose of BIKTARVY after completion of hemodialysis treatment *[see Use in Specific Populations (8.4, 8.6) and Clinical Pharmacology (12.3)]*.

2.3 Recommended Dosage in Pediatric Patients Weighing at Least 14 kg to Less than 25 kg

The recommended dosage of BIKTARVY 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 in:

- pediatric patients weighing at least 14 kg to less than 25 kg with an estimated creatinine clearance greater than or equal to 30 mL/min *[see Use in Specific Populations (8.4, 8.6) and Clinical Pharmacology (12.3)]*.

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.

2.4 Not Recommended in Patients with Severe Renal Impairment

BIKTARVY is not recommended in patients with *[see Dosage and Administration (2.2, 2.3) and Use in Specific Populations (8.6)]*.:

- severe renal impairment (estimated creatinine clearance of 15 to below 30 mL/min); or
- end stage renal disease (ESRD; estimated creatinine clearance below 15 mL/min who are not receiving chronic hemodialysis; or
- no antiretroviral treatment history and ESRD who are receiving chronic hemodialysis.

2.5 Not Recommended in Patients with Severe Hepatic Impairment

BIKTARVY is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].*

3 DOSAGE FORMS AND STRENGTHS

BIKTARVY tablets are available in two dose strengths:

- 50 mg/200 mg/25 mg tablets: 50 mg of bictegravir (BIC) (equivalent to 52.5 mg of bictegravir sodium), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate). These tablets are purplish brown, capsule-shaped, film-coated, and debossed with “GSI” on one side and “9883” on the other side.
- 30 mg/120 mg/15 mg tablets: 30 mg of BIC (equivalent to 31.5 mg of bictegravir sodium), 120 mg of FTC, and 15 mg of TAF (equivalent to 16.8 mg of tenofovir alafenamide fumarate). These tablets are pink, capsule-shaped, film-coated, and debossed with “GSI” on one side and “B” on the other side.

4 CONTRAINDICATIONS

BIKTARVY is contraindicated to be co-administered with:

- dofetilide due to the potential for increased dofetilide plasma concentrations and associated serious and/or life-threatening events *[see Drug Interactions (7.5)]*.
- rifampin due to decreased BIC plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to BIKTARVY *[see Drug Interactions (7.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV

Patients with HIV-1 should be tested for the presence of chronic hepatitis B virus (HBV) infection before or when initiating antiretroviral therapy *[see Dosage and Administration (2.1)]*.

Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing FTC and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of BIKTARVY. Patients coinfected with HIV-1 and HBV who discontinue BIKTARVY should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

5.2 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of BIKTARVY with certain other drugs may result in known or potentially significant drug interactions, some of which may lead to *[see Contraindications (4) and Drug Interactions (7.5)]:*

- Loss of therapeutic effect of BIKTARVY and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

See Table 3 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during BIKTARVY therapy; review concomitant medications during BIKTARVY therapy; and monitor for the adverse reactions associated with the concomitant drugs.

5.3 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

5.4 New Onset or Worsening Renal Impairment

Postmarketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT), and Fanconi syndrome, have been reported with TAF-containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related adverse events *[see Adverse Reactions (6.1, 6.2)].* BIKTARVY is not recommended in patients with severe renal impairment (estimated creatinine clearance of 15 to below 30 mL/min), or patients with ESRD (estimated creatinine clearance below 15 mL/min) who are not receiving chronic hemodialysis, or patients with no antiretroviral treatment history and ESRD who are receiving chronic hemodialysis *[see Dosage and Administration (2.4), Use in Specific Populations (8.6)].*

Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

Prior to or when initiating BIKTARVY, and during treatment with BIKTARVY, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue BIKTARVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

5.5 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine, a component of BIKTARVY, and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with BIKTARVY should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Severe Acute Exacerbations of Hepatitis B *[see Warnings and Precautions (5.1)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.3)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.4)].*
- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[see Warnings and Precautions (5.5)].*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials in Adults with No Antiretroviral Treatment History

The primary safety assessment of BIKTARVY 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 antiretroviral treatment history through Week 144. After Week 144, subjects received open-label BIKTARVY in an optional extension phase for an additional 96 weeks (end of study). A total of 634 and 1025 subjects received one tablet of BIKTARVY once daily during the double-blind (Week 144) and extension phases, respectively *[see Clinical Studies (14.2)]*.

The most common adverse reactions (all Grades) reported in at least 5% of subjects in the BIKTARVY group in either Trial 1489 or Trial 1490 were diarrhea, nausea, and

headache. The proportion of subjects who discontinued treatment through Week 144 with BIKTARVY, abacavir [ABC]/dolutegravir [DTG]/ lamivudine [3TC]), or DTG + FTC/TAF, due to adverse events, regardless of severity, was 1%, 2%, and 2%, respectively. Table 1 displays the frequency of adverse reactions (all Grades) greater than or equal to 2% in the BIKTARVY group.

Table 1 Adverse Reactions[a] (All Grades) Reported in ≥ 2% of HIV-1 Infected Adults with No Antiretroviral Treatment History Receiving BIKTARVY in Trials 1489 or 1490 (Week 144 analysis)

	Trial 1489		Trial 1490	
Adverse Reactions	**BIKTARVY** N=314	**ABC/DTG/3TC** N=315	**BIKTARVY** N=320	**DTG + FTC/TAF** N=325
Diarrhea	6%	4%	3%	3%
Nausea	6%	18%	3%	5%
Headache	5%	5%	4%	3%
Fatigue	3%	4%	2%	2%
Abnormal dreams	3%	3%	<1%	1%
Dizziness	2%	3%	2%	1%
Insomnia	2%	3%	2%	<1%
Abdominal distention	2%	2%	1%	2%

a. Frequencies of adverse reactions are based on all adverse events attributed to trial drugs by the investigator. No adverse reactions of Grade 2 or higher occurred in > 1% of subjects treated with BIKTARVY.

Additional adverse reactions (all Grades) occurring in less than 2% of subjects administered BIKTARVY in Trials 1489 and 1490 included vomiting, flatulence, dyspepsia, abdominal pain, rash, and depression.

Suicidal ideation, suicide attempt, and depression suicidal occurred in 2% of subjects administered BIKTARVY; these events occurred primarily in subjects with a preexisting history of depression, prior suicide attempt or psychiatric illness.

The majority (84%) of adverse events associated with BIKTARVY were Grade 1.

Adverse reactions in the open-label extension phases of Trials 1489 and 1490 were similar to those observed in subjects administered BIKTARVY in the Week 144 analysis.

Clinical Trials in Virologically Suppressed Adults

The safety of BIKTARVY in virologically-suppressed adults was based on Week 48 data from 282 subjects in a randomized, double-blind, active-controlled trial (Trial 1844) in which virologically-suppressed subjects were switched from either DTG + ABC/3TC or ABC/DTG/3TC to BIKTARVY; and Week 48 data from 290 subjects in an open-label,

active-controlled trial in which virologically-suppressed subjects were switched from a regimen containing atazanavir (ATV) (given with cobicistat or ritonavir) or darunavir (DRV) (given with cobicistat or ritonavir) plus either FTC/TDF or ABC/3TC, to BIKTARVY (Trial 1878). Overall, the safety profile in virologically-suppressed adult subjects in Trials 1844 and 1878 was similar to that in subjects with no antiretroviral treatment history *[see Clinical Studies (14.3)]*.

Clinical Trial in Adults with End Stage Renal Disease (ESRD) Receiving Chronic Hemodialysis

The safety of FTC and TAF (components of BIKTARVY) was evaluated in a single arm, open-label trial (Trial 1825) in virologically-suppressed adults with ESRD (estimated creatinine clearance of less than 15 mL/min) on chronic hemodialysis treated with FTC+TAF in combination with elvitegravir and cobicistat as a fixed-dose combination tablet for 96 weeks (N=55). The most commonly reported adverse reaction (adverse event assessed as causally related by investigator and all grades) was nausea (7%). Serious adverse events were reported in 65% of subjects and the most common serious adverse events were pneumonia (15%), fluid overload (7%), hyperkalemia (11%) and osteomyelitis (7%). Overall 7% of subjects permanently discontinued treatment due to an adverse event. In an extension phase of Trial 1825 in which 10 subjects switched to BIKTARVY for 48 weeks, the safety findings were similar to those in the initial phase of the open-label trial *[see Use in Specific Populations (8.6), Clinical Studies (14.3)]*.

Laboratory Abnormalities

The frequency of laboratory abnormalities (Grades 3–4) occurring in at least 2% of subjects receiving BIKTARVY in Trials 1489 and 1490 are presented in Table 2.

Table 2 Laboratory Abnormalities (Grades 3–4) Reported in ≥ 2% of Subjects Receiving BIKTARVY in Trials 1489 or 1490 (Week 144 analysis)

	Trial 1489		Trial 1490	
Laboratory Parameter Abnormality[a]	**BIKTARVY** N=314	**ABC/DTG/3TC** N=315	**BIKTARVY** N=320	**DTG + FTC/TAF** N=325
Amylase (>2.0 x ULN)	3%	4%	3%	4%
ALT (>5.0 × ULN)	2%	2%	3%	1%
AST (>5.0 × ULN)	5%	3%	2%	3%
Creatine Kinase (≥10.0 × ULN)	8%	8%	6%	4%
Neutrophils (<750 mm^3)	3%	4%	3%	2%
LDL-cholesterol (fasted) (>190 mg/dL)	5%	5%	4%	6%
Lipase (> 3.0 x ULN)[b]	2%	2%	<1%	2%
GGT (>5.0 x ULN)	2%	2%	1%	1%

ULN = Upper limit of normal

a. Frequencies are based on treatment-emergent laboratory abnormalities.

b. Lipase test performed only in subjects with serum amylase > 1.5 x ULN.

Changes in Serum Creatinine: BIC has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function *[see Clinical Pharmacology (12.2)]*. Increases in serum creatinine occurred by Week 4 of treatment and remained stable through Week 144. In Trials 1489 and 1490, median (Q1, Q3) serum creatinine increased by 0.11 (0.03, 0.19) mg per dL from baseline to Week 144 in the BIKTARVY group and was similar to the comparator groups who received ABC/DTG/3TC, or DTG + FTC/TAF. There were no discontinuations due to renal adverse events and renal serious adverse events were encountered in less than 1% of participants treated with BIKTARVY through Week 144 in clinical trials.

Changes in Bilirubin: In Trials 1489 and 1490, total bilirubin increases were observed in 17% of subjects administered BIKTARVY through Week 144. Increases were primarily Grade 1 (1.0 to 1.5 x ULN) (12%) and Grade 2 (1.5 to 2.5 x ULN) (4%). Graded bilirubin increases in the ABC/DTG/3TC, and DTG + FTC/TAF groups, were 7% and 8%, respectively. Increases were primarily Grade 1 (5% ABC/DTG/3TC and 7% DTG + FTC/TAF) or Grade 2 (2% ABC/DTG/3TC and 2% DTG + FTC/TAF). There were no discontinuations due to hepatic adverse events through Week 144 in BIKTARVY clinical studies.

Clinical Trials in Pediatric Subjects

The safety of BIKTARVY was evaluated in HIV-1 infected virologically-suppressed subjects between the ages of 12 to less than 18 years and weighing at least 35 kg (N=50) through Week 48 (cohort 1), in virologically-suppressed subjects between the ages of 6 to less than 12 years and weighing at least 25 kg (N=50) through Week 24 (cohort 2), and in virologically suppressed subjects at least 2 years of age and weighing at least 14 to less than 25 kg (N=22) through Week 24 (cohort 3) in an open label clinical trial (Trial 1474) *[see Clinical Studies (14.4)]*. No new adverse reactions or laboratory abnormalities were identified compared to those observed in adults. Adverse reactions were reported in 11% of pediatric subjects. The majority (76%) of adverse reactions were Grade 1. No Grade 3 or 4 adverse reactions were reported. The adverse reaction reported by more than one subject (regardless of severity) was abdominal discomfort (n=2). One subject (1%) had Grade 2 adverse reactions of insomnia and anxiety that led to discontinuation of BIKTARVY. The other adverse reactions that occurred in single subjects were similar to those seen in adults.

6.2 Postmarketing Experience

The following events have been identified during post approval use of BIKTARVY or products containing TAF. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Renal and Urinary Disorders

Acute renal failure, acute tubular necrosis, proximal renal tubulopathy, and Fanconi syndrome

Skin and Subcutaneous Tissue Disorders

Angioedema, Stevens-Johnson syndrome/toxic epidermal necrolysis, and urticaria

7 DRUG INTERACTIONS

7.1 Other Antiretroviral Medications

Because BIKTARVY is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended *[see Indications and Usage (1)]*. Comprehensive information regarding potential drug-drug interactions with other antiretroviral medications is not provided because the safety and efficacy of concomitant HIV-1 antiretroviral therapy is unknown.

7.2 Potential for BIKTARVY to Affect Other Drugs

BIC inhibits organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1) *in vitro*. Coadministration of BIKTARVY with drugs that are substrates of OCT2 and MATE1 (e.g., dofetilide) may increase their plasma concentrations (see Table 3).

7.3 Potential Effect of Other Drugs on One or More Components of BIKTARVY

BIC is a substrate of CYP3A and UGT1A1. A drug that is a strong inducer of CYP3A and also an inducer of UGT1A1 can substantially decrease the plasma concentrations of BIC which may lead to loss of therapeutic effect of BIKTARVY and development of resistance *[see Clinical Pharmacology (12.3)]*.

The use of BIKTARVY with a drug that is a strong inhibitor of CYP3A and also an inhibitor of UGT1A1 may significantly increase the plasma concentrations of BIC.

TAF is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Co-administration of drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentrations of TAF *[see Clinical Pharmacology (12.3)]*. Co-administration of drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect of BIKTARVY and development of resistance (see Table 3).

7.4 Drugs Affecting Renal Function

Because FTC and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of BIKTARVY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, tenofovir, and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[see Warnings and Precautions (5.4)]*.

7.5 Established and Potentially Significant Drug Interactions

Table 3 provides a listing of established or potentially clinically significant druginteractions with recommended prevention or management strategies. The drug interactions described are based on studies conducted with either BIKTARVY, the components of BIKTARVY (BIC, FTC, and TAF) as individual agents, or are drug interactions that may occur with BIKTARVY *[see Contraindications (4), Warnings and Precautions (5.2), and Clinical Pharmacology (12.3)]*.

Table 3 Established and Potentially Significant[a] Drug Interactions: Alteration in Regimen May be Recommended

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiarrhythmics: dofetilide	↑ Dofetilide	Coadministration is contraindicated due to the potential for serious and/or life-threatening events associated with dofetilide therapy *[see Contraindications (4)]*.
Anticonvulsants: carbamazepine[c] oxcarbazepine phenobarbital phenytoin	↓ BIC ↓ TAF	Coadministration with alternative anticonvulsants should be considered.
Antimycobacterials: rifabutin[c] rifampin[c,d] rifapentine	↓ BIC ↓ TAF	Coadministration with rifampin is contraindicated due to the effect of rifampin on the BIC component of BIKTARVY *[see Contraindications (4)]*. Coadministration with rifabutin or rifapentine is not recommended.
Herbal Products: St. John's wort[e]	↓ BIC ↓ TAF	Coadministration with St. John's wort is not recommended.
Medications or oral supplements containing polyvalent cations (e.g., Mg, Al, Ca, Fe): Calcium or iron supplements[c] Cation-containing antacids or laxatives[c] Sucralfate Buffered medications	↓ BIC	Antacids containing Al/Mg: BIKTARVY can be taken at least 2 hours before or 6 hours after taking antacids containing Al/Mg. Routine administration of BIKTARVY together with, or 2 hours after, antacids containing Al/Mg is not recommended. Supplements or Antacids containing Calcium or Iron: BIKTARVY and supplements or antacids containing calcium or iron can be taken together with food. Routine administration of BIKTARVY under fasting conditions together with, or 2 hours after, supplements or antacids containing calcium or iron is not recommended.
Metformin	↑ Metformin	Refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use of BIKTARVY and metformin.

a. Table is not all inclusive.

b. ↑ = Increase, ↓ = Decrease.

c. Drug-drug interaction study was conducted with either BIKTARVY or its components as individual agents.

d. Strong inducer of CYP3Aand P-gp, and inducer of UGT1A1.
e. The induction potency of St. John's wort may vary widely based on preparation.

7.6 Drugs without Clinically Significant Interactions with BIKTARVY

Based on drug interaction studies conducted with BIKTARVY or the components of BIKTARVY, no clinically significant drug interactions have been observed when BIKTARVY is combined with the following drugs: ethinyl estradiol, ledipasvir/sofosbuvir, midazolam, norgestimate, sertraline, sofosbuvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to BIKTARVY during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

There are insufficient human data on the use of BIKTARVY during pregnancy to inform a drug-associated risk of birth defects and miscarriage. Dolutegravir, another integrase inhibitor, has been associated with neural tube defects (NTDs) *(see Data)*. Discuss the benefit-risk of using BIKTARVY with individuals of childbearing potential, particularly if pregnancy is being planned. BIKTARVY use during pregnancy has been evaluated in a limited number of women reported to the APR; consequently, there are insufficient BIC data from the APR to adequately assess the risk of major birth defects. Reports of pregnant individuals treated with other drug products containing TAF or FTC contribute to APR's overall risk assessment for these components. Available data from the APR show no statistically significant difference in the overall risk of major birth defects for FTC or TAF compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data)*. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in the clinically recognized pregnancies in the U.S. general population is 15-20%.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the components of BIKTARVY at exposures that were either not maternally toxic (rabbits) or greater than (rats and mice) those in humans at the recommended human dose (RHD) (*see Data*). During organogenesis, systemic exposures (AUC) to BIC were approximately 36 (rats) and 0.6 times (rabbits), to FTC were approximately 60 (mice) and 108 times (rabbits), and to TAF were approximately 2 (rats) and 78 times (rabbits) the exposure at the RHD of BIKTARVY. In rat pre/postnatal development studies, maternal systemic exposures (AUC) were 30 times (BIC), 60

times (FTC), and 19 times (TDF) the exposures of each component in humans at the RHD.

Data

Human Data

Prospective reports from the APR of overall major birth defects in pregnancies exposed to the components of BIKTARVY are compared with a U.S. background major birth defect rate. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at less than 20 weeks gestation.

Bictegravir (BIC):

Data from an observational study in Botswana showed that dolutegravir, another integrase inhibitor, was associated with increased risk of neural tube defects when administered at the time of conception and in early pregnancy. Data available to date from other sources including the APR, clinical trials, and postmarketing data are insufficient to address this risk with BIC.

There are an insufficient number of reports to the APR to adequately assess the risk of major birth defects associated with BIC exposure. The APR has received prospective reports of 3 birth defects among 100 (3.0%) first trimester exposures to BIC-containing regimens during pregnancy resulting in live births. No birth defects were reported among 40 exposures during the second/third trimester.

Emtricitabine (FTC):

Based on prospective reports to the APR of over 5,400 exposures to FTC-containing regimens during pregnancy resulting in live births (including over 3,900 exposed in the first trimester and over 1,500 exposed in the second/third trimester), the prevalence of birth defects in live births was 2.6% (95% CI: 2.2% to 3.2%) and 2.7% (95% CI: 1.9% to 3.7%) following first and second/third trimester exposure, respectively, to FTC-containing regimens.

Tenofovir Alafenamide (TAF):

Based on prospective reports to the APR of over 660 exposures to TAF-containing regimens during pregnancy resulting in live births (including over 520 exposed in the first trimester and over 130 exposed in the second/third trimester), the prevalence of birth defects in live births was 4.2% (95% CI: 2.6% to 6.3%) and 3.0% (95% CI: 0.8% to 7.5%) following first and second/third trimester exposure, respectively, to TAF-containing regimens.

Animal Data

Bictegravir: BIC was administered orally to pregnant rats (5, 30, or 300 mg/kg/day) and rabbits (100, 300, or 1000 mg/kg/day) on gestation days 7 through 17, and 7 through 19, respectively. No adverse embryo-fetal effects were observed in rats and

rabbits at BIC exposures (AUC) of up to approximately 36 (rats) and 0.6 (rabbits) times the exposure in humans at the RHD of BIKTARVY. Spontaneous abortion, increased clinical signs [fecal changes, thin body, and cold-to-touch], and decreased body weight were observed at a maternally toxic dose in rabbits (1000 mg/kg/day; approximately 1.4 times higher than human exposure at the RHD).

In a pre/postnatal development study, BIC was administered orally to pregnant rats (up to 300 mg/kg/day) from gestation days 6 to lactation/post-partum day 24. No significant adverse effects were observed in the offspring exposed daily from before birth (*in utero*) through lactation at maternal and pup exposures (AUC) of approximately 30 and 11 times higher, respectively, than human exposures at the RHD.

Emtricitabine: FTC was administered orally to pregnant mice (250, 500, or 1000 mg/kg/day) and rabbits (100, 300, or 1000 mg/kg/day) through organogenesis (on gestation days 6 through 15, and 7 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with emtricitabine in mice at exposures approximately 60 times higher and in rabbits at approximately 108 times higher than human exposures at the RHD.

In a pre/postnatal development study with FTC, mice were administered doses up to 1000 mg/kg/day; no significant adverse effects directly related to drug were observed in the offspring exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 60 times higher than human exposures at the RHD.

Tenofovir alafenamide: TAF was administered orally to pregnant rats (25, 100, or 250 mg/kg/day) and rabbits (10, 30, or 100 mg/kg/day) through organogenesis (on gestation days 6 through 17, and 7 through 20, respectively). No adverse embryo-fetal effects were observed in rats and rabbits at TAF exposures of approximately 2 (rats) and 78 (rabbits) times higher than the exposure in humans at the recommended daily dose of BIKTARVY. TAF is rapidly converted to tenofovir; the observed tenofovir exposure in rats and rabbits were 55 (rats) and 86 (rabbits) times higher than human tenofovir exposures at the RHD. Since TAF is rapidly converted to tenofovir and lower tenofovir exposures in rats and mice were observed after TAF administration compared to TDF administration, a pre/postnatal development study in rats was conducted only with TDF. Doses up to 600 mg/kg/day were administered through lactation; no adverse effects were observed in the offspring on gestation day 7 [and lactation day 20] at tenofovir exposures of approximately 12 [19] times higher than the exposures in humans at the RHD of BIKTARVY.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

It is not known whether BIKTARVY or all of the components of BIKTARVY are present in human breast milk, affects human milk production, or has effects on the breastfed infant. Based on published data, FTC has been shown to be present in human breast milk. BIC was detected in the plasma of nursing rat pups likely due to the presence of BIC in milk, and tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF *(see Data)*. It is unknown if TAF is present in animal milk.

Because of the potential for 1) HIV transmission (in HIV-negative infants); 2) developing viral resistance (in HIV-positive infants); and 3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving BIKTARVY.

Data

Animal Data

Bictegravir: BIC was detected in the plasma of nursing rat pups in the pre/postnatal development study (post-natal day 10), likely due to the presence of BIC in milk.

Tenofovir alafenamide: Studies in rats and monkeys have demonstrated that tenofovir is secreted in milk. Tenofovir was excreted into the milk of lactating rats following oral administration of TDF (up to 600 mg/kg/day) at up to approximately 24% of the median plasma concentration in the highest dosed animals at lactation day 11. Tenofovir was excreted into the milk of lactating monkeys following a single subcutaneous (30 mg/kg) dose of tenofovir at concentrations up to approximately 4% of plasma concentration, resulting in exposure (AUC) of approximately 20% of plasma exposure.

8.4 Pediatric Use

The safety and effectiveness of BIKTARVY have been established as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in pediatric patients weighing at least 14 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY *[see Indications and Usage (1) and Dosage and Administration (2.2, 2.3)]*.

Use of BIKTARVY in pediatric patients weighing at least 14 kg is supported by the

following:

- trials in adults *[see Clinical Studies (14.1)]*
- an open-label trial in three age-based cohorts of virologically-suppressed pediatric subjects *[see Clinical Studies (14.4)]*
    - Cohort 1: 12 to less than 18 years of age and weighing at least 35 kg receiving BIKTARVY through Week 48 (N=50),
    - Cohort 2: 6 to less than 12 years of age and weighing at least 25 kg receiving BIKTARVY through Week 24 (N=50), and
    - Cohort 3: at least 2 years of age and weighing at least 14 to less than 25 kg through Week 24 (N=22). No pediatric subjects 2 years of age were enrolled; of the 6 pediatric subjects who were 3 years of age at enrollment, 3 subjects weighed between 14 to less than 15 kg.

The safety and efficacy of BIKTARVY in these pediatric subjects were similar to that in adults, and there was no clinically significant change in exposure for the components of BIKTARVY *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.4)]*.

Safety and effectiveness of BIKTARVY in pediatric patients weighing less than 14 kg have not been established.

8.5 Geriatric Use

Clinical trials in virologically-suppressed subjects (Trials 4449, 1844, and 1878) included 111 subjects aged 65 years and over who received BIKTARVY, including 86 patients from an open-label, single-arm trial of subjects aged 65 years and over who were switched from their previous antiretroviral regimen to BIKTARVY *[see Clinical Studies (14.3)*]. Of the total number of BIKTARVY-treated patients in these trials, 100 (90%) were 65 to 74 years of age, and 11 (10%) were 75 to 84 years of age. No overall differences in safety or effectiveness were observed between elderly subjects and adults between 18 and less than 65 years of age, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

The pharmacokinetics, safety, virologic and immunologic responses of FTC and TAF (components of BIKTARVY) were evaluated in a single arm, open-label trial (Trial 1825) in virologically-suppressed adults with ESRD (estimated creatinine clearance of less than 15 mL/min) on chronic hemodialysis treated with FTC+TAF in combination with elvitegravir and cobicistat as a fixed-dose combination tablet for 96 weeks (N=55). In an extension phase of Trial 1825, 10 virologically-suppressed subjects switched to BIKTARVY and all remained virologically suppressed for 48 weeks *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.3)]*.

No dosage adjustment of BIKTARVY is recommended in patients with estimated creatinine clearance greater than or equal to 30 mL/min, or in virologically-suppressed

adults (estimated creatinine clearance below 15 mL/min) who are receiving chronic hemodialysis. On days of hemodialysis, administer the daily dose of BIKTARVY after completion of hemodialysis treatment *[see Dosage and Administration (2.2)]*

BIKTARVY is not recommended in patients with estimated creatinine clearance of below 30 mL/min, by Cockcroft-Gault, or patients with ESRD (estimated creatinine clearance below 15 mL/min) who are not receiving chronic dialysis, or patients with no antiretroviral treatment history and ESRD who are receiving chronic dialysis, as the safety and/or efficacy of BIKTARVY has not been established in these populations *[see Dosage and Administration (2.4), Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dosage adjustment of BIKTARVY is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. BIKTARVY has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, BIKTARVY is not recommended for use in patients with severe hepatic impairment *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

No data are available on overdose of BIKTARVY in patients. If overdose occurs, monitor the patient for evidence of toxicity. Treatment of overdose with BIKTARVY consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

Hemodialysis treatment removes approximately 30% of the FTC dose over a 3-hour dialysis period starting within 1.5 hours of FTC dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether FTC can be removed by peritoneal dialysis.

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

11 DESCRIPTION

BIKTARVY (bictegravir, emtricitabine, and tenofovir alafenamide) is a fixed dose combination tablet containing bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF) for oral administration.

- BIC is an integrase strand transfer inhibitor (INSTI).
- FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- TAF, an HIV NRTI, is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

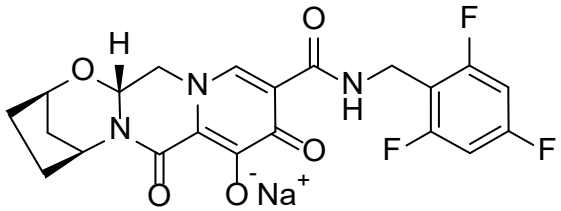
BIKTARVY tablets are available in two dose strengths:

- 50 mg/200 mg/25 mg tablet containing 50 mg of BIC (equivalent to 52.5 mg of bictegravir sodium), 200 mg of FTC, and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate).
- 30 mg/120 mg/15 mg tablet containing 30 mg of BIC (equivalent to 31.5 mg of bictegravir sodium), 120 mg of FTC, and 15 mg of TAF (equivalent to 16.8 mg of tenofovir alafenamide fumarate).

Both dose strengths of BIKTARVY tablets include the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets for both dose strengths are film-coated with a coating material containing iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Bictegravir: The chemical name of bictegravir sodium is 2,5-Methanopyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazepine-10-carboxamide, 2,3,4,5,7,9,13,13a-octahydro-8-hydroxy-7,9-dioxo-*N*-[(2,4,6-trifluorophenyl)methyl]-, sodium salt (1:1), (2*R*,5*S*,13a*R*)-.

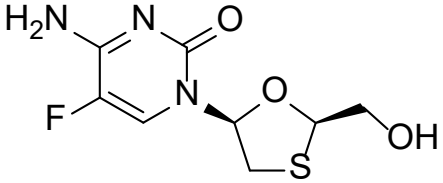
Bictegravir sodium has a molecular formula of $C_{21}H_{17}F_3N_3NaO_5$ and a molecular weight of 471.4 and has the following structural formula:



Bictegravir sodium is an off-white to yellow solid with a solubility of 0.1 mg per mL in water at 20 °C.

Emtricitabine: The chemical name of FTC is 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S*-yl)-(1H)-pyrimidin-2-one. FTC is the (-)enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5 position.

FTC has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.2 and has the following structural formula:

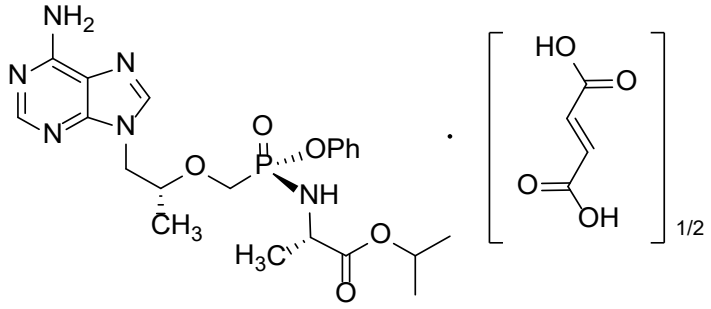


FTC is a white to off-white powder with a solubility of approximately 112 mg per mL in water at 25 °C.

Tenofovir alafenamide: The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-

methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1).

Tenofovir alafenamide fumarate has an empirical formula of $C_{21}H_{29}O_5N_6P•½(C_4H_4O_4)$ and a formula weight of 534.5 and has the following structural formula:



Tenofovir alafenamide fumarate is a white to off-white or tan powder with a solubility of 4.7 mg per mL in water at 20 °C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

BIKTARVY is a fixed dose combination of antiretroviral drugs bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF) *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a thorough QT/QTc trial in 48 healthy subjects, BIC at doses 1.5 and 6 times the recommended dose did not affect the QT/QTc interval and did not prolong the PR interval. In a thorough QT/QTc trial in 48 healthy subjects, TAF at the recommended dose or at a dose 5 times the recommended dose, did not affect the QT/QTc interval and did not prolong the PR interval. The effect of FTC on the QT interval is not known.

Effects on Serum Creatinine

Mean change from baseline in serum creatinine in healthy subjects who received BIC 75 mg (1.5 times the approved recommended dosage) once daily with food for 14 days was 0.1 mg per dL on Days 7 and 14 compared to placebo. BIC did not have a significant effect on the estimated creatinine clearance or on the actual glomerular filtration rate (determined by the clearance of probe drug, iohexol).

12.3 Pharmacokinetics

The pharmacokinetic (PK) properties of BIKTARVY components are provided in Table 4. The multiple dose PK parameters of BIKTARVY components (based on population pharmacokinetic analysis) are provided in Table 5.

Table 4 Pharmacokinetic Properties of the Components of BIKTARVY

		Bictegravir (BIC)	Emtricitabine (FTC)	Tenofovir Alafenamide (TAF)
Absorption				
T_{max} (h)[a]		2.0–4.0	1.5–2.0	0.5–2.0
Effect of high-fat meal (relative to fasting)[b]	AUC ratio	1.24 (1.16, 1.33)	0.96 (0.93, 0.99)	1.63 (1.43, 1.85)
	C_{max} ratio	1.13 (1.06, 1.20)	0.86 (0.78, 0.93)	0.92 (0.73, 1.14)
Distribution				
% bound to human plasma proteins		>99	<4	~80
Blood-to-plasma ratio		0.64	0.6	1.0
Elimination				
$t_{1/2}$ (h)[c]		17.3 (14.8, 20.7)	10.4 (9.0, 12.0)	0.51 (0.45, 0.62)[c]
Metabolism				
Metabolic pathway(s)		CYP3A UGT1A1	Not significantly metabolized	Cathepsin A[d] (PBMCs) CES1 (hepatocytes)
Excretion				
Major route of elimination		Metabolism	Glomerular filtration and active tubular secretion	Metabolism
% of dose excreted in urine[e]		35	70	<1
% of dose excreted in feces[e]		60.3	13.7	31.7

PBMCs=peripheral blood mononuclear cells; CES1=carboxylesterase 1

a. Values reflect administration of BIKTARVY with or without food.

b. Values refer to geometric mean ratio [high-fat meal/ fasting] in PK parameters and (90% confidence interval). High fat meal is approximately 800 kcal, 50% fat.

c. $t_{1/2}$ values refer to median (Q1, Q3) terminal plasma half-life. Note that the active metabolite of TAF, tenofovir diphosphate, has a half-life of 150-180 hours within PBMCs.

d. *In vivo*, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. *In vitro* studies have shown that TAF is metabolized to tenofovir by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes.

e. Dosing in mass balance studies: single dose administration of [^{14}C] BIC; single dose administration of [^{14}C] FTC after multiple dosing of FTC for ten days; single dose administration of [^{14}C] TAF.

Table 5 Multiple Dose PK Parameters of BIC, FTC, and TAF Following Oral Administration of BIKTARVY in HIV-Infected Adults

Parameter Mean (CV%)	Bictegravir	Emtricitabine	Tenofovir Alafenamide
C_{max} (microgram per mL)	6.15 (22.9)	2.13 (34.7)	0.121 (15.4)
AUC_{tau} (microgram•h per mL)	102 (26.9)	12.3 (29.2)	0.142 (17.3)
C_{trough} (microgram per mL)	2.61 (35.2)	0.096 (37.4)	NA

CV=Coefficient of Variation; NA=Not Applicable

Specific Populations

Patients with Renal Impairment

No clinically relevant differences in the pharmacokinetics of BIC, TAF, or its metabolite tenofovir were observed between subjects with severe renal impairment (estimated creatinine clearance of 15 to less than 30 mL/min, by Cockcroft-Gault method) and healthy subjects in Phase 1 studies. In a separate Phase 1 study of FTC alone, FTC exposures were increased in subjects with severe renal impairment.

The pharmacokinetics of BIC, FTC and TAF were evaluated in a subset of HIV-1 infected virologically-suppressed subjects with ESRD (estimated creatinine clearance less than 15 mL/min, by Cockcroft-Gault method) receiving chronic hemodialysis in Trial 1825. The pharmacokinetics of TAF were similar between healthy subjects and subjects with ESRD receiving chronic hemodialysis; increases in FTC and tenofovir exposures in subjects with ESRD were not considered clinically relevant. Median (minimum, maximum) BIC C_{trough} values in subjects (n=7) with ESRD who received BIKTARVY were 846 ng/mL (288, 1810) compared to 2540 ng/mL (757, 6499) in subjects (N=584) with normal renal function. Despite significantly lower BIC C_{trough} values in the virologically-suppressed ESRD population, virologic suppression was maintained *[see Use in Specific Populations (8.6), Clinical Studies (14.3)]*.

Patients with Hepatic Impairment

Bictegravir: Clinically relevant changes in the pharmacokinetics of BIC were not observed in subjects with moderate (Child-Pugh Class B) hepatic impairment.

Emtricitabine: The pharmacokinetics of FTC has not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of hepatic impairment should be limited.

Tenofovir Alafenamide: Clinically relevant changes in the pharmacokinetics of TAF or its metabolite tenofovir were not observed in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment *[see Use in Specific Populations (8.7)]*.

Hepatitis B and/or Hepatitis C Virus Coinfection

The pharmacokinetics of BIC, FTC, and TAF have not been evaluated in subjects coinfected with hepatitis B and/or C virus.

Geriatric Patients

The pharmacokinetics of BIC, FTC, and TAF have not been fully evaluated in the elderly (65 years of age and older). Population pharmacokinetics analysis of HIV-infected subjects in Phase 3 trials of BIKTARVY showed that age did not have a clinically relevant effect on exposures of BIC and TAF up to 74 years of age *[see Use in Specific Populations (8.5)]*.

Pediatric Patients

Mean BIC C_{trough} was lower in 50 pediatric patients aged 12 to less than 18 years and weighing at least 35 kg who received BIKTARVY in Trial 1474 relative to adults following administration of BIKTARVY, but was not considered clinically significant based on exposure-response relationships; exposures of FTC and TAF in these pediatric patients were similar to those in adults (Table 6).

Table 6 Multiple Dose PK Parameters of BIC, FTC, and TAF Following Oral Administration of BIKTARVY in HIV-Infected Pediatric Subjects Aged 12 to less than 18 years

Parameter Mean (CV%)	Bictegravir[a]	Emtricitabine[b]	Tenofovir Alafenamide[a]
C_{max} (microgram per mL)	6.24 (27.1)	2.69 (34.0)	0.133 (70.2)
AUC_{tau} (microgram•h per mL)	89.1 (31.0)	13.6 (21.7)	0.196 (50.3)
C_{trough} (microgram per mL)	1.78 (44.4)	0.064 (25.0)	NA

CV=Coefficient of Variation; NA=Not Applicable

a. From Population PK analysis of cohort 1 of Trial 1474 (n=50 for BIC; n=49 for TAF).

b. From Intensive PK analysis of cohort 1 of Trial 1474 (n=24).

Mean BIC C_{max}, and exposures of FTC and TAF (AUC_{tau} and C_{max}) achieved in 50 pediatric patients between the ages of 6 to less than 12 years and weighing at least 25 kg, and in 22 pediatric patients at least 2 years of age and weighing at least 14 to less than 25 kg who received BIKTARVY in Trial 1474 were higher than exposures

in adults; however, the increases were not considered clinically significant as the safety profiles were similar in adult and pediatric patients (Tables 7 and 8) *[see Use in Specific Populations (8.4)]*.

Table 7 Multiple Dose PK Parameters of BIC, FTC, and TAF Following Oral Administration of BIKTARVY in HIV-Infected Pediatric Subjects Aged 6 to less than 12 years

Parameter Mean (CV%)	Bictegravir[a]	Emtricitabine[b]	Tenofovir Alafenamide[a]
C_{max} (microgram per mL)	9.46 (24.3)	3.89 (31.0)	0.205 (44.6)
AUC_{tau} (microgram•h per mL)	128 (27.8)	17.6 (36.9)	0.278 (40.3)
C_{trough} (microgram per mL)	2.36 (39.0)	0.227 (323)	NA

CV=Coefficient of Variation; NA=Not Applicable

a. From Population PK analysis of cohort 2 of Trial 1474 (n=50 for BIC; n=47 for TAF).

b. From Intensive PK analysis of cohort 2 of Trial 1474 (n=25 except n=24 for C_{trough}).

Table 8 Multiple Dose PK Parameters of BIC, FTC, and TAF Following Oral Administration of BIKTARVY in HIV-Infected Pediatric Subjects at Least 2 Years of Age[a] and Weighing at Least 14 to Less than 25 kg

Parameter Mean (CV%)	Bictegravir[b]	Emtricitabine[c]	Tenofovir Alafenamide[c]
C_{max} (microgram per mL)	9.15 (44.8)	3.85 (34.7)	0.414 (31.0)
AUC_{tau} (microgram•h per mL)	126 (42.4)	15.0 (21.9)	0.305 (42.6)
C_{trough} (microgram per mL)	2.43 (40.1)	0.210 (243)	NA

CV=Coefficient of Variation; NA=Not Applicable

a. Cohort 3 of Trial 1474 enrolled pediatric subjects from 3 to 9 years of age.

b. From Population PK analysis of cohort 3 of Trial 1474 (n=22).

c. From Intensive PK analysis of cohort 3 of Trial 1474 (n=12 except n=11 for C_{trough} for FTC).

Race and Gender

No clinically relevant changes in the pharmacokinetics of BIC, FTC, and TAF were observed based on gender or race.

Drug Interaction Studies

As BIKTARVY is a complete regimen for the treatment of HIV-1 infection, comprehensive information regarding potential drug-drug interactions with other antiretroviral agents is not provided.

BIC is a substrate of CYP3A and UGT1A1.

BIC is an inhibitor of OCT2 and MATE1. At clinically relevant concentrations, BIC is not an inhibitor of hepatic transporters OATP1B1, OATP1B3, OCT1, BSEP, renal transporters OAT1 and OAT3, or CYP (including CYP3A) or UGT1A1 enzymes.

TAF is a substrate of P-gp and BCRP.

At clinically relevant concentrations, TAF is not an inhibitor of drug transporters P-gp, BCRP, hepatic transporters OATP1B1, OATP1B3, OCT1, BSEP, renal transporters OAT1, OAT3, OCT2, MATE1, or CYP (including CYP3A) or UGT1A1 enzymes.

Drug interaction studies were conducted with BIKTARVY or its components. Tables 9 and 10 summarize the pharmacokinetic effects of other drugs on BIC and TAF, respectively. Table 11 summarizes the pharmacokinetic effects of BIKTARVY or its components on other drugs.

Effect of Other Drugs on BIKTARVY Components

Table 9 Effect of Other Drugs on BIC[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	BIC (mg)	Mean Ratio of BIC Pharmacokinetic Parameters (90% CI); No effect = 1.00		
			C_{max}	AUC	C_{min}
Ledipasvir/ Sofosbuvir (fed)	90/400 once daily	75 once daily	0.98 (0.94, 1.03)	1.00 (0.97, 1.03)	1.04 (0.99, 1.09)
Rifabutin (fasted)	300 once daily	75 once daily	0.80 (0.67, 0.97)	0.62 (0.53, 0.72)	0.44 (0.37, 0.52)
Rifampin (fed)	600 once daily	75 single dose	0.72 (0.67, 0.78)	0.25 (0.22, 0.27)	NA
Sofosbuvir/ velpatasvir/ voxilaprevir (fed)	400/100/100+100 voxilaprevir[b] once daily	50 once daily	0.98 (0.94, 1.01)	1.07 (1.03, 1.10)	1.10 (1.05, 1.17)
Voriconazole (fasted)	300 twice daily	75 single dose	1.09 (0.96, 1.23)	1.61 (1.41, 1.84)	NA

Coadministered Drug	Dose of Coadministered Drug (mg)	BIC (mg)	Mean Ratio of BIC Pharmacokinetic Parameters (90% CI); No effect = 1.00		
			C_{max}	AUC	C_{min}
Maximum strength antacid (simultaneous administration, fasted)	20 mL[c] single dose (oral)	50 single dose	0.20 (0.16, 0.24)	0.21 (0.18, 0.26)	NA
Maximum strength antacid (2 h after BIKTARVY fasted)	20 mL[c] single dose (oral)	50 single dose	0.93 (0.88, 1.00)	0.87 (0.81, 0.93)	NA
Maximum strength antacid (2 h before BIKTARVY fasted)	20 mL[c] single dose (oral)	50 single dose	0.42 (0.33, 0.52)	0.48 (0.38, 0.59)	NA
Maximum strength antacid (simultaneous administration, fed[d])	20 mL[c] single dose (oral)	50 single dose	0.51 (0.43, 0.62)	0.53 (0.44, 0.64)	NA
Calcium carbonate (simultaneous administration, fasted)	1200 single dose	50 single dose	0.58 (0.51, 0.67)	0.67 (0.57, 0.78)	NA
Calcium carbonate (simultaneous administration, fed[d])	1200 single dose	50 single dose	0.90 (0.78, 1.03)	1.03 (0.89, 1.20)	NA
Ferrous fumarate (simultaneous administration, fasted)	324 single dose	50 single dose	0.29 (0.26, 0.33)	0.37 (0.33, 0.42)	NA
Ferrous fumarate (simultaneous administration, fed[d])	324 single dose	50 single dose	0.75 (0.65, 0.87)	0.84 (0.74, 0.95)	NA

NA= Not Applicable

a. All interaction studies conducted in healthy volunteers.

b. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected

patients.

c. Maximum strength antacid contained 80 mg aluminum hydroxide, 80 mg magnesium hydroxide, and 8 mg simethicone, per mL.

d. Reference treatment administered under fasted conditions.

Table 10 Effect of Other Drugs on TAF[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Tenofovir Alafenamide (mg)	Mean Ratio of Tenofovir Alafenamide Pharmacokinetic Parameters (90% CI); No effect = 1.00		
			C_{max}	AUC	C_{min}
Carbamazepine	300 twice daily	25 single dose[b]	0.43 (0.36, 0.51)	0.46 (0.40, 0.54)	NA
Ledipasvir/sofosbuvir	90/400 once daily	25 once daily	1.17 (1.00, 1.38)	1.27 (1.19, 1.34)	NA
Sofosbuvir/ velpatasvir/ voxilaprevir	400/100/100 +100 voxilaprevir[c] once daily	25 once daily	1.28 (1.09, 1.51)	1.57 (1.44, 1.71)	NA

NA= Not Applicable

a. All interaction studies conducted in healthy volunteers.

b. Study conducted with emtricitabine/tenofovir alafenamide.

c. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Effect of BIKTARVY Components on Other Drugs

Table 11 Effect of Components of BIKTARVY on Other Drugs[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	BIC (mg)	TAF (mg)	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Ledipasvir	90/400 once daily	75 once daily	25 once daily	0.85 (0.81, 0.90)	0.87 (0.83, 0.92)	0.90 (0.84, 0.96)
Sofosbuvir				1.11 (1.00, 1.24)	1.07 (1.01, 1.13)	NA
GS-331007[b]				1.10 (1.07, 1.13)	1.11 (1.08, 1.14)	1.02 (0.99, 1.06)
Metformin	500 twice daily	50 once daily	25 once daily	1.28 (1.21, 1.36)	1.39 (1.31, 1.48)	1.36 (1.21, 1.53)
Midazolam	2 single dose	50 once daily	25 once daily	1.03 (0.87, 1.23)	1.15 (1.00, 1.31)	NA
Norelgestromin	norgestimate 0.180/0.215/0.250 once daily / ethinyl estradiol 0.025 once daily	75 once daily	-	1.23 (1.14, 1.32)	1.08 (1.05, 1.10)	1.10 (1.05, 1.15)
Norgestrel				1.15 (1.10, 1.21)	1.13 (1.07, 1.19)	1.14 (1.06, 1.22)

Coadministered Drug	Dose of Coadministered Drug (mg)	BIC (mg)	TAF (mg)	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Ethinyl estradiol				1.15 (1.03, 1.27)	1.04 (0.99, 1.10)	1.05 (0.95, 1.14)
Norelgestromin	norgestimate 0.180/0.215/0.250 once daily / ethinyl estradiol 0.025 once daily	-	25 once daily [c]	1.17 (1.07,1.26)	1.12 (1.07,1.17)	1.16 (1.08, 1.24)
Norgestrel				1.10 (1.02, 1.18)	1.09 (1.01, 1.18)	1.11 (1.03, 1.20)
Ethinyl estradiol				1.22 (1.15, 1.29)	1.11 (1.07, 1.16)	1.02 (0.92, 1.12)
Sertraline	50 single dose	-	10 once daily [d]	1.14 (0.94, 1.38)	0.93 (0.77, 1.13)	NA
Sofosbuvir	400/100/100+ 100[e] once daily	50 once daily	25 once daily	1.14 (1.04,1.25)	1.09 (1.02, 1.15)	NA
GS-331007[b]				1.03 (0.99,1.06)	1.03 (1.00,1.06)	1.01 (0.98, 1.05)
Velpatasvir				0.96 (0.91,1.01)	0.96 (0.90, 1.02)	0.94 (0.88, 1.01)
Voxilaprevir				0.90 (0.76, 1.06)	0.91 (0.80, 1.03)	0.97 (0.88, 1.06)

NA= Not Applicable

a. All interaction studies conducted in healthy volunteers.
b. The predominant circulating nucleoside metabolite of sofosbuvir.
c. Study conducted with emtricitabine/tenofovir alafenamide.
d. Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.
e. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

12.4 Microbiology

Mechanism of Action

Bictegravir: BIC inhibits the strand transfer activity of HIV-1 integrase (integrase strand transfer inhibitor; INSTI), an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the integration of linear HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the virus.

Emtricitabine: FTC, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5′-triphosphate is a weak

inhibitor of mammalian DNA polymerases α, β, Ɛ, and mitochondrial DNA polymerase γ.

Tenofovir Alafenamide: TAF is a phosphonamidate prodrug of tenofovir (2′-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

Antiviral Activity in Cell Culture

The triple combination of BIC, FTC, and TAF was not antagonistic with respect to antiviral activity in cell culture.

Bictegravir: The antiviral activity of BIC against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells, and CD4+ T-lymphocytes. In MT-4 cells (human lymphoblastoid T-cell line) acutely infected with HIV-1 IIIB, the mean 50% effective concentration (EC_{50}) was 2.4±0.4 nM, and the protein-adjusted EC_{95} value was 361 nM (0.162 micrograms per mL). BIC displayed antiviral activity in activated PBMCs against clinical isolates of HIV-1 representing groups M, N, and O, including subtypes A, B, C, D, E, F, and G, with a median EC_{50} value of 0.55 nM (range <0.05 to 1.71 nM). The EC_{50} value against a single HIV-2 isolate was 1.1 nM.

Emtricitabine: The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, the MAGI-CCR5 cell line, and PBMCs. In PBMCs acutely infected with HIV-1 subtypes A, B, C, D, E, F, and G, the median EC_{50} value for FTC was 9.5 nM (range 1 to 30 nM) and against HIV-2 was 7 nM.

Tenofovir Alafenamide: The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4-T lymphocytes. The EC_{50} values for TAF ranged from 2.0 to 14.7 nM. TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including subtypes A, B, C, D, E, F, and G (EC_{50} values ranged from 0.1 to 12 nM) and strain specific activity against HIV-2 (EC_{50} values ranged from 0.9 to 2.6 nM).

Resistance

In Cell Culture

Bictegravir: HIV-1 isolates with reduced susceptibility to BIC have been selected in cell culture. In one selection with BIC, a virus pool emerged expressing amino acid substitutions M50I and R263K in the HIV-1 integrase. M50I, R263K, and M50I+R263K substitutions, when introduced into a wild-type virus by site-directed

mutagenesis, conferred 1.3-, 2.2-, and 2.9-fold reduced susceptibility to BIC, respectively. In a second selection, emergence of amino acid substitutions T66I and S153F was detected, and 0.4-, 1.9-, and 0.5-fold reductions in BIC susceptibility were observed with T66I, S153F, and T66I+S153F, respectively. In addition, S24G and E157K substitutions emerged during the selection process.

Emtricitabine: HIV-1 isolates with reduced susceptibility to FTC were selected in cell culture and in subjects treated with FTC. Reduced susceptibility to FTC was associated with M184V or I substitutions in HIV-1 RT.

Tenofovir Alafenamide: HIV-1 isolates with reduced susceptibility to TAF were selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R substitution in HIV-1 RT, sometimes in the presence of S68N or L429I substitutions; in addition, a K70E substitution in HIV-1 RT was observed.

In Clinical Trials

In Subjects with No Antiretroviral Treatment History: Pooled results of genotypic resistance analyses were performed on paired baseline and on-treatment HIV-1 isolates from subjects receiving BIKTARVY in Trials 1489 and 1490 through Week 144 of the double-blind phase (N=634) or Week 96 of the extension phase (n=1025) *[see Clinical Studies (14.2)]* who had HIV-1 RNA greater than or equal to 200 copies/mL at the time of confirmed virologic failure or early study drug discontinuation. In the final resistance analysis population, no specific amino acid substitutions emerged consistently in the 11 treatment failure subjects with evaluable genotypic resistance data and failed to establish an association with genotypic BIC resistance. There were no treatment-emergent NRTI resistance-associated substitutions detected in the 11 evaluated treatment failure isolates. Phenotypic resistance analyses of failure isolates found fold-changes in drug susceptibility below the biological or clinical cutoffs for BIC, FTC, and TFV, compared to wild-type reference HIV-1.

In Virologically Suppressed Adult Subjects: In 2 switch trials, Trials 1844 and 1878 *[see Clinical Studies (14.3)]*, of virologically suppressed HIV-1 infected subjects (n=572), only one subject with virologic rebound in the resistance analysis population had IN genotypic and phenotypic data, and 2 rebounders had RT genotypic and phenotypic data. No subjects had HIV-1 with treatment-emergent genotypic or phenotypic resistance to BIC, FTC, or TAF.

In Virologically Suppressed Pediatric Subjects: In Trial 1474 *[see Clinical Studies (14.4)]*, two of 50 subjects in cohort 1 were evaluated for the development of resistance through Week 48; no amino acid substitutions known to be associated with resistance to BIC, FTC, or TFV were detected. No subjects in cohort 2 or 3 met the criteria for resistance analyses through Week 24.

Cross-Resistance

Bictegravir: Cross-resistance has been observed among INSTIs. The susceptibility of BIC was tested against 64 clinical isolates expressing known INSTI resistance-

associated substitutions listed by IAS-USA (20 with single substitutions and 44 with 2 or more substitutions). Isolates with a single INSTI-resistance substitution including E92Q, T97A, Y143C/R, Q148R, and N155H showed less than 2-fold reduced susceptibility to BIC. All isolates (n=14) with more than 2.5-fold reduced susceptibility to BIC (above the biological cutoff for BIC) contained G140A/C/S and Q148H/R/K substitutions; the majority (64.3%, 9/14) had a complex INSTI resistance pattern with an additional INSTI-resistance substitution L74M, T97A, or E138A/K. Of those evaluated isolates containing G140A/C/S and Q148H/R/K substitutions in the absence of additional INSTI-resistance substitutions, 38.5% (5/13) showed more than 2.5-fold reduction. In addition, site-directed mutant viruses with G118R (dolutegravir and raltegravir treatment-emergent substitution) and G118R+T97A had 3.4- and 2.8-fold reduced susceptibility to BIC, respectively.

BIC demonstrated equivalent antiviral activity with less than 2-fold reductions in susceptibility against HIV-1 variants expressing substitutions associated with resistance to NNRTIs, NRTIs, and PIs, compared with the wild-type virus.

Emtricitabine: Cross-resistance has been observed among NRTIs. FTC-resistant viruses with an M184V/I substitution in HIV-1 RT were cross-resistant to lamivudine. HIV-1 isolates containing the K65R RT substitution, selected *in vivo* by abacavir, didanosine, and tenofovir, demonstrated reduced susceptibility to inhibition by FTC.

Tenofovir Alafenamide: Cross-resistance has been observed among NRTIs. Tenofovir resistance substitutions K65R and K70E result in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir. HIV-1 with multiple thymidine analog substitutions (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N/R), or multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M substitution complex including K65R, showed reduced susceptibility to TAF in cell culture.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Bictegravir

BIC was not carcinogenic in a 6-month rasH2 transgenic mouse study at doses of up to 100 mg/kg/day in males and 300 mg/kg/day in females. BIC was not carcinogenic in a 2-year rat study at doses up to 300 mg/kg/day, which resulted in exposures of approximately 31 times the exposure in humans at the recommended dose of BIKTARVY.

BIC was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

BIC did not affect fertility, reproductive performance or embryonic viability in male and female rats at 29 times higher exposures (AUC) than in humans at the recommended dose of BIKTARVY.

Emtricitabine

In long-term carcinogenicity studies of FTC, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg per kg per day (25 times the human systemic exposure at the recommended dose of BIKTARVY) or in rats at doses up to 600 mg per kg per day (30 times the human systemic exposure at the recommended dose of BIKTARVY).

FTC was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

FTC did not affect fertility in male rats at approximately 140 times or in male and female mice at approximately 60 times higher exposures (AUC) than in humans given the recommended dose of BIKTARVY. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60 times higher than human exposures at the recommended dose of BIKTARVY.

Tenofovir Alafenamide

Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans following a 300 mg dose of TDF. The tenofovir exposure in these studies was approximately 151 times (mice) and 51 times (rat) those observed in humans after administration of the daily recommended dose of BIKTARVY. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 151 times the exposure observed in humans at the recommended dose of BIKTARVY. In rats, the study was negative for carcinogenic findings.

TAF was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

There were no effects on fertility, mating performance or early embryonic development when TAF was administered to male rats at a dose equivalent to 155 times the human dose of BIKTARVY based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through Day 7 of gestation.

13.2 Animal Toxicology and/or Pharmacology

Minimal to slight infiltration of mononuclear cells in the posterior uvea was observed in dogs with similar severity after three and nine month administration of TAF; reversibility was seen after a three month recovery period. No eye toxicity was observed in the dog at systemic exposures of 7 (TAF) and 14 (tenofovir) times the exposure seen in humans with the recommended daily dose of BIKTARVY.

14 CLINICAL STUDIES

14.1 Description of Clinical Trials

The efficacy and safety of BIKTARVY were evaluated in the trials summarized in Table 12.

Table 12 Trials Conducted with BIKTARVY in Subjects with HIV-1 Infection

Trial	Population	Trial Arms (N)	Timepoint (Week)
Trial 1489[a] (NCT 02607930)	Adults with no antiretroviral treatment history	BIKTARVY (314) ABC/DTG/3TC (315)	144 + 96 (OLE)[b]
Trial 1490[a] (NCT 02607956)		BIKTARVY (320) DTG + FTC/TAF(325)	144 + 96 (OLE)[b]
Trial 1844[a] (NCT 02603120)	Virologically-suppressed[d] adults	BIKTARVY (282) ABC/DTG/3TC (281)	48
Trial 1878[c] (NCT 02603107)		BIKTARVY (290) ATV or DRV (with cobicistat or ritonavir) plus either FTC/TDF or ABC/3TC (287)	48
Trial 1825[e] (NCT 02600819)	Virologically-suppressed[d] adults with ESRD[f] receiving chronic hemodialysis	FTC+TAF in combination with elvitegravir and cobicistat as a fixed-dose combination (55). In an extension phase of Trial 1825, 10 virologically-suppressed subjects switched to BIKTARVY.	48[g]
Trial 4449[e] (NCT 03405935)	Virologically-suppressed[d] adults aged 65 years and over	BIKTARVY (86)	48
Trial 1474[e] (cohort 1) (NCT 02881320)	Virologically-suppressed[d] adolescents between the ages of 12 to less than 18 years (at least 35 kg)	BIKTARVY (50)	48
Trial 1474[e] (cohort 2) (NCT 02881320)	Virologically-suppressed[d] children between the ages of 6 to less than 12 years (at least 25 kg)	BIKTARVY (50)	24
Trial 1474[e] (cohort 3) (NCT 02881320)	Virologically- suppressed[d] children at least 2 years of age (at least 14 to less than 25 kg)	BIKTARVY (22)	24

OLE = open-label extension

a. Randomized, double blind, active controlled trial.

b. 144-week double-blind active controlled phase followed by an extension phase in which 1025 subjects from Trials 1489 and 1490 received open-label BIKTARVY for 96 weeks.

c. Randomized, open-label, active controlled trial.

d. HIV-1 RNA less than 50 copies per mL.

e. Open-label trial.

f. End stage renal disease (estimated creatinine clearance of less than 15 mL/min by Cockcroft-Gault method).
g. Subjects received FTC+TAF in combination with elvitegravir and cobicistat for 96 weeks, followed by an extension phase in which 10 subjects received BIKTARVY for 48 weeks.

14.2 Clinical Trial Results in Adults with HIV-1 and No Antiretroviral Treatment History

In Trial 1489, adults were randomized in a 1:1 ratio to receive either BIKTARVY (containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF) (N=314) or ABC/DTG/3TC (600 mg/50 mg/300 mg) (N=315) once daily. In Trial 1490, subjects were randomized in a 1:1 ratio to receive either BIKTARVY (N=320) or DTG + FTC/TAF (50 mg + 200 mg/25 mg) (N=325) once daily.

In Trial 1489, the mean age was 34 years (range 18–71), 90% were male, 57% were White, 36% were Black, and 3% were Asian. 22% of patients identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.4 $\log_{10}$ copies/mL (range 1.3–6.5). The mean baseline CD4+ cell count was 464 cells per mm^3 (range 0–1424) and 11% had CD4+ cell counts less than 200 cells per mm^3. 16% of subjects had baseline viral loads greater than 100,000 copies per mL.

In Trial 1490, the mean age was 37 years (range 18–77), 88% were male, 59% were White, 31% were Black, and 3% were Asian. 25% of patients identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.4 $\log_{10}$ copies/mL (range 2.3–6.6). The mean baseline CD4+ cell count was 456 cells per mm^3 (range 2–1636) and 12% had CD4+ cell counts less than 200 cells per mm^3. 19% of subjects had baseline viral loads greater than 100,000 copies per mL.

In both trials, subjects were stratified by baseline HIV-1 RNA (less than or equal to 100,000 copies per mL, greater than 100,000 copies per mL to less than or equal to 400,000 copies per mL, or greater than 400,000 copies per mL), by CD4 count (less than 50 cells per mm^3, 50-199 cells per mm^3, or greater than or equal to 200 cells per mm^3), and by region (US or ex-US).

Treatment outcomes of Trials 1489 and 1490 through Week 144 are presented in Table 13.

Table 13 Virologic Outcomes of Randomized Treatment in Trials 1489 and 1490 at Week 144[a] in Adults with No Antiretroviral Treatment History

	Trial 1489		Trial 1490	
	BIKTARVY (N=314)	**ABC/DTG/3TC** (N=315)	**BIKTARVY** (N=320)	**DTG + FTC/TAF** (N=325)
HIV-1 RNA < 50 copies/mL	82%	84%	82%	84%
Treatment Difference (95% CI) BIKTARVY vs. Comparator	-2.6% (-8.5% to 3.4%)		-1.9% (-7.8% to 3.9%)	
HIV-1 RNA ≥ 50 copies/mL[b]	1%	3%	5%	3%
No Virologic Data at Week 144 Window	18%	13%	13%	13%
Discontinued Study Drug Due to AE or Death[c]	1%	2%	3%	3%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL[d]	16%	11%	11%	9%
Missing Data During Window but on Study Drug	1%	<1%	0%	1%

a. Week 144 window was between Day 967 and 1050 (inclusive).

b. Includes subjects who had ≥ 50 copies/mL in the Week 144 window; subjects who discontinued early due to lack or loss of efficacy; subjects who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

c. Includes subjects who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

d. Includes subjects who discontinued for reasons other than an AE, death, or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Treatment outcomes were similar across subgroups by age, sex, race, baseline viral load, and baseline CD4+ cell count.

In Trials 1489 and 1490, the mean increase from baseline in CD4+ count at Week 144 was 299 and 317 cells per mm^3 in the BIKTARVY and ABC/DTG/3TC groups, respectively, and 278 and 289 cells per mm^3 in the BIKTARVY and DTG + FTC/TAF groups, respectively.

14.3 Clinical Trial Results in Adults with Virologically-Suppressed HIV-1 Who Switched to BIKTARVY

In Trial 1844, the efficacy and safety of switching from a regimen of DTG + ABC/3TC or ABC/DTG/3TC to BIKTARVY were evaluated in a randomized, double-blind trial of virologically-suppressed (HIV-1 RNA less than 50 copies per mL) HIV-1 infected adults (N=563, randomized and dosed). Subjects must have been stably suppressed (HIV-1 RNA less than 50 copies per mL) on their baseline regimen for at least 3 months prior to trial entry and had no history of treatment failure. Subjects were randomized in a 1:1 ratio to either switch to BIKTARVY (containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF) at baseline (N=282), or stay on their baseline antiretroviral regimen

(N=281). Subjects had a mean age of 45 years (range 20–71), 89% were male, 73% were White, and 22% were Black. 17% of subjects identified as Hispanic/Latino. The mean baseline CD4+ cell count was 723 cells per mm^3 (range 124–2444).

In Trial 1878, the efficacy and safety of switching from either ABC/3TC or FTC/TDF (200/300 mg) plus ATV or DRV (given with either cobicistat or ritonavir) to BIKTARVY (containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF) were evaluated in a randomized, open-label study of virologically-suppressed HIV-1 infected adults (N=577, randomized and dosed). Subjects must have been stably suppressed on their baseline regimen for at least 6 months, must not have been previously treated with any INSTI, and had no history of treatment failure. Subjects were randomized in a 1:1 ratio to either switch to BIKTARVY (N=290) or stay on their baseline antiretroviral regimen (N=287). Subjects had a mean age of 46 years (range 20–79), 83% were male, 66% were White, and 26% were Black. 19% of subjects identified as Hispanic/Latino. The mean baseline CD4+ cell count was 663 cells per mm^3 (range 62–2582). Subjects were stratified by prior treatment regimen. At screening, 15% of subjects were receiving ABC/3TC plus ATV or DRV (given with either cobicistat or ritonavir) and 85% of subjects were receiving FTC/TDF plus ATV or DRV (given with either cobicistat or ritonavir).

Treatment outcomes of Trials 1844 and 1878 through Week 48 are presented in Table 14.

Table 14 Virologic Outcomes of Trials 1844 and 1878 at Week 48[a] in Virologically-Suppressed Adults who Switched to BIKTARVY

	Trial 1844		Trial 1878	
	BIKTARVY (N=282)	**ABC/DTG/3TC** (N=281)	**BIKTARVY** (N=290)	**ATV- or DRV-based regimen[b]** (N=287)
HIV-1 RNA ≥ 50 copies/mL[c]	1%	<1%	2%	2%
Treatment Difference (95% CI)	0.7% (-1.0% to 2.8%)		0.0% (-2.5% to 2.5%)	
HIV-1 RNA < 50 copies/mL	94%	95%	92%	89%
No Virologic Data at Week 48 Window	5%	5%	6%	9%
Discontinued Study Drug Due to AE or Death and Last Available HIV-1 RNA < 50 copies/mL	2%	1%	1%	1%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d]	2%	3%	3%	7%
Missing Data During Window but on Study Drug	2%	1%	2%	2%

a. Week 48 window was between Day 295 and 378 (inclusive).
b. ATV given with cobicistat or ritonavir or DRV given with cobicistat or ritonavir plus either FTC/TDF or ABC/3TC.
c. Includes subjects who had ≥ 50 copies/mL in the Week 48 window; subjects who discontinued early due to lack or loss of efficacy; subjects who discontinued for reasons other than lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
d. Includes subjects who discontinued for reasons other than an AE, death, or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

In Trial 1844, treatment outcomes between treatment groups were similar across subgroups by age, sex, race, and region. The mean change from baseline in CD4+ count at Week 48 was -31 cells per mm^3 in subjects who switched to BIKTARVY and 4 cells per mm^3 in subjects who stayed on ABC/DTG/3TC.

In Trial 1878, treatment outcomes between treatment groups were similar across subgroups by age, sex, race, and region. The mean change from baseline in CD4+ count at Week 48 was 25 cells per mm^3 in patients who switched to BIKTARVY and 0 cells per mm^3 in patients who stayed on their baseline regimen.

In Trial 1825, an open-label single arm trial, the efficacy, safety, and pharmacokinetics of FTC and TAF (components of BIKTARVY) were evaluated in virologically-suppressed adults with ESRD (estimated creatinine clearance of less than 15 mL/min) on chronic hemodialysis treated with FTC+TAF in combination with elvitegravir and cobicistat as a fixed-dose combination tablet for 96 weeks (N=55). In an extension phase of Trial 1825,

10 virologically-suppressed subjects switched to BIKTARVY and all subjects remained virologically suppressed (HIV-1 RNA < 50 copies/mL) for 48 weeks.

In Trial 4449, the efficacy and safety of switching from a stable antiretroviral regimen to BIKTARVY (containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF) were evaluated in an open-label, single arm trial of virologically-suppressed (HIV-1 RNA less than 50 copies per mL) HIV-1 infected adults aged 65 years and over (N=86). Subjects treated with BIKTARVY had a mean age of 70 years (range: 65 to 80). The primary endpoint was the proportion of subjects with HIV RNA > 50 copies/mL at Week 48. No subjects had HIV RNA > 50 copies/mL. Ninety-one percent (78/86) of subjects remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 48. Eight subjects did not have virologic data at the Week 48 timepoint due to discontinuation or missing data.

14.4 Clinical Trial Results in Pediatric Subjects with HIV-1

In Trial 1474, an open-label, single arm trial the efficacy, safety, and pharmacokinetics of BIKTARVY in HIV-1 infected pediatric subjects were evaluated in virologically-suppressed adolescents between the ages of 12 to less than 18 years weighing at least 35 kg (N=50), in virologically-suppressed children between the ages of 6 to less than 12 years weighing at least 25 kg (N=50), and in virologically-suppressed children at least 2 years of age and weighing at least 14 to less than 25 kg (N=22).

Cohort 1: Virologically-suppressed adolescents (12 to less than 18 years; at least 35 kg)

Subjects in cohort 1 treated with BIKTARVY (containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF) once daily had a mean age of 14 years (range: 12 to 17) and a mean baseline weight of 51.7 kg (range: 35 to 123), 64% were female, 27% were Asian and 65% were black. At baseline, median CD4+ cell count was 750 cells per mm^3 (range: 337 to 1207), and median CD4+% was 33% (range: 19% to 45%).

After switching to BIKTARVY, 98% (49/50) of subjects in cohort 1 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 48. The mean change from baseline in CD4+ cell count at Week 48 was -22 cells per mm^3.

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Subjects in cohort 2 treated with BIKTARVY once daily had a mean age of 10 years (range: 6 to 11) and a mean baseline weight of 31.9 kg (range: 25 to 69), 54% were female, 22% were Asian and 72% were black. At baseline, median CD4+ cell count was 898 cells per mm^3 (range 390 to 1991) and median CD4+% was 37% (range: 19% to 53%).

After switching to BIKTARVY (containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF), 100% (50/50) of subjects in cohort 2 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 24. The mean change from baseline in CD4+ cell count at Week 24 was -24 cells per mm^3.

Cohort 3: Virologically-suppressed children (at least 2 years; at least 14 to less than 25 kg)

Subjects in cohort 3 treated with BIKTARVY (containing 30 mg of BIC, 120 mg of FTC, and 15 mg of TAF) once daily had a mean age of 5 years (range: 3 to 9) and a mean baseline weight of 18.8 kg (range: 14 to 24), 50% were female, 23% were Asian and 73% were black. At baseline, the mean CD4+ cell count (SD) was 1104 (440), and the mean CD4% (SD) was 33.4% (6.0%).

After switching to BIKTARVY, 91% (20/22) of subjects in cohort 3 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 24. HIV-1 RNA was not collected at Week 24 for 2 subjects because of COVID-19 pandemic-related study disruption. The mean change from baseline to Week 24 in CD4+ cell count (SD) was −126 (264.2) cells per mm^3 ; and the mean change in CD4% (SD) from baseline to Week 24 was 0.2% (4.4%).

16 HOW SUPPLIED/STORAGE AND HANDLING

BIKTARVY tablets are available in bottles and blister packs:

Bottle

- 50 mg/200 mg/25 mg tablets each contain 50 mg of bictegravir (BIC), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF). These tablets are purplish brown, capsule-shaped, and film-coated with “GSI” debossed on one side and “9883” on the other side (NDC 61958-2501-1).
- 30 mg/120 mg/15 mg tablets each contain 30 mg of BIC,120 mg of FTC, and 15 mg of TAF. These tablets are pink, capsule-shaped, and film-coated with “GSI” debossed on one side and “B” on the other side (NDC 61958-2505-1).

Each bottle contains 30 tablets, a silica gel desiccant, polyester coil, and is closed with a child-resistant closure. Do not remove the desiccant packet.

Store bottle below 30 °C (86 °F).

Keep bottle tightly closed.

Blister Pack

- 50 mg/200 mg/25 mg tablets each contain 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF. These tablets are purplish brown, capsule-shaped, and film-coated with “GSI” debossed on one side and “9883” on the other side (NDC 61958-2501-3).

Each blister pack contains 30 tablets (4 strips each containing 7 tablets and 1 strip containing 2 tablets). Blister packs are sealed with a child-resistant laminated foil lidding material (peel-push), and each blister cavity contains a die-cut desiccant film which is heat staked to the foil lidding material.

Store blister pack at 25 °C (77 °F), excursions permitted to 15–30 °C (59–86 °F) (see USP Controlled Room Temperature).

Dispense only in original containers.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Post-treatment Acute Exacerbation of Hepatitis B in Patients with HBV Coinfection

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued products containing FTC and/or TDF, and may likewise occur with discontinuation of BIKTARVY *[see Warnings and Precautions (5.1)]*. Advise the patient to not discontinue BIKTARVY without first informing their healthcare provider.

Drug Interactions

BIKTARVY may interact with certain drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or non-prescription medication or herbal products including St. John's wort *[see Contraindications (4) and Drug Interactions (7)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any symptoms of infection, as in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started *[see Warnings and Precautions (5.3)]*.

Renal Impairment

Advise patients to avoid taking BIKTARVY with concurrent or recent use of nephrotoxic agents. Postmarketing cases of renal impairment, including acute renal failure, have been reported *[see Warnings and Precautions (5.4)].*

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to BIKTARVY. Advise patients that they should stop BIKTARVY if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.5)]*.

Missed Dosage

Inform patients that it is important to take BIKTARVY on a regular dosing schedule with or without food and to avoid missing doses as it can result in development of resistance *[see Dosage and Administration (2.2)]*.

Tablet Splitting

Advise caregivers that, 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 *[see Dosage and Administration (2.3)]*.

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to BIKTARVY *[see Use in Specific Populations (8.1)].*

Lactation

Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in breast milk *[see Use in Specific Populations (8.2)].*

Patient Information
BIKTARVY® (bik-TAR-vee)
(bictegravir, emtricitabine,
and tenofovir alafenamide)
tablets

Important: Ask your healthcare provider or pharmacist about medicines that should not be taken with BIKTARVY. For more information, see "What should I tell my healthcare provider before taking BIKTARVY?"

What is the most important information I should know about BIKTARVY?

BIKTARVY can cause serious side effects, including:

- **Worsening of hepatitis B virus (HBV) infection. Your healthcare provider will test you for HBV infection before or when you start treatment with BIKTARVY. If you have HBV infection and take BIKTARVY, your HBV may get worse (flare-up) if you stop taking BIKTARVY. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.**
  - Do not run out of BIKTARVY. Refill your prescription or talk to your healthcare provider before your BIKTARVY is all gone.
  - Do not stop taking BIKTARVY without first talking to your healthcare provider.
  - If you stop taking BIKTARVY, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver, and may give you a medicine to treat hepatitis B. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking BIKTARVY.

For more information about side effects, see "What are the possible side effects of BIKTARVY?"

What is BIKTARVY?

BIKTARVY is a prescription medicine that is used without other human immunodeficiency virus-1 (HIV-1) medicines to treat HIV-1 infection in adults and children who weigh at least 31 pounds (14 kg):

- who have not received HIV-1 medicines in the past, **or**
- to replace their current HIV-1 medicines for people whose healthcare provider determines that they meet certain requirements.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

BIKTARVY contains the medicines bictegravir, emtricitabine, and tenofovir alafenamide.

It is not known if BIKTARVY is safe and effective in children who weigh less than 31 pounds (14 kg).

Do not take BIKTARVY if you also take a medicine that contains:

- dofetilide
- rifampin

What should I tell my healthcare provider before taking BIKTARVY?

Before taking BIKTARVY, tell your healthcare provider about all your medical conditions, including if you:

- have liver problems, including HBV infection
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if BIKTARVY can harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with BIKTARVY.

  Pregnancy Registry: There is a pregnancy registry for women who take BIKTARVY during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. Do not breastfeed if you take BIKTARVY.
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - At least one of the medicines in BIKTARVY can pass to your baby in your breast milk. It is not known if the other medicines in BIKTARVY can pass into your breast milk.

  Talk with your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, antacids, laxatives, vitamins, and herbal supplements.

Some medicines may interact with BIKTARVY. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with BIKTARVY.

- **Do not start a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take BIKTARVY with other medicines.

How should I take BIKTARVY?

- Take BIKTARVY exactly as your healthcare provider tells you to take it. BIKTARVY is taken by itself (not with other HIV-1 medicines) to treat HIV-1 infection.
- Take BIKTARVY 1 time each day 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 swallowed within about 10 minutes.
- If you are on dialysis, take your daily dose of BIKTARVY following dialysis.
- Do not change your dose or stop taking BIKTARVY without first talking with your healthcare provider. Stay under a healthcare provider's care during treatment with BIKTARVY.
- If you take antacids that contain aluminum or magnesium, take BIKTARVY at least 2 hours before or 6 hours after you take these antacids.
- If you take supplements or antacids that contain iron or calcium, take BIKTARVY with food at the same time that you take these supplements or antacids.
- Do not miss a dose of BIKTARVY.
- If you take too much BIKTARVY, call your healthcare provider or go to the nearest hospital emergency room right away.
- When your BIKTARVY supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to BIKTARVY and become harder to treat.

What are the possible side effects of BIKTARVY?

BIKTARVY may cause serious side effects, including:

- **See "What is the most important information I should know about BIKTARVY?"**
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having any new symptoms after starting your HIV-1 medicine.
- **New or worse kidney problems, including kidney failure.** Your healthcare provider should do blood and urine tests to check your kidneys when starting and during treatment with BIKTARVY. Your healthcare provider may tell you to stop taking BIKTARVY if you develop new or worse kidney problems.
- **Too much lactic acid in your blood (lactic acidosis).** Too much lactic acid is a serious but rare medical emergency that can lead to death. **Tell your healthcare provider right away if you get these symptoms:** weakness or being more tired than usual, unusual muscle pain, being short of breath or fast breathing, stomach pain with nausea and vomiting, cold or blue hands and feet, feel dizzy or lightheaded, or a fast or abnormal heartbeat.
- **Severe liver problems.** In rare cases, severe liver problems can happen that can lead to death. **Tell your healthcare provider right away if you get these symptoms:** skin or the white part of your eyes turns yellow, dark "tea-colored" urine, light-colored stools, loss of appetite for several days or longer, nausea, or stomach-area pain.

The most common side effects of BIKTARVY are diarrhea, nausea, and headache.
These are not all of the possible side effects of BIKTARVY.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BIKTARVY?

- Store BIKTARVY bottle below 86 °F (30 °C).
- Keep the bottle tightly closed.
- BIKTARVY contains a desiccant packet to help keep your medicine dry (protect it from moisture). Keep the desiccant packet in the bottle. **Do not eat the desiccant packet.**
- Store BIKTARVY blister pack at room temperature between 68 °F to 77 °F (20 °C to 25 °C).
- Keep BIKTARVY in its original bottle or blister pack.
- BIKTARVY comes in a child-resistant package.

Keep BIKTARVY and all medicines out of reach of children.

General information about the safe and effective use of BIKTARVY.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use BIKTARVY for a condition for which it was not prescribed. Do not give BIKTARVY to other people, even if they have the

same symptoms you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about BIKTARVY that is written for health professionals.

What are the ingredients in BIKTARVY?

Active ingredients: bictegravir, emtricitabine, and tenofovir alafenamide.

Inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

The tablets are film-coated with a coating material containing iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404

For more information, call 1-800-445-3235 or go to www.BIKTARVY.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised:10/2022

Proposed Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BIKTARVY safely and effectively. See full prescribing information for BIKTARVY.

BIKTARVY® (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, for oral use
Initial U.S. Approval: 2018

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B
See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of BIKTARVY. Closely monitor hepatic function in these patients. If appropriate, anti-hepatitis B therapy may be warranted. (5.1)

----------INDICATIONS AND USAGE----------
BIKTARVY is a three-drug combination of bictegravir (BIC), a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI), and emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV-1 nucleoside analog reverse transcriptase inhibitors (NRTIs), and is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 14 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY. (1)

----------DOSAGE AND ADMINISTRATION----------
- Testing: Prior to or when initiating BIKTARVY test for hepatitis B virus infection. Prior to or when initiating BIKTARVY, and during treatment, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus. (2.1)
- Recommended dosage in adults and pediatric patients weighing at least 25 kg: One tablet containing 50 mg BIC, 200 mg FTC, and 25 mg TAF taken once daily with or without food. (2.2)
- Recommended dosage in pediatric patients weighing at least 14 kg to less than 25 kg: One tablet containing 30 mg BIC, 120 mg FTC, and 15 mg TAF taken once daily with or without food. (2.3)
- Renal impairment: BIKTARVY is not recommended in patients with estimated creatinine clearance of 15 to below 30 mL/min, or below 15 mL/min who are not receiving chronic hemodialysis, or below 15 mL/min who have no antiretroviral treatment history. (2.4)
- Hepatic impairment: BIKTARVY is not recommended in patients with severe hepatic impairment. (2.5)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF. (3)
The 30 mg/120/mg/15mg tablets will not be imported by LifeScience Logistics.

----------CONTRAINDICATIONS----------
BIKTARVY is contraindicated to be co-administered with:
- dofetilide. (4)
- rifampin. (4)

----------WARNINGS AND PRECAUTIONS----------
- Immune reconstitution syndrome: May necessitate further evaluation and treatment. (5.3)
- New onset or worsening renal impairment: Assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein when initiating BIKTARVY and during therapy as clinically appropriate in all patients. Also assess serum phosphorus in patients with chronic kidney disease. (5.4)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.5)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence greater than or equal to 5%, all grades) are diarrhea, nausea, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact LifeScience Logistics at 1-855-738-6171 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Because BIKTARVY is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended. (7.1)
- Consult the Full Prescribing Information prior to and during treatment for important drug interactions. (4, 5.2, 7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission. (8.2)
- Pediatrics: Not recommended for patients weighing less than 14 kg. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of BIKTARVY.

Closely monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue BIKTARVY. If appropriate, anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

BIKTARVY is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing at least 14 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY.

2 DOSAGE AND ADMINISTRATION

2.1 Testing When Initiating and During Treatment with BIKTARVY

Prior to or when initiating BIKTARVY, test patients for hepatitis B virus infection *[see Warnings and Precautions (5.1)]*.

Prior to or when initiating BIKTARVY, and during treatment with BIKTARVY, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus *[see Warnings and Precautions (5.4)].*

2.2 Recommended Dosage in Adults and Pediatric Patients Weighing at Least 25 kg

BIKTARVY is a three-drug fixed dose combination product containing bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF). The recommended dosage of BIKTARVY 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:

- adults and pediatric patients weighing at least 25 kg with an estimated creatinine clearance greater than or equal to 30 mL/min; or
- virologically-suppressed adults with an estimated creatinine clearance below 15 mL/min who are receiving chronic hemodialysis. On days of hemodialysis, administer the daily dose of BIKTARVY after completion of hemodialysis treatment *[see Use in Specific Populations (8.4, 8.6) and Clinical Pharmacology (12.3)]*.

2.3 Recommended Dosage in Pediatric Patients Weighing at Least 14 kg to Less than 25 kg

The recommended dosage of BIKTARVY 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 in:

- pediatric patients weighing at least 14 kg to less than 25 kg with an estimated creatinine clearance greater than or equal to 30 mL/min *[see Use in Specific Populations (8.4, 8.6) and Clinical Pharmacology (12.3)]*.

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.

2.4 Not Recommended in Patients with Severe Renal Impairment

BIKTARVY is not recommended in patients with *[see Dosage and Administration (2.2, 2.3) and Use in Specific Populations (8.6)]*.:

- severe renal impairment (estimated creatinine clearance of 15 to below 30 mL/min); or
- end stage renal disease (ESRD; estimated creatinine clearance below 15 mL/min who are not receiving chronic hemodialysis; or
- no antiretroviral treatment history and ESRD who are receiving chronic hemodialysis.

2.5 Not Recommended in Patients with Severe Hepatic Impairment

BIKTARVY is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].*

3 DOSAGE FORMS AND STRENGTHS

BIKTARVY tablets are available in two dose strengths:

- 50 mg/200 mg/25 mg tablets: 50 mg of bictegravir (BIC) (equivalent to 52.5 mg of bictegravir sodium), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate). These tablets are purplish brown, capsule-shaped, film-coated, and debossed with “GSI” on one side and “9883” on the other side.
- The 30 mg/120/mg/15mg tablets will not be imported by LifeScience Logistics.

4 CONTRAINDICATIONS

BIKTARVY is contraindicated to be co-administered with:

- dofetilide due to the potential for increased dofetilide plasma concentrations and associated serious and/or life-threatening events *[see Drug Interactions (7.5)]*.
- rifampin due to decreased BIC plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to BIKTARVY *[see Drug Interactions (7.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV

Patients with HIV-1 should be tested for the presence of chronic hepatitis B virus (HBV) infection before or when initiating antiretroviral therapy *[see Dosage and Administration (2.1)]*.

Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing FTC and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of BIKTARVY. Patients coinfected with HIV-1 and HBV who discontinue BIKTARVY should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

5.2 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of BIKTARVY with certain other drugs may result in known or potentially significant drug interactions, some of which may lead to *[see Contraindications (4) and Drug Interactions (7.5)]:*

- Loss of therapeutic effect of BIKTARVY and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

See Table 3 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during BIKTARVY therapy; review concomitant medications during BIKTARVY therapy; and monitor for the adverse reactions associated with the concomitant drugs.

5.3 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

5.4 New Onset or Worsening Renal Impairment

Postmarketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT), and Fanconi syndrome, have been reported with TAF-containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related adverse events *[see Adverse Reactions (6.1, 6.2)].* BIKTARVY is not recommended in patients with severe renal impairment (estimated creatinine clearance of 15 to below 30 mL/min), or patients with ESRD (estimated creatinine clearance below 15 mL/min) who are not receiving chronic hemodialysis, or patients with no antiretroviral treatment history and ESRD who are receiving chronic hemodialysis *[see Dosage and Administration (2.4), Use in Specific Populations (8.6)].*

Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

Prior to or when initiating BIKTARVY, and during treatment with BIKTARVY, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue BIKTARVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

5.5 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine, a component of BIKTARVY, and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with BIKTARVY should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Severe Acute Exacerbations of Hepatitis B *[see Warnings and Precautions (5.1)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.3)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.4)].*
- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[see Warnings and Precautions (5.5)].*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials in Adults with No Antiretroviral Treatment History

The primary safety assessment of BIKTARVY 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 antiretroviral treatment history through Week 144. After Week 144, subjects received open-label BIKTARVY in an optional extension phase for an additional 96 weeks (end of study). A total of 634 and 1025 subjects received one tablet of BIKTARVY once daily during the double-blind (Week 144) and extension phases, respectively *[see Clinical Studies (14.2)]*.

The most common adverse reactions (all Grades) reported in at least 5% of subjects in the BIKTARVY group in either Trial 1489 or Trial 1490 were diarrhea, nausea, and

headache. The proportion of subjects who discontinued treatment through Week 144 with BIKTARVY, abacavir [ABC]/dolutegravir [DTG]/ lamivudine [3TC]), or DTG + FTC/TAF, due to adverse events, regardless of severity, was 1%, 2%, and 2%, respectively. Table 1 displays the frequency of adverse reactions (all Grades) greater than or equal to 2% in the BIKTARVY group.

Table 1 Adverse Reactions[a] (All Grades) Reported in ≥ 2% of HIV-1 Infected Adults with No Antiretroviral Treatment History Receiving BIKTARVY in Trials 1489 or 1490 (Week 144 analysis)

	Trial 1489		Trial 1490	
Adverse Reactions	**BIKTARVY** N=314	**ABC/DTG/3TC** N=315	**BIKTARVY** N=320	**DTG + FTC/TAF** N=325
Diarrhea	6%	4%	3%	3%
Nausea	6%	18%	3%	5%
Headache	5%	5%	4%	3%
Fatigue	3%	4%	2%	2%
Abnormal dreams	3%	3%	<1%	1%
Dizziness	2%	3%	2%	1%
Insomnia	2%	3%	2%	<1%
Abdominal distention	2%	2%	1%	2%

a. Frequencies of adverse reactions are based on all adverse events attributed to trial drugs by the investigator. No adverse reactions of Grade 2 or higher occurred in > 1% of subjects treated with BIKTARVY.

Additional adverse reactions (all Grades) occurring in less than 2% of subjects administered BIKTARVY in Trials 1489 and 1490 included vomiting, flatulence, dyspepsia, abdominal pain, rash, and depression.

Suicidal ideation, suicide attempt, and depression suicidal occurred in 2% of subjects administered BIKTARVY; these events occurred primarily in subjects with a preexisting history of depression, prior suicide attempt or psychiatric illness.

The majority (84%) of adverse events associated with BIKTARVY were Grade 1.

Adverse reactions in the open-label extension phases of Trials 1489 and 1490 were similar to those observed in subjects administered BIKTARVY in the Week 144 analysis.

Clinical Trials in Virologically Suppressed Adults

The safety of BIKTARVY in virologically-suppressed adults was based on Week 48 data from 282 subjects in a randomized, double-blind, active-controlled trial (Trial 1844) in which virologically-suppressed subjects were switched from either DTG + ABC/3TC or ABC/DTG/3TC to BIKTARVY; and Week 48 data from 290 subjects in an open-label,

active-controlled trial in which virologically-suppressed subjects were switched from a regimen containing atazanavir (ATV) (given with cobicistat or ritonavir) or darunavir (DRV) (given with cobicistat or ritonavir) plus either FTC/TDF or ABC/3TC, to BIKTARVY (Trial 1878). Overall, the safety profile in virologically-suppressed adult subjects in Trials 1844 and 1878 was similar to that in subjects with no antiretroviral treatment history *[see Clinical Studies (14.3)]*.

Clinical Trial in Adults with End Stage Renal Disease (ESRD) Receiving Chronic Hemodialysis

The safety of FTC and TAF (components of BIKTARVY) was evaluated in a single arm, open-label trial (Trial 1825) in virologically-suppressed adults with ESRD (estimated creatinine clearance of less than 15 mL/min) on chronic hemodialysis treated with FTC+TAF in combination with elvitegravir and cobicistat as a fixed-dose combination tablet for 96 weeks (N=55). The most commonly reported adverse reaction (adverse event assessed as causally related by investigator and all grades) was nausea (7%). Serious adverse events were reported in 65% of subjects and the most common serious adverse events were pneumonia (15%), fluid overload (7%), hyperkalemia (11%) and osteomyelitis (7%). Overall 7% of subjects permanently discontinued treatment due to an adverse event. In an extension phase of Trial 1825 in which 10 subjects switched to BIKTARVY for 48 weeks, the safety findings were similar to those in the initial phase of the open-label trial *[see Use in Specific Populations (8.6), Clinical Studies (14.3)]*.

Laboratory Abnormalities

The frequency of laboratory abnormalities (Grades 3–4) occurring in at least 2% of subjects receiving BIKTARVY in Trials 1489 and 1490 are presented in Table 2.

Table 2 Laboratory Abnormalities (Grades 3–4) Reported in ≥ 2% of Subjects Receiving BIKTARVY in Trials 1489 or 1490 (Week 144 analysis)

	Trial 1489		Trial 1490	
Laboratory Parameter Abnormality[a]	**BIKTARVY** N=314	**ABC/DTG/3TC** N=315	**BIKTARVY** N=320	**DTG + FTC/TAF** N=325
Amylase (>2.0 x ULN)	3%	4%	3%	4%
ALT (>5.0 × ULN)	2%	2%	3%	1%
AST (>5.0 × ULN)	5%	3%	2%	3%
Creatine Kinase (≥10.0 × ULN)	8%	8%	6%	4%
Neutrophils (<750 mm^3)	3%	4%	3%	2%
LDL-cholesterol (fasted) (>190 mg/dL)	5%	5%	4%	6%
Lipase (> 3.0 x ULN)[b]	2%	2%	<1%	2%
GGT (>5.0 x ULN)	2%	2%	1%	1%

ULN = Upper limit of normal

a. Frequencies are based on treatment-emergent laboratory abnormalities.

b. Lipase test performed only in subjects with serum amylase > 1.5 x ULN.

Changes in Serum Creatinine: BIC has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function *[see Clinical Pharmacology (12.2)]*. Increases in serum creatinine occurred by Week 4 of treatment and remained stable through Week 144. In Trials 1489 and 1490, median (Q1, Q3) serum creatinine increased by 0.11 (0.03, 0.19) mg per dL from baseline to Week 144 in the BIKTARVY group and was similar to the comparator groups who received ABC/DTG/3TC, or DTG + FTC/TAF. There were no discontinuations due to renal adverse events and renal serious adverse events were encountered in less than 1% of participants treated with BIKTARVY through Week 144 in clinical trials.

Changes in Bilirubin: In Trials 1489 and 1490, total bilirubin increases were observed in 17% of subjects administered BIKTARVY through Week 144. Increases were primarily Grade 1 (1.0 to 1.5 x ULN) (12%) and Grade 2 (1.5 to 2.5 x ULN) (4%). Graded bilirubin increases in the ABC/DTG/3TC, and DTG + FTC/TAF groups, were 7% and 8%, respectively. Increases were primarily Grade 1 (5% ABC/DTG/3TC and 7% DTG + FTC/TAF) or Grade 2 (2% ABC/DTG/3TC and 2% DTG + FTC/TAF). There were no discontinuations due to hepatic adverse events through Week 144 in BIKTARVY clinical studies.

Clinical Trials in Pediatric Subjects

The safety of BIKTARVY was evaluated in HIV-1 infected virologically-suppressed subjects between the ages of 12 to less than 18 years and weighing at least 35 kg (N=50) through Week 48 (cohort 1), in virologically-suppressed subjects between the ages of 6 to less than 12 years and weighing at least 25 kg (N=50) through Week 24 (cohort 2), and in virologically suppressed subjects at least 2 years of age and weighing at least 14 to less than 25 kg (N=22) through Week 24 (cohort 3) in an open label clinical trial (Trial 1474) *[see Clinical Studies (14.4)]*. No new adverse reactions or laboratory abnormalities were identified compared to those observed in adults. Adverse reactions were reported in 11% of pediatric subjects. The majority (76%) of adverse reactions were Grade 1. No Grade 3 or 4 adverse reactions were reported. The adverse reaction reported by more than one subject (regardless of severity) was abdominal discomfort (n=2). One subject (1%) had Grade 2 adverse reactions of insomnia and anxiety that led to discontinuation of BIKTARVY. The other adverse reactions that occurred in single subjects were similar to those seen in adults.

6.2 Postmarketing Experience

The following events have been identified during post approval use of BIKTARVY or products containing TAF. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Renal and Urinary Disorders

Acute renal failure, acute tubular necrosis, proximal renal tubulopathy, and Fanconi syndrome

Skin and Subcutaneous Tissue Disorders

Angioedema, Stevens-Johnson syndrome/toxic epidermal necrolysis, and urticaria

7 DRUG INTERACTIONS

7.1 Other Antiretroviral Medications

Because BIKTARVY is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended *[see Indications and Usage (1)]*. Comprehensive information regarding potential drug-drug interactions with other antiretroviral medications is not provided because the safety and efficacy of concomitant HIV-1 antiretroviral therapy is unknown.

7.2 Potential for BIKTARVY to Affect Other Drugs

BIC inhibits organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1) *in vitro*. Coadministration of BIKTARVY with drugs that are substrates of OCT2 and MATE1 (e.g., dofetilide) may increase their plasma concentrations (see Table 3).

7.3 Potential Effect of Other Drugs on One or More Components of BIKTARVY

BIC is a substrate of CYP3A and UGT1A1. A drug that is a strong inducer of CYP3A and also an inducer of UGT1A1 can substantially decrease the plasma concentrations of BIC which may lead to loss of therapeutic effect of BIKTARVY and development of resistance *[see Clinical Pharmacology (12.3)]*.

The use of BIKTARVY with a drug that is a strong inhibitor of CYP3A and also an inhibitor of UGT1A1 may significantly increase the plasma concentrations of BIC.

TAF is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Co-administration of drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentrations of TAF *[see Clinical Pharmacology (12.3)]*. Co-administration of drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect of BIKTARVY and development of resistance (see Table 3).

7.4 Drugs Affecting Renal Function

Because FTC and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of BIKTARVY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, tenofovir, and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *[see Warnings and Precautions (5.4)]*.

7.5 Established and Potentially Significant Drug Interactions

Table 3 provides a listing of established or potentially clinically significant druginteractions with recommended prevention or management strategies. The drug interactions described are based on studies conducted with either BIKTARVY, the components of BIKTARVY (BIC, FTC, and TAF) as individual agents, or are drug interactions that may occur with BIKTARVY *[see Contraindications (4), Warnings and Precautions (5.2), and Clinical Pharmacology (12.3)]*.

Table 3 Established and Potentially Significant[a] Drug Interactions: Alteration in Regimen May be Recommended

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiarrhythmics: dofetilide	↑ Dofetilide	Coadministration is contraindicated due to the potential for serious and/or life-threatening events associated with dofetilide therapy *[see Contraindications (4)]*.
Anticonvulsants: carbamazepine[c] oxcarbazepine phenobarbital phenytoin	↓ BIC ↓ TAF	Coadministration with alternative anticonvulsants should be considered.
Antimycobacterials: rifabutin[c] rifampin[c,d] rifapentine	↓ BIC ↓ TAF	Coadministration with rifampin is contraindicated due to the effect of rifampin on the BIC component of BIKTARVY *[see Contraindications (4)]*. Coadministration with rifabutin or rifapentine is not recommended.
Herbal Products: St. John's wort[e]	↓ BIC ↓ TAF	Coadministration with St. John's wort is not recommended.
Medications or oral supplements containing polyvalent cations (e.g., Mg, Al, Ca, Fe): Calcium or iron supplements[c] Cation-containing antacids or laxatives[c] Sucralfate Buffered medications	↓ BIC	Antacids containing Al/Mg: BIKTARVY can be taken at least 2 hours before or 6 hours after taking antacids containing Al/Mg. Routine administration of BIKTARVY together with, or 2 hours after, antacids containing Al/Mg is not recommended. Supplements or Antacids containing Calcium or Iron: BIKTARVY and supplements or antacids containing calcium or iron can be taken together with food. Routine administration of BIKTARVY under fasting conditions together with, or 2 hours after, supplements or antacids containing calcium or iron is not recommended.
Metformin	↑ Metformin	Refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use of BIKTARVY and metformin.

a. Table is not all inclusive.

b. ↑ = Increase, ↓ = Decrease.

c. Drug-drug interaction study was conducted with either BIKTARVY or its components as individual agents.

d. Strong inducer of CYP3Aand P-gp, and inducer of UGT1A1.
e. The induction potency of St. John's wort may vary widely based on preparation.

7.6 Drugs without Clinically Significant Interactions with BIKTARVY

Based on drug interaction studies conducted with BIKTARVY or the components of BIKTARVY, no clinically significant drug interactions have been observed when BIKTARVY is combined with the following drugs: ethinyl estradiol, ledipasvir/sofosbuvir, midazolam, norgestimate, sertraline, sofosbuvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to BIKTARVY during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

There are insufficient human data on the use of BIKTARVY during pregnancy to inform a drug-associated risk of birth defects and miscarriage. Dolutegravir, another integrase inhibitor, has been associated with neural tube defects (NTDs) *(see Data)*. Discuss the benefit-risk of using BIKTARVY with individuals of childbearing potential, particularly if pregnancy is being planned. BIKTARVY use during pregnancy has been evaluated in a limited number of women reported to the APR; consequently, there are insufficient BIC data from the APR to adequately assess the risk of major birth defects. Reports of pregnant individuals treated with other drug products containing TAF or FTC contribute to APR's overall risk assessment for these components. Available data from the APR show no statistically significant difference in the overall risk of major birth defects for FTC or TAF compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data)*. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in the clinically recognized pregnancies in the U.S. general population is 15-20%.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the components of BIKTARVY at exposures that were either not maternally toxic (rabbits) or greater than (rats and mice) those in humans at the recommended human dose (RHD) (*see Data*). During organogenesis, systemic exposures (AUC) to BIC were approximately 36 (rats) and 0.6 times (rabbits), to FTC were approximately 60 (mice) and 108 times (rabbits), and to TAF were approximately 2 (rats) and 78 times (rabbits) the exposure at the RHD of BIKTARVY. In rat pre/postnatal development studies, maternal systemic exposures (AUC) were 30 times (BIC), 60

times (FTC), and 19 times (TDF) the exposures of each component in humans at the RHD.

Data

Human Data

Prospective reports from the APR of overall major birth defects in pregnancies exposed to the components of BIKTARVY are compared with a U.S. background major birth defect rate. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at less than 20 weeks gestation.

Bictegravir (BIC):

Data from an observational study in Botswana showed that dolutegravir, another integrase inhibitor, was associated with increased risk of neural tube defects when administered at the time of conception and in early pregnancy. Data available to date from other sources including the APR, clinical trials, and postmarketing data are insufficient to address this risk with BIC.

There are an insufficient number of reports to the APR to adequately assess the risk of major birth defects associated with BIC exposure. The APR has received prospective reports of 3 birth defects among 100 (3.0%) first trimester exposures to BIC-containing regimens during pregnancy resulting in live births. No birth defects were reported among 40 exposures during the second/third trimester.

Emtricitabine (FTC):

Based on prospective reports to the APR of over 5,400 exposures to FTC-containing regimens during pregnancy resulting in live births (including over 3,900 exposed in the first trimester and over 1,500 exposed in the second/third trimester), the prevalence of birth defects in live births was 2.6% (95% CI: 2.2% to 3.2%) and 2.7% (95% CI: 1.9% to 3.7%) following first and second/third trimester exposure, respectively, to FTC-containing regimens.

Tenofovir Alafenamide (TAF):

Based on prospective reports to the APR of over 660 exposures to TAF-containing regimens during pregnancy resulting in live births (including over 520 exposed in the first trimester and over 130 exposed in the second/third trimester), the prevalence of birth defects in live births was 4.2% (95% CI: 2.6% to 6.3%) and 3.0% (95% CI: 0.8% to 7.5%) following first and second/third trimester exposure, respectively, to TAF-containing regimens.

Animal Data

Bictegravir: BIC was administered orally to pregnant rats (5, 30, or 300 mg/kg/day) and rabbits (100, 300, or 1000 mg/kg/day) on gestation days 7 through 17, and 7 through 19, respectively. No adverse embryo-fetal effects were observed in rats and

rabbits at BIC exposures (AUC) of up to approximately 36 (rats) and 0.6 (rabbits) times the exposure in humans at the RHD of BIKTARVY. Spontaneous abortion, increased clinical signs [fecal changes, thin body, and cold-to-touch], and decreased body weight were observed at a maternally toxic dose in rabbits (1000 mg/kg/day; approximately 1.4 times higher than human exposure at the RHD).

In a pre/postnatal development study, BIC was administered orally to pregnant rats (up to 300 mg/kg/day) from gestation days 6 to lactation/post-partum day 24. No significant adverse effects were observed in the offspring exposed daily from before birth (*in utero*) through lactation at maternal and pup exposures (AUC) of approximately 30 and 11 times higher, respectively, than human exposures at the RHD.

Emtricitabine: FTC was administered orally to pregnant mice (250, 500, or 1000 mg/kg/day) and rabbits (100, 300, or 1000 mg/kg/day) through organogenesis (on gestation days 6 through 15, and 7 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with emtricitabine in mice at exposures approximately 60 times higher and in rabbits at approximately 108 times higher than human exposures at the RHD.

In a pre/postnatal development study with FTC, mice were administered doses up to 1000 mg/kg/day; no significant adverse effects directly related to drug were observed in the offspring exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 60 times higher than human exposures at the RHD.

Tenofovir alafenamide: TAF was administered orally to pregnant rats (25, 100, or 250 mg/kg/day) and rabbits (10, 30, or 100 mg/kg/day) through organogenesis (on gestation days 6 through 17, and 7 through 20, respectively). No adverse embryo-fetal effects were observed in rats and rabbits at TAF exposures of approximately 2 (rats) and 78 (rabbits) times higher than the exposure in humans at the recommended daily dose of BIKTARVY. TAF is rapidly converted to tenofovir; the observed tenofovir exposure in rats and rabbits were 55 (rats) and 86 (rabbits) times higher than human tenofovir exposures at the RHD. Since TAF is rapidly converted to tenofovir and lower tenofovir exposures in rats and mice were observed after TAF administration compared to TDF administration, a pre/postnatal development study in rats was conducted only with TDF. Doses up to 600 mg/kg/day were administered through lactation; no adverse effects were observed in the offspring on gestation day 7 [and lactation day 20] at tenofovir exposures of approximately 12 [19] times higher than the exposures in humans at the RHD of BIKTARVY.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

It is not known whether BIKTARVY or all of the components of BIKTARVY are present in human breast milk, affects human milk production, or has effects on the breastfed infant. Based on published data, FTC has been shown to be present in human breast milk. BIC was detected in the plasma of nursing rat pups likely due to the presence of BIC in milk, and tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF *(see Data)*. It is unknown if TAF is present in animal milk.

Because of the potential for 1) HIV transmission (in HIV-negative infants); 2) developing viral resistance (in HIV-positive infants); and 3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving BIKTARVY.

Data

Animal Data

Bictegravir: BIC was detected in the plasma of nursing rat pups in the pre/postnatal development study (post-natal day 10), likely due to the presence of BIC in milk.

Tenofovir alafenamide: Studies in rats and monkeys have demonstrated that tenofovir is secreted in milk. Tenofovir was excreted into the milk of lactating rats following oral administration of TDF (up to 600 mg/kg/day) at up to approximately 24% of the median plasma concentration in the highest dosed animals at lactation day 11. Tenofovir was excreted into the milk of lactating monkeys following a single subcutaneous (30 mg/kg) dose of tenofovir at concentrations up to approximately 4% of plasma concentration, resulting in exposure (AUC) of approximately 20% of plasma exposure.

8.4 Pediatric Use

The safety and effectiveness of BIKTARVY have been established as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in pediatric patients weighing at least 14 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY *[see Indications and Usage (1) and Dosage and Administration (2.2, 2.3)]*.

Use of BIKTARVY in pediatric patients weighing at least 14 kg is supported by the

following:

- trials in adults *[see Clinical Studies (14.1)]*
- an open-label trial in three age-based cohorts of virologically-suppressed pediatric subjects *[see Clinical Studies (14.4)]*
    - Cohort 1: 12 to less than 18 years of age and weighing at least 35 kg receiving BIKTARVY through Week 48 (N=50),
    - Cohort 2: 6 to less than 12 years of age and weighing at least 25 kg receiving BIKTARVY through Week 24 (N=50), and
    - Cohort 3: at least 2 years of age and weighing at least 14 to less than 25 kg through Week 24 (N=22). No pediatric subjects 2 years of age were enrolled; of the 6 pediatric subjects who were 3 years of age at enrollment, 3 subjects weighed between 14 to less than 15 kg.

The safety and efficacy of BIKTARVY in these pediatric subjects were similar to that in adults, and there was no clinically significant change in exposure for the components of BIKTARVY *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.4)]*.

Safety and effectiveness of BIKTARVY in pediatric patients weighing less than 14 kg have not been established.

8.5 Geriatric Use

Clinical trials in virologically-suppressed subjects (Trials 4449, 1844, and 1878) included 111 subjects aged 65 years and over who received BIKTARVY, including 86 patients from an open-label, single-arm trial of subjects aged 65 years and over who were switched from their previous antiretroviral regimen to BIKTARVY *[see Clinical Studies (14.3)*]. Of the total number of BIKTARVY-treated patients in these trials, 100 (90%) were 65 to 74 years of age, and 11 (10%) were 75 to 84 years of age. No overall differences in safety or effectiveness were observed between elderly subjects and adults between 18 and less than 65 years of age, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

The pharmacokinetics, safety, virologic and immunologic responses of FTC and TAF (components of BIKTARVY) were evaluated in a single arm, open-label trial (Trial 1825) in virologically-suppressed adults with ESRD (estimated creatinine clearance of less than 15 mL/min) on chronic hemodialysis treated with FTC+TAF in combination with elvitegravir and cobicistat as a fixed-dose combination tablet for 96 weeks (N=55). In an extension phase of Trial 1825, 10 virologically-suppressed subjects switched to BIKTARVY and all remained virologically suppressed for 48 weeks *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.3)]*.

No dosage adjustment of BIKTARVY is recommended in patients with estimated creatinine clearance greater than or equal to 30 mL/min, or in virologically-suppressed

adults (estimated creatinine clearance below 15 mL/min) who are receiving chronic hemodialysis. On days of hemodialysis, administer the daily dose of BIKTARVY after completion of hemodialysis treatment *[see Dosage and Administration (2.2)]*

BIKTARVY is not recommended in patients with estimated creatinine clearance of below 30 mL/min, by Cockcroft-Gault, or patients with ESRD (estimated creatinine clearance below 15 mL/min) who are not receiving chronic dialysis, or patients with no antiretroviral treatment history and ESRD who are receiving chronic dialysis, as the safety and/or efficacy of BIKTARVY has not been established in these populations *[see Dosage and Administration (2.4), Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dosage adjustment of BIKTARVY is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. BIKTARVY has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, BIKTARVY is not recommended for use in patients with severe hepatic impairment *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

No data are available on overdose of BIKTARVY in patients. If overdose occurs, monitor the patient for evidence of toxicity. Treatment of overdose with BIKTARVY consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

Hemodialysis treatment removes approximately 30% of the FTC dose over a 3-hour dialysis period starting within 1.5 hours of FTC dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether FTC can be removed by peritoneal dialysis.

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

11 DESCRIPTION

BIKTARVY (bictegravir, emtricitabine, and tenofovir alafenamide) is a fixed dose combination tablet containing bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF) for oral administration.

- BIC is an integrase strand transfer inhibitor (INSTI).
- FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- TAF, an HIV NRTI, is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

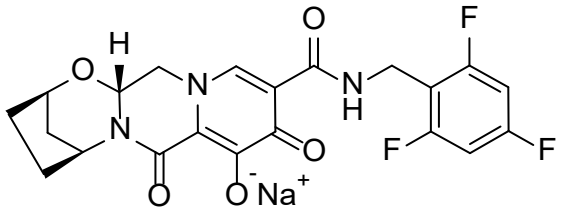
BIKTARVY tablets are available in two dose strengths:

- 50 mg/200 mg/25 mg tablet containing 50 mg of BIC (equivalent to 52.5 mg of bictegravir sodium), 200 mg of FTC, and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate).
- The 30 mg/120/mg/15mg tablets will not be imported by LifeScience Logistics.

Both dose strengths of BIKTARVY tablets include the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets for both dose strengths are film-coated with a coating material containing iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Bictegravir: The chemical name of bictegravir sodium is 2,5-Methanopyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazepine-10-carboxamide, 2,3,4,5,7,9,13,13a-octahydro-8-hydroxy-7,9-dioxo-*N*-[(2,4,6-trifluorophenyl)methyl]-, sodium salt (1:1), (2*R*,5*S*,13a*R*)-.

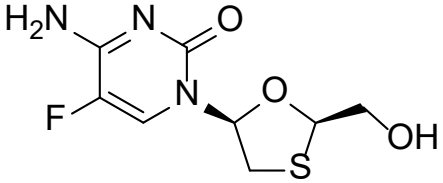
Bictegravir sodium has a molecular formula of $C_{21}H_{17}F_3N_3NaO_5$ and a molecular weight of 471.4 and has the following structural formula:



Bictegravir sodium is an off-white to yellow solid with a solubility of 0.1 mg per mL in water at 20 °C.

Emtricitabine: The chemical name of FTC is 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S*-yl)-(1H)-pyrimidin-2-one. FTC is the (-)enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5 position.

FTC has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.2 and has the following structural formula:

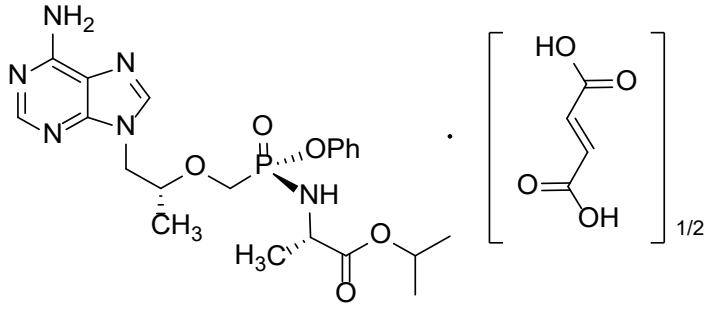


FTC is a white to off-white powder with a solubility of approximately 112 mg per mL in water at 25 °C.

Tenofovir alafenamide: The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-

methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1).

Tenofovir alafenamide fumarate has an empirical formula of $C_{21}H_{29}O_5N_6P•½(C_4H_4O_4)$ and a formula weight of 534.5 and has the following structural formula:



Tenofovir alafenamide fumarate is a white to off-white or tan powder with a solubility of 4.7 mg per mL in water at 20 °C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

BIKTARVY is a fixed dose combination of antiretroviral drugs bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF) *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a thorough QT/QTc trial in 48 healthy subjects, BIC at doses 1.5 and 6 times the recommended dose did not affect the QT/QTc interval and did not prolong the PR interval. In a thorough QT/QTc trial in 48 healthy subjects, TAF at the recommended dose or at a dose 5 times the recommended dose, did not affect the QT/QTc interval and did not prolong the PR interval. The effect of FTC on the QT interval is not known.

Effects on Serum Creatinine

Mean change from baseline in serum creatinine in healthy subjects who received BIC 75 mg (1.5 times the approved recommended dosage) once daily with food for 14 days was 0.1 mg per dL on Days 7 and 14 compared to placebo. BIC did not have a significant effect on the estimated creatinine clearance or on the actual glomerular filtration rate (determined by the clearance of probe drug, iohexol).

12.3 Pharmacokinetics

The pharmacokinetic (PK) properties of BIKTARVY components are provided in Table 4. The multiple dose PK parameters of BIKTARVY components (based on population pharmacokinetic analysis) are provided in Table 5.

Table 4 Pharmacokinetic Properties of the Components of BIKTARVY

		Bictegravir (BIC)	Emtricitabine (FTC)	Tenofovir Alafenamide (TAF)
Absorption				
T_{max} (h)[a]		2.0–4.0	1.5–2.0	0.5–2.0
Effect of high-fat meal (relative to fasting)[b]	AUC ratio	1.24 (1.16, 1.33)	0.96 (0.93, 0.99)	1.63 (1.43, 1.85)
	C_{max} ratio	1.13 (1.06, 1.20)	0.86 (0.78, 0.93)	0.92 (0.73, 1.14)
Distribution				
% bound to human plasma proteins		>99	<4	~80
Blood-to-plasma ratio		0.64	0.6	1.0
Elimination				
$t_{1/2}$ (h)[c]		17.3 (14.8, 20.7)	10.4 (9.0, 12.0)	0.51 (0.45, 0.62)[c]
Metabolism				
Metabolic pathway(s)		CYP3A UGT1A1	Not significantly metabolized	Cathepsin A[d] (PBMCs) CES1 (hepatocytes)
Excretion				
Major route of elimination		Metabolism	Glomerular filtration and active tubular secretion	Metabolism
% of dose excreted in urine[e]		35	70	<1
% of dose excreted in feces[e]		60.3	13.7	31.7

PBMCs=peripheral blood mononuclear cells; CES1=carboxylesterase 1

a. Values reflect administration of BIKTARVY with or without food.

b. Values refer to geometric mean ratio [high-fat meal/ fasting] in PK parameters and (90% confidence interval). High fat meal is approximately 800 kcal, 50% fat.

c. $t_{1/2}$ values refer to median (Q1, Q3) terminal plasma half-life. Note that the active metabolite of TAF, tenofovir diphosphate, has a half-life of 150-180 hours within PBMCs.

d. *In vivo*, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. *In vitro* studies have shown that TAF is metabolized to tenofovir by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes.

e. Dosing in mass balance studies: single dose administration of [^{14}C] BIC; single dose administration of [^{14}C] FTC after multiple dosing of FTC for ten days; single dose administration of [^{14}C] TAF.

Table 5 Multiple Dose PK Parameters of BIC, FTC, and TAF Following Oral Administration of BIKTARVY in HIV-Infected Adults

Parameter Mean (CV%)	Bictegravir	Emtricitabine	Tenofovir Alafenamide
C_{max} (microgram per mL)	6.15 (22.9)	2.13 (34.7)	0.121 (15.4)
AUC_{tau} (microgram•h per mL)	102 (26.9)	12.3 (29.2)	0.142 (17.3)
C_{trough} (microgram per mL)	2.61 (35.2)	0.096 (37.4)	NA

CV=Coefficient of Variation; NA=Not Applicable

Specific Populations

Patients with Renal Impairment

No clinically relevant differences in the pharmacokinetics of BIC, TAF, or its metabolite tenofovir were observed between subjects with severe renal impairment (estimated creatinine clearance of 15 to less than 30 mL/min, by Cockcroft-Gault method) and healthy subjects in Phase 1 studies. In a separate Phase 1 study of FTC alone, FTC exposures were increased in subjects with severe renal impairment.

The pharmacokinetics of BIC, FTC and TAF were evaluated in a subset of HIV-1 infected virologically-suppressed subjects with ESRD (estimated creatinine clearance less than 15 mL/min, by Cockcroft-Gault method) receiving chronic hemodialysis in Trial 1825. The pharmacokinetics of TAF were similar between healthy subjects and subjects with ESRD receiving chronic hemodialysis; increases in FTC and tenofovir exposures in subjects with ESRD were not considered clinically relevant. Median (minimum, maximum) BIC C_{trough} values in subjects (n=7) with ESRD who received BIKTARVY were 846 ng/mL (288, 1810) compared to 2540 ng/mL (757, 6499) in subjects (N=584) with normal renal function. Despite significantly lower BIC C_{trough} values in the virologically-suppressed ESRD population, virologic suppression was maintained *[see Use in Specific Populations (8.6), Clinical Studies (14.3)]*.

Patients with Hepatic Impairment

Bictegravir: Clinically relevant changes in the pharmacokinetics of BIC were not observed in subjects with moderate (Child-Pugh Class B) hepatic impairment.

Emtricitabine: The pharmacokinetics of FTC has not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of hepatic impairment should be limited.

Tenofovir Alafenamide: Clinically relevant changes in the pharmacokinetics of TAF or its metabolite tenofovir were not observed in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment *[see Use in Specific Populations (8.7)]*.

Hepatitis B and/or Hepatitis C Virus Coinfection

The pharmacokinetics of BIC, FTC, and TAF have not been evaluated in subjects coinfected with hepatitis B and/or C virus.

Geriatric Patients

The pharmacokinetics of BIC, FTC, and TAF have not been fully evaluated in the elderly (65 years of age and older). Population pharmacokinetics analysis of HIV-infected subjects in Phase 3 trials of BIKTARVY showed that age did not have a clinically relevant effect on exposures of BIC and TAF up to 74 years of age *[see Use in Specific Populations (8.5)]*.

Pediatric Patients

Mean BIC C_{trough} was lower in 50 pediatric patients aged 12 to less than 18 years and weighing at least 35 kg who received BIKTARVY in Trial 1474 relative to adults following administration of BIKTARVY, but was not considered clinically significant based on exposure-response relationships; exposures of FTC and TAF in these pediatric patients were similar to those in adults (Table 6).

Table 6 Multiple Dose PK Parameters of BIC, FTC, and TAF Following Oral Administration of BIKTARVY in HIV-Infected Pediatric Subjects Aged 12 to less than 18 years

Parameter Mean (CV%)	Bictegravir[a]	Emtricitabine[b]	Tenofovir Alafenamide[a]
C_{max} (microgram per mL)	6.24 (27.1)	2.69 (34.0)	0.133 (70.2)
AUC_{tau} (microgram•h per mL)	89.1 (31.0)	13.6 (21.7)	0.196 (50.3)
C_{trough} (microgram per mL)	1.78 (44.4)	0.064 (25.0)	NA

CV=Coefficient of Variation; NA=Not Applicable

a. From Population PK analysis of cohort 1 of Trial 1474 (n=50 for BIC; n=49 for TAF).

b. From Intensive PK analysis of cohort 1 of Trial 1474 (n=24).

Mean BIC C_{max}, and exposures of FTC and TAF (AUC_{tau} and C_{max}) achieved in 50 pediatric patients between the ages of 6 to less than 12 years and weighing at least 25 kg, and in 22 pediatric patients at least 2 years of age and weighing at least 14 to less than 25 kg who received BIKTARVY in Trial 1474 were higher than exposures

in adults; however, the increases were not considered clinically significant as the safety profiles were similar in adult and pediatric patients (Tables 7 and 8) *[see Use in Specific Populations (8.4)]*.

Table 7 Multiple Dose PK Parameters of BIC, FTC, and TAF Following Oral Administration of BIKTARVY in HIV-Infected Pediatric Subjects Aged 6 to less than 12 years

Parameter Mean (CV%)	Bictegravir[a]	Emtricitabine[b]	Tenofovir Alafenamide[a]
C_{max} (microgram per mL)	9.46 (24.3)	3.89 (31.0)	0.205 (44.6)
AUC_{tau} (microgram•h per mL)	128 (27.8)	17.6 (36.9)	0.278 (40.3)
C_{trough} (microgram per mL)	2.36 (39.0)	0.227 (323)	NA

CV=Coefficient of Variation; NA=Not Applicable

a. From Population PK analysis of cohort 2 of Trial 1474 (n=50 for BIC; n=47 for TAF).

b. From Intensive PK analysis of cohort 2 of Trial 1474 (n=25 except n=24 for C_{trough}).

Table 8 Multiple Dose PK Parameters of BIC, FTC, and TAF Following Oral Administration of BIKTARVY in HIV-Infected Pediatric Subjects at Least 2 Years of Age[a] and Weighing at Least 14 to Less than 25 kg

Parameter Mean (CV%)	Bictegravir[b]	Emtricitabine[c]	Tenofovir Alafenamide[c]
C_{max} (microgram per mL)	9.15 (44.8)	3.85 (34.7)	0.414 (31.0)
AUC_{tau} (microgram•h per mL)	126 (42.4)	15.0 (21.9)	0.305 (42.6)
C_{trough} (microgram per mL)	2.43 (40.1)	0.210 (243)	NA

CV=Coefficient of Variation; NA=Not Applicable

a. Cohort 3 of Trial 1474 enrolled pediatric subjects from 3 to 9 years of age.

b. From Population PK analysis of cohort 3 of Trial 1474 (n=22).

c. From Intensive PK analysis of cohort 3 of Trial 1474 (n=12 except n=11 for C_{trough} for FTC).

Race and Gender

No clinically relevant changes in the pharmacokinetics of BIC, FTC, and TAF were observed based on gender or race.

Drug Interaction Studies

As BIKTARVY is a complete regimen for the treatment of HIV-1 infection, comprehensive information regarding potential drug-drug interactions with other antiretroviral agents is not provided.

BIC is a substrate of CYP3A and UGT1A1.

BIC is an inhibitor of OCT2 and MATE1. At clinically relevant concentrations, BIC is not an inhibitor of hepatic transporters OATP1B1, OATP1B3, OCT1, BSEP, renal transporters OAT1 and OAT3, or CYP (including CYP3A) or UGT1A1 enzymes.

TAF is a substrate of P-gp and BCRP.

At clinically relevant concentrations, TAF is not an inhibitor of drug transporters P-gp, BCRP, hepatic transporters OATP1B1, OATP1B3, OCT1, BSEP, renal transporters OAT1, OAT3, OCT2, MATE1, or CYP (including CYP3A) or UGT1A1 enzymes.

Drug interaction studies were conducted with BIKTARVY or its components. Tables 9 and 10 summarize the pharmacokinetic effects of other drugs on BIC and TAF, respectively. Table 11 summarizes the pharmacokinetic effects of BIKTARVY or its components on other drugs.

Effect of Other Drugs on BIKTARVY Components

Table 9 Effect of Other Drugs on BIC[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	BIC (mg)	Mean Ratio of BIC Pharmacokinetic Parameters (90% CI); No effect = 1.00		
			C_{max}	AUC	C_{min}
Ledipasvir/ Sofosbuvir (fed)	90/400 once daily	75 once daily	0.98 (0.94, 1.03)	1.00 (0.97, 1.03)	1.04 (0.99, 1.09)
Rifabutin (fasted)	300 once daily	75 once daily	0.80 (0.67, 0.97)	0.62 (0.53, 0.72)	0.44 (0.37, 0.52)
Rifampin (fed)	600 once daily	75 single dose	0.72 (0.67, 0.78)	0.25 (0.22, 0.27)	NA
Sofosbuvir/ velpatasvir/ voxilaprevir (fed)	400/100/100+100 voxilaprevir[b] once daily	50 once daily	0.98 (0.94, 1.01)	1.07 (1.03, 1.10)	1.10 (1.05, 1.17)
Voriconazole (fasted)	300 twice daily	75 single dose	1.09 (0.96, 1.23)	1.61 (1.41, 1.84)	NA

Coadministered Drug	Dose of Coadministered Drug (mg)	BIC (mg)	Mean Ratio of BIC Pharmacokinetic Parameters (90% CI); No effect = 1.00		
			C_{max}	AUC	C_{min}
Maximum strength antacid (simultaneous administration, fasted)	20 mL[c] single dose (oral)	50 single dose	0.20 (0.16, 0.24)	0.21 (0.18, 0.26)	NA
Maximum strength antacid (2 h after BIKTARVY fasted)	20 mL[c] single dose (oral)	50 single dose	0.93 (0.88, 1.00)	0.87 (0.81, 0.93)	NA
Maximum strength antacid (2 h before BIKTARVY fasted)	20 mL[c] single dose (oral)	50 single dose	0.42 (0.33, 0.52)	0.48 (0.38, 0.59)	NA
Maximum strength antacid (simultaneous administration, fed[d])	20 mL[c] single dose (oral)	50 single dose	0.51 (0.43, 0.62)	0.53 (0.44, 0.64)	NA
Calcium carbonate (simultaneous administration, fasted)	1200 single dose	50 single dose	0.58 (0.51, 0.67)	0.67 (0.57, 0.78)	NA
Calcium carbonate (simultaneous administration, fed[d])	1200 single dose	50 single dose	0.90 (0.78, 1.03)	1.03 (0.89, 1.20)	NA
Ferrous fumarate (simultaneous administration, fasted)	324 single dose	50 single dose	0.29 (0.26, 0.33)	0.37 (0.33, 0.42)	NA
Ferrous fumarate (simultaneous administration, fed[d])	324 single dose	50 single dose	0.75 (0.65, 0.87)	0.84 (0.74, 0.95)	NA

NA= Not Applicable

a. All interaction studies conducted in healthy volunteers.

b. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected

patients.

c. Maximum strength antacid contained 80 mg aluminum hydroxide, 80 mg magnesium hydroxide, and 8 mg simethicone, per mL.

d. Reference treatment administered under fasted conditions.

Table 10 Effect of Other Drugs on TAF[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Tenofovir Alafenamide (mg)	Mean Ratio of Tenofovir Alafenamide Pharmacokinetic Parameters (90% CI); No effect = 1.00		
			C_{max}	AUC	C_{min}
Carbamazepine	300 twice daily	25 single dose[b]	0.43 (0.36, 0.51)	0.46 (0.40, 0.54)	NA
Ledipasvir/sofosbuvir	90/400 once daily	25 once daily	1.17 (1.00, 1.38)	1.27 (1.19, 1.34)	NA
Sofosbuvir/ velpatasvir/ voxilaprevir	400/100/100 +100 voxilaprevir[c] once daily	25 once daily	1.28 (1.09, 1.51)	1.57 (1.44, 1.71)	NA

NA= Not Applicable

a. All interaction studies conducted in healthy volunteers.

b. Study conducted with emtricitabine/tenofovir alafenamide.

c. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Effect of BIKTARVY Components on Other Drugs

Table 11 Effect of Components of BIKTARVY on Other Drugs[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	BIC (mg)	TAF (mg)	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Ledipasvir	90/400 once daily	75 once daily	25 once daily	0.85 (0.81, 0.90)	0.87 (0.83, 0.92)	0.90 (0.84, 0.96)
Sofosbuvir				1.11 (1.00, 1.24)	1.07 (1.01, 1.13)	NA
GS-331007[b]				1.10 (1.07, 1.13)	1.11 (1.08, 1.14)	1.02 (0.99, 1.06)
Metformin	500 twice daily	50 once daily	25 once daily	1.28 (1.21, 1.36)	1.39 (1.31, 1.48)	1.36 (1.21, 1.53)
Midazolam	2 single dose	50 once daily	25 once daily	1.03 (0.87, 1.23)	1.15 (1.00, 1.31)	NA
Norelgestromin	norgestimate 0.180/0.215/0.250 once daily / ethinyl estradiol 0.025 once daily	75 once daily	-	1.23 (1.14, 1.32)	1.08 (1.05, 1.10)	1.10 (1.05, 1.15)
Norgestrel				1.15 (1.10, 1.21)	1.13 (1.07, 1.19)	1.14 (1.06, 1.22)

Coadministered Drug	Dose of Coadministered Drug (mg)	BIC (mg)	TAF (mg)	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Ethinyl estradiol				1.15 (1.03, 1.27)	1.04 (0.99, 1.10)	1.05 (0.95, 1.14)
Norelgestromin	norgestimate 0.180/0.215/0.250 once daily / ethinyl estradiol 0.025 once daily	-	25 once daily [c]	1.17 (1.07,1.26)	1.12 (1.07,1.17)	1.16 (1.08, 1.24)
Norgestrel				1.10 (1.02, 1.18)	1.09 (1.01, 1.18)	1.11 (1.03, 1.20)
Ethinyl estradiol				1.22 (1.15, 1.29)	1.11 (1.07, 1.16)	1.02 (0.92, 1.12)
Sertraline	50 single dose	-	10 once daily [d]	1.14 (0.94, 1.38)	0.93 (0.77, 1.13)	NA
Sofosbuvir	400/100/100+ 100[e] once daily	50 once daily	25 once daily	1.14 (1.04,1.25)	1.09 (1.02, 1.15)	NA
GS-331007[b]				1.03 (0.99,1.06)	1.03 (1.00,1.06)	1.01 (0.98, 1.05)
Velpatasvir				0.96 (0.91,1.01)	0.96 (0.90, 1.02)	0.94 (0.88, 1.01)
Voxilaprevir				0.90 (0.76, 1.06)	0.91 (0.80, 1.03)	0.97 (0.88, 1.06)

NA= Not Applicable

a. All interaction studies conducted in healthy volunteers.
b. The predominant circulating nucleoside metabolite of sofosbuvir.
c. Study conducted with emtricitabine/tenofovir alafenamide.
d. Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.
e. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

12.4 Microbiology

Mechanism of Action

Bictegravir: BIC inhibits the strand transfer activity of HIV-1 integrase (integrase strand transfer inhibitor; INSTI), an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the integration of linear HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the virus.

Emtricitabine: FTC, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5′-triphosphate is a weak

inhibitor of mammalian DNA polymerases α, β, Ɛ, and mitochondrial DNA polymerase γ.

Tenofovir Alafenamide: TAF is a phosphonamidate prodrug of tenofovir (2′-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

Antiviral Activity in Cell Culture

The triple combination of BIC, FTC, and TAF was not antagonistic with respect to antiviral activity in cell culture.

Bictegravir: The antiviral activity of BIC against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells, and CD4+ T-lymphocytes. In MT-4 cells (human lymphoblastoid T-cell line) acutely infected with HIV-1 IIIB, the mean 50% effective concentration (EC_{50}) was 2.4±0.4 nM, and the protein-adjusted EC_{95} value was 361 nM (0.162 micrograms per mL). BIC displayed antiviral activity in activated PBMCs against clinical isolates of HIV-1 representing groups M, N, and O, including subtypes A, B, C, D, E, F, and G, with a median EC_{50} value of 0.55 nM (range <0.05 to 1.71 nM). The EC_{50} value against a single HIV-2 isolate was 1.1 nM.

Emtricitabine: The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, the MAGI-CCR5 cell line, and PBMCs. In PBMCs acutely infected with HIV-1 subtypes A, B, C, D, E, F, and G, the median EC_{50} value for FTC was 9.5 nM (range 1 to 30 nM) and against HIV-2 was 7 nM.

Tenofovir Alafenamide: The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4-T lymphocytes. The EC_{50} values for TAF ranged from 2.0 to 14.7 nM. TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including subtypes A, B, C, D, E, F, and G (EC_{50} values ranged from 0.1 to 12 nM) and strain specific activity against HIV-2 (EC_{50} values ranged from 0.9 to 2.6 nM).

Resistance

In Cell Culture

Bictegravir: HIV-1 isolates with reduced susceptibility to BIC have been selected in cell culture. In one selection with BIC, a virus pool emerged expressing amino acid substitutions M50I and R263K in the HIV-1 integrase. M50I, R263K, and M50I+R263K substitutions, when introduced into a wild-type virus by site-directed

mutagenesis, conferred 1.3-, 2.2-, and 2.9-fold reduced susceptibility to BIC, respectively. In a second selection, emergence of amino acid substitutions T66I and S153F was detected, and 0.4-, 1.9-, and 0.5-fold reductions in BIC susceptibility were observed with T66I, S153F, and T66I+S153F, respectively. In addition, S24G and E157K substitutions emerged during the selection process.

Emtricitabine: HIV-1 isolates with reduced susceptibility to FTC were selected in cell culture and in subjects treated with FTC. Reduced susceptibility to FTC was associated with M184V or I substitutions in HIV-1 RT.

Tenofovir Alafenamide: HIV-1 isolates with reduced susceptibility to TAF were selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R substitution in HIV-1 RT, sometimes in the presence of S68N or L429I substitutions; in addition, a K70E substitution in HIV-1 RT was observed.

In Clinical Trials

In Subjects with No Antiretroviral Treatment History: Pooled results of genotypic resistance analyses were performed on paired baseline and on-treatment HIV-1 isolates from subjects receiving BIKTARVY in Trials 1489 and 1490 through Week 144 of the double-blind phase (N=634) or Week 96 of the extension phase (n=1025) *[see Clinical Studies (14.2)]* who had HIV-1 RNA greater than or equal to 200 copies/mL at the time of confirmed virologic failure or early study drug discontinuation. In the final resistance analysis population, no specific amino acid substitutions emerged consistently in the 11 treatment failure subjects with evaluable genotypic resistance data and failed to establish an association with genotypic BIC resistance. There were no treatment-emergent NRTI resistance-associated substitutions detected in the 11 evaluated treatment failure isolates. Phenotypic resistance analyses of failure isolates found fold-changes in drug susceptibility below the biological or clinical cutoffs for BIC, FTC, and TFV, compared to wild-type reference HIV-1.

In Virologically Suppressed Adult Subjects: In 2 switch trials, Trials 1844 and 1878 *[see Clinical Studies (14.3)]*, of virologically suppressed HIV-1 infected subjects (n=572), only one subject with virologic rebound in the resistance analysis population had IN genotypic and phenotypic data, and 2 rebounders had RT genotypic and phenotypic data. No subjects had HIV-1 with treatment-emergent genotypic or phenotypic resistance to BIC, FTC, or TAF.

In Virologically Suppressed Pediatric Subjects: In Trial 1474 *[see Clinical Studies (14.4)]*, two of 50 subjects in cohort 1 were evaluated for the development of resistance through Week 48; no amino acid substitutions known to be associated with resistance to BIC, FTC, or TFV were detected. No subjects in cohort 2 or 3 met the criteria for resistance analyses through Week 24.

Cross-Resistance

Bictegravir: Cross-resistance has been observed among INSTIs. The susceptibility of BIC was tested against 64 clinical isolates expressing known INSTI resistance-

associated substitutions listed by IAS-USA (20 with single substitutions and 44 with 2 or more substitutions). Isolates with a single INSTI-resistance substitution including E92Q, T97A, Y143C/R, Q148R, and N155H showed less than 2-fold reduced susceptibility to BIC. All isolates (n=14) with more than 2.5-fold reduced susceptibility to BIC (above the biological cutoff for BIC) contained G140A/C/S and Q148H/R/K substitutions; the majority (64.3%, 9/14) had a complex INSTI resistance pattern with an additional INSTI-resistance substitution L74M, T97A, or E138A/K. Of those evaluated isolates containing G140A/C/S and Q148H/R/K substitutions in the absence of additional INSTI-resistance substitutions, 38.5% (5/13) showed more than 2.5-fold reduction. In addition, site-directed mutant viruses with G118R (dolutegravir and raltegravir treatment-emergent substitution) and G118R+T97A had 3.4- and 2.8-fold reduced susceptibility to BIC, respectively.

BIC demonstrated equivalent antiviral activity with less than 2-fold reductions in susceptibility against HIV-1 variants expressing substitutions associated with resistance to NNRTIs, NRTIs, and PIs, compared with the wild-type virus.

Emtricitabine: Cross-resistance has been observed among NRTIs. FTC-resistant viruses with an M184V/I substitution in HIV-1 RT were cross-resistant to lamivudine. HIV-1 isolates containing the K65R RT substitution, selected *in vivo* by abacavir, didanosine, and tenofovir, demonstrated reduced susceptibility to inhibition by FTC.

Tenofovir Alafenamide: Cross-resistance has been observed among NRTIs. Tenofovir resistance substitutions K65R and K70E result in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir. HIV-1 with multiple thymidine analog substitutions (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N/R), or multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M substitution complex including K65R, showed reduced susceptibility to TAF in cell culture.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Bictegravir

BIC was not carcinogenic in a 6-month rasH2 transgenic mouse study at doses of up to 100 mg/kg/day in males and 300 mg/kg/day in females. BIC was not carcinogenic in a 2-year rat study at doses up to 300 mg/kg/day, which resulted in exposures of approximately 31 times the exposure in humans at the recommended dose of BIKTARVY.

BIC was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

BIC did not affect fertility, reproductive performance or embryonic viability in male and female rats at 29 times higher exposures (AUC) than in humans at the recommended dose of BIKTARVY.

Emtricitabine

In long-term carcinogenicity studies of FTC, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg per kg per day (25 times the human systemic exposure at the recommended dose of BIKTARVY) or in rats at doses up to 600 mg per kg per day (30 times the human systemic exposure at the recommended dose of BIKTARVY).

FTC was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

FTC did not affect fertility in male rats at approximately 140 times or in male and female mice at approximately 60 times higher exposures (AUC) than in humans given the recommended dose of BIKTARVY. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60 times higher than human exposures at the recommended dose of BIKTARVY.

Tenofovir Alafenamide

Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans following a 300 mg dose of TDF. The tenofovir exposure in these studies was approximately 151 times (mice) and 51 times (rat) those observed in humans after administration of the daily recommended dose of BIKTARVY. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 151 times the exposure observed in humans at the recommended dose of BIKTARVY. In rats, the study was negative for carcinogenic findings.

TAF was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

There were no effects on fertility, mating performance or early embryonic development when TAF was administered to male rats at a dose equivalent to 155 times the human dose of BIKTARVY based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through Day 7 of gestation.

13.2 Animal Toxicology and/or Pharmacology

Minimal to slight infiltration of mononuclear cells in the posterior uvea was observed in dogs with similar severity after three and nine month administration of TAF; reversibility was seen after a three month recovery period. No eye toxicity was observed in the dog at systemic exposures of 7 (TAF) and 14 (tenofovir) times the exposure seen in humans with the recommended daily dose of BIKTARVY.

14 CLINICAL STUDIES

14.1 Description of Clinical Trials

The efficacy and safety of BIKTARVY were evaluated in the trials summarized in Table 12.

Table 12 Trials Conducted with BIKTARVY in Subjects with HIV-1 Infection

Trial	Population	Trial Arms (N)	Timepoint (Week)
Trial 1489[a] (NCT 02607930)	Adults with no antiretroviral treatment history	BIKTARVY (314) ABC/DTG/3TC (315)	144 + 96 (OLE)[b]
Trial 1490[a] (NCT 02607956)		BIKTARVY (320) DTG + FTC/TAF(325)	144 + 96 (OLE)[b]
Trial 1844[a] (NCT 02603120)	Virologically-suppressed[d] adults	BIKTARVY (282) ABC/DTG/3TC (281)	48
Trial 1878[c] (NCT 02603107)		BIKTARVY (290) ATV or DRV (with cobicistat or ritonavir) plus either FTC/TDF or ABC/3TC (287)	48
Trial 1825[e] (NCT 02600819)	Virologically-suppressed[d] adults with ESRD[f] receiving chronic hemodialysis	FTC+TAF in combination with elvitegravir and cobicistat as a fixed-dose combination (55). In an extension phase of Trial 1825, 10 virologically-suppressed subjects switched to BIKTARVY.	48[g]
Trial 4449[e] (NCT 03405935)	Virologically-suppressed[d] adults aged 65 years and over	BIKTARVY (86)	48
Trial 1474[e] (cohort 1) (NCT 02881320)	Virologically-suppressed[d] adolescents between the ages of 12 to less than 18 years (at least 35 kg)	BIKTARVY (50)	48
Trial 1474[e] (cohort 2) (NCT 02881320)	Virologically-suppressed[d] children between the ages of 6 to less than 12 years (at least 25 kg)	BIKTARVY (50)	24
Trial 1474[e] (cohort 3) (NCT 02881320)	Virologically- suppressed[d] children at least 2 years of age (at least 14 to less than 25 kg)	BIKTARVY (22)	24

OLE = open-label extension

a. Randomized, double blind, active controlled trial.

b. 144-week double-blind active controlled phase followed by an extension phase in which 1025 subjects from Trials 1489 and 1490 received open-label BIKTARVY for 96 weeks.

c. Randomized, open-label, active controlled trial.

d. HIV-1 RNA less than 50 copies per mL.

e. Open-label trial.

f. End stage renal disease (estimated creatinine clearance of less than 15 mL/min by Cockcroft-Gault method).
g. Subjects received FTC+TAF in combination with elvitegravir and cobicistat for 96 weeks, followed by an extension phase in which 10 subjects received BIKTARVY for 48 weeks.

14.2 Clinical Trial Results in Adults with HIV-1 and No Antiretroviral Treatment History

In Trial 1489, adults were randomized in a 1:1 ratio to receive either BIKTARVY (containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF) (N=314) or ABC/DTG/3TC (600 mg/50 mg/300 mg) (N=315) once daily. In Trial 1490, subjects were randomized in a 1:1 ratio to receive either BIKTARVY (N=320) or DTG + FTC/TAF (50 mg + 200 mg/25 mg) (N=325) once daily.

In Trial 1489, the mean age was 34 years (range 18–71), 90% were male, 57% were White, 36% were Black, and 3% were Asian. 22% of patients identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.4 $\log_{10}$ copies/mL (range 1.3–6.5). The mean baseline CD4+ cell count was 464 cells per mm^3 (range 0–1424) and 11% had CD4+ cell counts less than 200 cells per mm^3. 16% of subjects had baseline viral loads greater than 100,000 copies per mL.

In Trial 1490, the mean age was 37 years (range 18–77), 88% were male, 59% were White, 31% were Black, and 3% were Asian. 25% of patients identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.4 $\log_{10}$ copies/mL (range 2.3–6.6). The mean baseline CD4+ cell count was 456 cells per mm^3 (range 2–1636) and 12% had CD4+ cell counts less than 200 cells per mm^3. 19% of subjects had baseline viral loads greater than 100,000 copies per mL.

In both trials, subjects were stratified by baseline HIV-1 RNA (less than or equal to 100,000 copies per mL, greater than 100,000 copies per mL to less than or equal to 400,000 copies per mL, or greater than 400,000 copies per mL), by CD4 count (less than 50 cells per mm^3, 50-199 cells per mm^3, or greater than or equal to 200 cells per mm^3), and by region (US or ex-US).

Treatment outcomes of Trials 1489 and 1490 through Week 144 are presented in Table 13.

Table 13 Virologic Outcomes of Randomized Treatment in Trials 1489 and 1490 at Week 144[a] in Adults with No Antiretroviral Treatment History

	Trial 1489		Trial 1490	
	BIKTARVY (N=314)	**ABC/DTG/3TC** (N=315)	**BIKTARVY** (N=320)	**DTG + FTC/TAF** (N=325)
HIV-1 RNA < 50 copies/mL	82%	84%	82%	84%
Treatment Difference (95% CI) BIKTARVY vs. Comparator	-2.6% (-8.5% to 3.4%)		-1.9% (-7.8% to 3.9%)	
HIV-1 RNA ≥ 50 copies/mL[b]	1%	3%	5%	3%
No Virologic Data at Week 144 Window	18%	13%	13%	13%
Discontinued Study Drug Due to AE or Death[c]	1%	2%	3%	3%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL[d]	16%	11%	11%	9%
Missing Data During Window but on Study Drug	1%	<1%	0%	1%

a. Week 144 window was between Day 967 and 1050 (inclusive).

b. Includes subjects who had ≥ 50 copies/mL in the Week 144 window; subjects who discontinued early due to lack or loss of efficacy; subjects who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

c. Includes subjects who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

d. Includes subjects who discontinued for reasons other than an AE, death, or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Treatment outcomes were similar across subgroups by age, sex, race, baseline viral load, and baseline CD4+ cell count.

In Trials 1489 and 1490, the mean increase from baseline in CD4+ count at Week 144 was 299 and 317 cells per mm^3 in the BIKTARVY and ABC/DTG/3TC groups, respectively, and 278 and 289 cells per mm^3 in the BIKTARVY and DTG + FTC/TAF groups, respectively.

14.3 Clinical Trial Results in Adults with Virologically-Suppressed HIV-1 Who Switched to BIKTARVY

In Trial 1844, the efficacy and safety of switching from a regimen of DTG + ABC/3TC or ABC/DTG/3TC to BIKTARVY were evaluated in a randomized, double-blind trial of virologically-suppressed (HIV-1 RNA less than 50 copies per mL) HIV-1 infected adults (N=563, randomized and dosed). Subjects must have been stably suppressed (HIV-1 RNA less than 50 copies per mL) on their baseline regimen for at least 3 months prior to trial entry and had no history of treatment failure. Subjects were randomized in a 1:1 ratio to either switch to BIKTARVY (containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF) at baseline (N=282), or stay on their baseline antiretroviral regimen

(N=281). Subjects had a mean age of 45 years (range 20–71), 89% were male, 73% were White, and 22% were Black. 17% of subjects identified as Hispanic/Latino. The mean baseline CD4+ cell count was 723 cells per mm^3 (range 124–2444).

In Trial 1878, the efficacy and safety of switching from either ABC/3TC or FTC/TDF (200/300 mg) plus ATV or DRV (given with either cobicistat or ritonavir) to BIKTARVY (containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF) were evaluated in a randomized, open-label study of virologically-suppressed HIV-1 infected adults (N=577, randomized and dosed). Subjects must have been stably suppressed on their baseline regimen for at least 6 months, must not have been previously treated with any INSTI, and had no history of treatment failure. Subjects were randomized in a 1:1 ratio to either switch to BIKTARVY (N=290) or stay on their baseline antiretroviral regimen (N=287). Subjects had a mean age of 46 years (range 20–79), 83% were male, 66% were White, and 26% were Black. 19% of subjects identified as Hispanic/Latino. The mean baseline CD4+ cell count was 663 cells per mm^3 (range 62–2582). Subjects were stratified by prior treatment regimen. At screening, 15% of subjects were receiving ABC/3TC plus ATV or DRV (given with either cobicistat or ritonavir) and 85% of subjects were receiving FTC/TDF plus ATV or DRV (given with either cobicistat or ritonavir).

Treatment outcomes of Trials 1844 and 1878 through Week 48 are presented in Table 14.

Table 14 Virologic Outcomes of Trials 1844 and 1878 at Week 48[a] in Virologically-Suppressed Adults who Switched to BIKTARVY

	Trial 1844		Trial 1878	
	BIKTARVY (N=282)	**ABC/DTG/3TC** (N=281)	**BIKTARVY** (N=290)	**ATV- or DRV-based regimen[b]** (N=287)
HIV-1 RNA ≥ 50 copies/mL[c]	1%	<1%	2%	2%
Treatment Difference (95% CI)	0.7% (-1.0% to 2.8%)		0.0% (-2.5% to 2.5%)	
HIV-1 RNA < 50 copies/mL	94%	95%	92%	89%
No Virologic Data at Week 48 Window	5%	5%	6%	9%
Discontinued Study Drug Due to AE or Death and Last Available HIV-1 RNA < 50 copies/mL	2%	1%	1%	1%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d]	2%	3%	3%	7%
Missing Data During Window but on Study Drug	2%	1%	2%	2%

a. Week 48 window was between Day 295 and 378 (inclusive).
b. ATV given with cobicistat or ritonavir or DRV given with cobicistat or ritonavir plus either FTC/TDF or ABC/3TC.
c. Includes subjects who had ≥ 50 copies/mL in the Week 48 window; subjects who discontinued early due to lack or loss of efficacy; subjects who discontinued for reasons other than lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
d. Includes subjects who discontinued for reasons other than an AE, death, or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

In Trial 1844, treatment outcomes between treatment groups were similar across subgroups by age, sex, race, and region. The mean change from baseline in CD4+ count at Week 48 was -31 cells per mm^3 in subjects who switched to BIKTARVY and 4 cells per mm^3 in subjects who stayed on ABC/DTG/3TC.

In Trial 1878, treatment outcomes between treatment groups were similar across subgroups by age, sex, race, and region. The mean change from baseline in CD4+ count at Week 48 was 25 cells per mm^3 in patients who switched to BIKTARVY and 0 cells per mm^3 in patients who stayed on their baseline regimen.

In Trial 1825, an open-label single arm trial, the efficacy, safety, and pharmacokinetics of FTC and TAF (components of BIKTARVY) were evaluated in virologically-suppressed adults with ESRD (estimated creatinine clearance of less than 15 mL/min) on chronic hemodialysis treated with FTC+TAF in combination with elvitegravir and cobicistat as a fixed-dose combination tablet for 96 weeks (N=55). In an extension phase of Trial 1825,

10 virologically-suppressed subjects switched to BIKTARVY and all subjects remained virologically suppressed (HIV-1 RNA < 50 copies/mL) for 48 weeks.

In Trial 4449, the efficacy and safety of switching from a stable antiretroviral regimen to BIKTARVY (containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF) were evaluated in an open-label, single arm trial of virologically-suppressed (HIV-1 RNA less than 50 copies per mL) HIV-1 infected adults aged 65 years and over (N=86). Subjects treated with BIKTARVY had a mean age of 70 years (range: 65 to 80). The primary endpoint was the proportion of subjects with HIV RNA > 50 copies/mL at Week 48. No subjects had HIV RNA > 50 copies/mL. Ninety-one percent (78/86) of subjects remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 48. Eight subjects did not have virologic data at the Week 48 timepoint due to discontinuation or missing data.

14.4 Clinical Trial Results in Pediatric Subjects with HIV-1

In Trial 1474, an open-label, single arm trial the efficacy, safety, and pharmacokinetics of BIKTARVY in HIV-1 infected pediatric subjects were evaluated in virologically-suppressed adolescents between the ages of 12 to less than 18 years weighing at least 35 kg (N=50), in virologically-suppressed children between the ages of 6 to less than 12 years weighing at least 25 kg (N=50), and in virologically-suppressed children at least 2 years of age and weighing at least 14 to less than 25 kg (N=22).

Cohort 1: Virologically-suppressed adolescents (12 to less than 18 years; at least 35 kg)

Subjects in cohort 1 treated with BIKTARVY (containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF) once daily had a mean age of 14 years (range: 12 to 17) and a mean baseline weight of 51.7 kg (range: 35 to 123), 64% were female, 27% were Asian and 65% were black. At baseline, median CD4+ cell count was 750 cells per mm^3 (range: 337 to 1207), and median CD4+% was 33% (range: 19% to 45%).

After switching to BIKTARVY, 98% (49/50) of subjects in cohort 1 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 48. The mean change from baseline in CD4+ cell count at Week 48 was -22 cells per mm^3.

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Subjects in cohort 2 treated with BIKTARVY once daily had a mean age of 10 years (range: 6 to 11) and a mean baseline weight of 31.9 kg (range: 25 to 69), 54% were female, 22% were Asian and 72% were black. At baseline, median CD4+ cell count was 898 cells per mm^3 (range 390 to 1991) and median CD4+% was 37% (range: 19% to 53%).

After switching to BIKTARVY (containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF), 100% (50/50) of subjects in cohort 2 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 24. The mean change from baseline in CD4+ cell count at Week 24 was -24 cells per mm^3.

Cohort 3: Virologically-suppressed children (at least 2 years; at least 14 to less than 25 kg)

Subjects in cohort 3 treated with BIKTARVY (containing 30 mg of BIC, 120 mg of FTC, and 15 mg of TAF) once daily had a mean age of 5 years (range: 3 to 9) and a mean baseline weight of 18.8 kg (range: 14 to 24), 50% were female, 23% were Asian and 73% were black. At baseline, the mean CD4+ cell count (SD) was 1104 (440), and the mean CD4% (SD) was 33.4% (6.0%).

After switching to BIKTARVY, 91% (20/22) of subjects in cohort 3 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 24. HIV-1 RNA was not collected at Week 24 for 2 subjects because of COVID-19 pandemic-related study disruption. The mean change from baseline to Week 24 in CD4+ cell count (SD) was −126 (264.2) cells per mm^3 ; and the mean change in CD4% (SD) from baseline to Week 24 was 0.2% (4.4%).

16 HOW SUPPLIED/STORAGE AND HANDLING

BIKTARVY tablets are available in bottles and blister packs:

Bottle

- 50 mg/200 mg/25 mg tablets each contain 50 mg of bictegravir (BIC), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF). These tablets are purplish brown, capsule-shaped, and film-coated with “GSI” debossed on one side and “9883” on the other side (NDC 42067-100-01).

Each bottle contains 30 tablets, a silica gel desiccant, polyester coil, and is closed with a child-resistant closure. Do not remove the desiccant packet.

Store bottle below 30 °C (86 °F).

Keep bottle tightly closed.

This drug was imported from Canada without the authorization of Gilead Sciences Inc. under the State of Florida Section 804 Importation Program.

Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Post-treatment Acute Exacerbation of Hepatitis B in Patients with HBV Coinfection

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued products containing FTC and/or TDF, and may likewise occur with discontinuation of BIKTARVY *[see Warnings and Precautions (5.1)]*. Advise the patient to not discontinue BIKTARVY without first informing their healthcare provider.

Drug Interactions

BIKTARVY may interact with certain drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or non-prescription medication or herbal products including St. John's wort *[see Contraindications (4) and Drug Interactions (7)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any symptoms of infection, as in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started *[see Warnings and Precautions (5.3)]*.

Renal Impairment

Advise patients to avoid taking BIKTARVY with concurrent or recent use of nephrotoxic agents. Postmarketing cases of renal impairment, including acute renal failure, have been reported *[see Warnings and Precautions (5.4)].*

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to BIKTARVY. Advise patients that they should stop BIKTARVY if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.5)]*.

Missed Dosage

Inform patients that it is important to take BIKTARVY on a regular dosing schedule with or without food and to avoid missing doses as it can result in development of resistance *[see Dosage and Administration (2.2)]*.

Tablet Splitting

Advise caregivers that, 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 *[see Dosage and Administration (2.3)]*.

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to BIKTARVY *[see Use in Specific Populations (8.1)].*

Lactation

Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in breast milk *[see Use in Specific Populations (8.2)].*

Patient Information
BIKTARVY® (bik-TAR-vee)
(bictegravir, emtricitabine,
and tenofovir alafenamide)
tablets

Important: Ask your healthcare provider or pharmacist about medicines that should not be taken with BIKTARVY. For more information, see "What should I tell my healthcare provider before taking BIKTARVY?"

What is the most important information I should know about BIKTARVY?

BIKTARVY can cause serious side effects, including:

- **Worsening of hepatitis B virus (HBV) infection. Your healthcare provider will test you for HBV infection before or when you start treatment with BIKTARVY. If you have HBV infection and take BIKTARVY, your HBV may get worse (flare-up) if you stop taking BIKTARVY. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.**
  - Do not run out of BIKTARVY. Refill your prescription or talk to your healthcare provider before your BIKTARVY is all gone.
  - Do not stop taking BIKTARVY without first talking to your healthcare provider.
  - If you stop taking BIKTARVY, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver, and may give you a medicine to treat hepatitis B. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking BIKTARVY.

For more information about side effects, see "What are the possible side effects of BIKTARVY?"

What is BIKTARVY?

BIKTARVY is a prescription medicine that is used without other human immunodeficiency virus-1 (HIV-1) medicines to treat HIV-1 infection in adults and children who weigh at least 31 pounds (14 kg):

- who have not received HIV-1 medicines in the past, **or**
- to replace their current HIV-1 medicines for people whose healthcare provider determines that they meet certain requirements.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

BIKTARVY contains the medicines bictegravir, emtricitabine, and tenofovir alafenamide.

It is not known if BIKTARVY is safe and effective in children who weigh less than 31 pounds (14 kg).

Do not take BIKTARVY if you also take a medicine that contains:

- dofetilide
- rifampin

What should I tell my healthcare provider before taking BIKTARVY?

Before taking BIKTARVY, tell your healthcare provider about all your medical conditions, including if you:

- have liver problems, including HBV infection
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if BIKTARVY can harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with BIKTARVY.

  Pregnancy Registry: There is a pregnancy registry for women who take BIKTARVY during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. Do not breastfeed if you take BIKTARVY.
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - At least one of the medicines in BIKTARVY can pass to your baby in your breast milk. It is not known if the other medicines in BIKTARVY can pass into your breast milk.

  Talk with your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, antacids, laxatives, vitamins, and herbal supplements.

Some medicines may interact with BIKTARVY. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with BIKTARVY.

- **Do not start a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take BIKTARVY with other medicines.

How should I take BIKTARVY?

- Take BIKTARVY exactly as your healthcare provider tells you to take it. BIKTARVY is taken by itself (not with other HIV-1 medicines) to treat HIV-1 infection.
- Take BIKTARVY 1 time each day 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 swallowed within about 10 minutes.
- If you are on dialysis, take your daily dose of BIKTARVY following dialysis.
- Do not change your dose or stop taking BIKTARVY without first talking with your healthcare provider. Stay under a healthcare provider's care during treatment with BIKTARVY.
- If you take antacids that contain aluminum or magnesium, take BIKTARVY at least 2 hours before or 6 hours after you take these antacids.
- If you take supplements or antacids that contain iron or calcium, take BIKTARVY with food at the same time that you take these supplements or antacids.
- Do not miss a dose of BIKTARVY.
- If you take too much BIKTARVY, call your healthcare provider or go to the nearest hospital emergency room right away.
- When your BIKTARVY supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to BIKTARVY and become harder to treat.

What are the possible side effects of BIKTARVY?

BIKTARVY may cause serious side effects, including:

- **See "What is the most important information I should know about BIKTARVY?"**
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having any new symptoms after starting your HIV-1 medicine.
- **New or worse kidney problems, including kidney failure.** Your healthcare provider should do blood and urine tests to check your kidneys when starting and during treatment with BIKTARVY. Your healthcare provider may tell you to stop taking BIKTARVY if you develop new or worse kidney problems.
- **Too much lactic acid in your blood (lactic acidosis).** Too much lactic acid is a serious but rare medical emergency that can lead to death. **Tell your healthcare provider right away if you get these symptoms:** weakness or being more tired than usual, unusual muscle pain, being short of breath or fast breathing, stomach pain with nausea and vomiting, cold or blue hands and feet, feel dizzy or lightheaded, or a fast or abnormal heartbeat.
- **Severe liver problems.** In rare cases, severe liver problems can happen that can lead to death. **Tell your healthcare provider right away if you get these symptoms:** skin or the white part of your eyes turns yellow, dark "tea-colored" urine, light-colored stools, loss of appetite for several days or longer, nausea, or stomach-area pain.

The most common side effects of BIKTARVY are diarrhea, nausea, and headache.
These are not all of the possible side effects of BIKTARVY.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BIKTARVY?

- Store BIKTARVY bottle below 86 °F (30 °C).
- Keep the bottle tightly closed.
- BIKTARVY contains a desiccant packet to help keep your medicine dry (protect it from moisture). Keep the desiccant packet in the bottle. **Do not eat the desiccant packet.**
- Store BIKTARVY blister pack at room temperature between 68 °F to 77 °F (20 °C to 25 °C).
- Keep BIKTARVY in its original bottle or blister pack.
- BIKTARVY comes in a child-resistant package.

Keep BIKTARVY and all medicines out of reach of children.

General information about the safe and effective use of BIKTARVY.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use BIKTARVY for a condition for which it was not prescribed. Do not give BIKTARVY to other people, even if they have the

same symptoms you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about BIKTARVY that is written for health professionals.

What are the ingredients in BIKTARVY?

Active ingredients: bictegravir, emtricitabine, and tenofovir alafenamide.

Inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.

The tablets are film-coated with a coating material containing iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404

For more information, call 1-800-445-3235 or go to www.BIKTARVY.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised:10/2022

Annotated Label Comparisons

PI Comparisons FDA VS. FLCPDIP
Differences
Updated information Adverse Reactions Contact
How Supplied/Storage and Handling added SIP804 language
Patient Information added SIP804 language
Listed new NDC #
Added Importation language & Importer name & address
Listed only drug strength purchased for program

FDA

----------**DOSAGE FORMS AND STRENGTHS**----------
Tablets: 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF. (3)
Tablets: 30 mg of BIC, 120 mg of FTC, and 15 mg of TAF. (3)

----------**ADVERSE REACTIONS**----------
Most common adverse reactions (incidence greater than or equal to 5%, all grades) are diarrhea, nausea, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

3 DOSAGE FORMS AND STRENGTHS

BIKTARVY tablets are available in two dose strengths:

- 50 mg/200 mg/25 mg tablets: 50 mg of bictegravir (BIC) (equivalent to 52.5 mg of bictegravir sodium), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate). These tablets are purplish brown, capsule-shaped, film-coated, and debossed with "GSI" on one side and "9883" on the other side.
- 30 mg/120 mg/15 mg tablets: 30 mg of BIC (equivalent to 31.5 mg of bictegravir sodium), 120 mg of FTC, and 15 mg of TAF (equivalent to 16.8 mg of tenofovir alafenamide fumarate). These tablets are pink, capsule-shaped, film-coated, and debossed with "GSI" on one side and "B" on the other side.

FLSIP 804

----------**DOSAGE FORMS AND STRENGTHS**----------
Tablets: 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF. (3)
The 30 mg/120/mg/15mg tablets will not be imported by LifeScience Logistics.

----------**ADVERSE REACTIONS**----------
Most common adverse reactions (incidence greater than or equal to 5%, all grades) are diarrhea, nausea, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact LifeScience Logistics at 1-855-738-6171 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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- The 30 mg/120/mg/15mg tablets will not be imported by LifeScience Logistics.

FDA

11 DESCRIPTION

BIKTARVY (bictegravir, emtricitabine, and tenofovir alafenamide) is a fixed dose combination tablet containing bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF) for oral administration.

- BIC is an integrase strand transfer inhibitor (INSTI).
- FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- TAF, an HIV NRTI, is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

BIKTARVY tablets are available in two dose strengths:

- 50 mg/200 mg/25 mg tablet containing 50 mg of BIC (equivalent to 52.5 mg of bictegravir sodium), 200 mg of FTC, and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate).
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16 HOW SUPPLIED/STORAGE AND HANDLING

BIKTARVY tablets are available in bottles and blister packs:

Bottle

- 50 mg/200 mg/25 mg tablets each contain 50 mg of bictegravir (BIC), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF). These tablets are purplish brown, capsule-shaped, and film-coated with "GSI" debossed on one side and "9883" on the other side (NDC 61958-2501-1).
- 30 mg/120 mg/15 mg tablets each contain 30 mg of BIC,120 mg of FTC, and 15 mg of TAF. These tablets are pink, capsule-shaped, and film-coated with "GSI" debossed on one side and "B" on the other side (NDC 61958-2505-1).

Each bottle contains 30 tablets, a silica gel desiccant, polyester coil, and is closed with a child-resistant closure. Do not remove the desiccant packet.

Store bottle below 30 °C (86 °F).

Keep bottle tightly closed.

Blister Pack

- 50 mg/200 mg/25 mg tablets each contain 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF. These tablets are purplish brown, capsule-shaped, and film-coated with "GSI" debossed on one side and "9883" on the other side (NDC 61958-2501-3).

Each blister pack contains 30 tablets (4 strips each containing 7 tablets and 1 strip containing 2 tablets). Blister packs are sealed with a child-resistant laminated foil lidding material (peel-push), and each blister cavity contains a die-cut desiccant film which is heat staked to the foil lidding material.

Store blister pack at 25 °C (77 °F), excursions permitted to 15–30 °C (59–86 °F) (see USP Controlled Room Temperature).

FLSIP 804

11 DESCRIPTION

BIKTARVY (bictegravir, emtricitabine, and tenofovir alafenamide) is a fixed dose combination tablet containing bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF) for oral administration.

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Each bottle contains 30 tablets, a silica gel desiccant, polyester coil, and is closed with a child-resistant closure. Do not remove the desiccant packet.

Store bottle below 30 °C (86 °F).

Keep bottle tightly closed.

This drug was imported from Canada without the authorization of Gilead Sciences Inc. under the State of Florida Section 804 Importation Program.

Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

FDA

same symptoms you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about BIKTARVY that is written for health professionals.

What are the ingredients in BIKTARVY?
Active ingredients: bictegravir, emtricitabine, and tenofovir alafenamide.
Inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.
The tablets are film-coated with a coating material containing iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

For more information, call 1-800-445-3235 or go to www.BIKTARVY.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised:10/2022

FLSIP 804

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Manufactured and distributed by: Gilead Sciences, Inc. Foster City, CA 94404
BIKTARVY is a trademark of Gilead Sciences, Inc., or its related companies. All other trademarks referenced herein are the property of their respective owners.
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For more information, call 1-800-445-3235 or go to www.BIKTARVY.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised:10/2022

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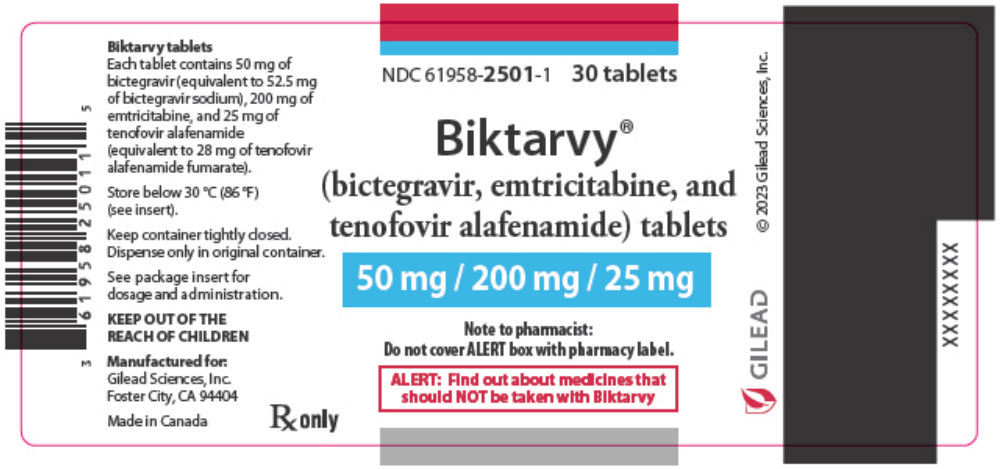
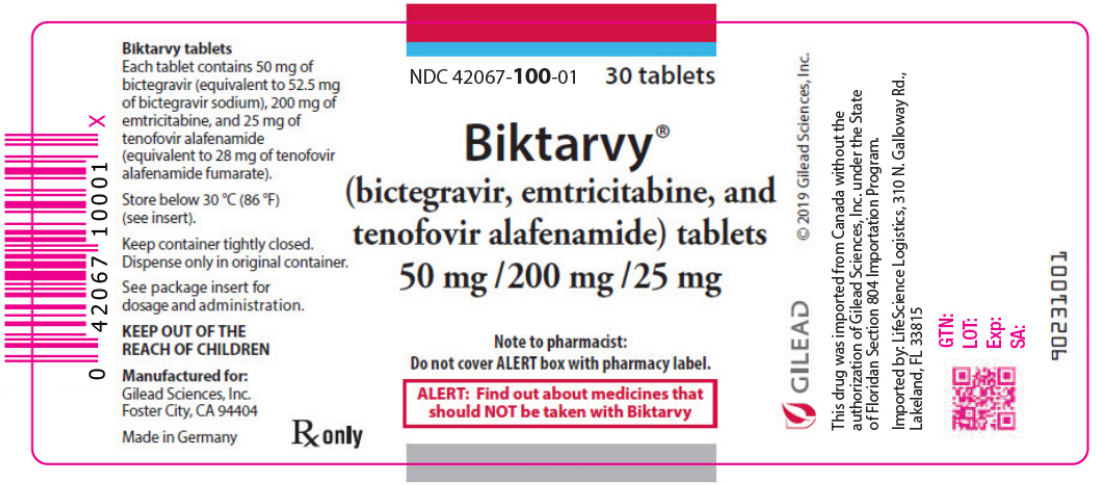
Proposed Package Label

Label Comparisons FDA VS. FLCPDIP
Differences
NDC
GTN
Bar Codes FPO with Associated NDCs
SIP804 Importation Language
Label SIZE due to production process & adding SIP804 language
Importer Name & Address
Brand logos FPO low resolution. Native art files requested upon SIP804 approval.





Comparisons FDA to FLSIP

Recent FDA Approved Label	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	Applicant Holder Address	US Active Ingredients	Date Labeling Prepared for FLSIP	FLSIP Proprietary Name	FLSIP Generic Name	FLSIP Strength	LSL NDC	Relabeler Name	Applicant Holder Name	Applicant Holder Address	Active Ingredients	FDA Comments
May-23	BIKTARVY	bictegrav-emtricit-tenofov ala	50-200-25 mg	61958-2501-1	210251	Gilead Sciences, Inc.	333 Lakeside Dr Foster City, CA 94404	bictegravir, emtricitabine, and tenofovir alafenamide	Aug-23	BIKTARVY	bictegrav-emtricit-tenofov ala	50-200-25 mg	42067-100-1	LifeScience Logistics, LLC	Gilead Sciences, Inc.	Foster City, CA 94404	bictegravir, emtricitabine, and tenofovir alafenamide	none

Canadian to FDA Drug Comparison

Comparisons

Canada to FDA

Active Ingredient	Canadian Submission Number	Canadian Proprietary Name	Canadian Generic Name	DIN	Date Labeling Approved	Company Name	Address	Canadian Strength	Dosage Form	# of active Ingred.	Canadian Ingredients	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	US Ingredients	Comments for FDA
Bictegravir/emtricitabine/tenofovir alafenamide	240953	BIKTARVY	bictegravir-emtricit-tenofov ala	02478579	Revision: November 2, 2021	Gilead Sciences Canada, Inc.	6711 Mississauga Rd, Suite 600 Mississauga, ON L5N 2W3	50-200-25 mg	Oral Tablet, Once daily	3	bictegravir, emtricitabine, and tenofovir alafenamide	BIKTARVY	bictegrav-emtricit-tenofov ala	50-200-25 mg	61958-2501-1	210251	Gilead Sciences, Inc. Foster City, CA 94404	bictegravir, emtricitabine, and tenofovir alafenamide	Generic not available.

Canadian Monograph

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr BIKTARVY®

Bictegravir/emtricitabine/tenofovir alafenamide tablets
50 mg bictegravir (as bictegravir sodium) / 200 mg emtricitabine / 25 mg tenofovir alafenamide (as tenofovir alafenamide hemifumarate), Oral

Antiretroviral Agent

Gilead Sciences Canada, Inc.
6711 Mississauga Rd, Suite 600
Mississauga, ON, Canada L5N 2W3

www.gilead.ca

Submission Control No: 250704

Date of Initial Authorization:
July 10, 2018

Date of Revision:
November 2, 2021

RECENT MAJOR LABEL CHANGES

1 Indications	10/2019
1 Indications, 1.1 Pediatrics	10/2019
1 Indications, 1.2 Geriatrics	05/2021
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	10/2019
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	05/2021
4 Dosage and Administration, 4.3 Administration	10/2019
7 Warnings and Precautions, General	12/2020
7 Warnings and Precautions, Endocrine and Metabolism	10/2019
7 Warnings and Precautions, Immune Reconstitution Syndrome	05/2019
7 Warnings and Precautions, Renal	05/2021
7 Warnings and Precautions, 7.1 Special Populations, 7.1.1 Pregnant Women	10/2019
7 Warnings and Precautions, 7.1 Special Populations, 7.1.3 Pediatrics	10/2019
7 Warnings and Precautions, 7.1 Special Populations, 7.1.4 Geriatrics	05/2021

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

BIKTARVY (bictegravir/emtricitabine/tenofovir alafenamide) is indicated as a complete regimen for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and pediatric patients weighing ≥ 25 kg with no known substitution associated with resistance to the individual components of BIKTARVY.

1.1 Pediatrics

Pediatrics (weighing ≥ 25 kg): The safety and efficacy in pediatric patients weighing ≥ 25 kg are based on data from an open-label clinical study (see **8 ADVERSE REACTIONS** and **14 CLINICAL TRIALS**).

Safety and efficacy of BIKTARVY in children weighing < 25 kg have not been established.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No differences in safety or efficacy have been observed between elderly patients and adult patients < 65 years of age (see **8 ADVERSE REACTIONS** and **14 CLINICAL TRIALS**).

2 CONTRAINDICATIONS

BIKTARVY is contraindicated in patients who are hypersensitive to bictegravir (BIC), emtricitabine (FTC), tenofovir alafenamide (TAF) or to any ingredient in the formulation or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.**

Coadministration of BIKTARVY is contraindicated with:

- dofetilide* due to the potential for increased dofetilide plasma concentrations and associated serious and/or life-threatening events (see **9 DRUG INTERACTIONS**).
- rifampin due to decreased BIC plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to BIKTARVY (see **9 DRUG INTERACTIONS**).
- St. John's wort due to the effect of St. John's wort on the BIC component of BIKTARVY. This may result in loss of therapeutic effect and development of resistance (see **9 DRUG INTERACTIONS**).

*Product not marketed in Canada

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Post-treatment Exacerbation of Hepatitis B**

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing FTC and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of BIKTARVY. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue BIKTARVY. If appropriate, anti-hepatitis B therapy may be warranted (see **7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

BIKTARVY is a three-drug fixed dose combination product containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF.

Testing
Prior to or when initiating BIKTARVY, test for hepatitis B virus infection.

Prior to or when initiating BIKTARVY, and during treatment with BIKTARVY, assess serum creatinine, estimated creatinine clearance (CrCl), urine glucose, and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus.

4.2 Recommended Dose and Dosage Adjustment

Adults and Pediatric Patients weighing ≥ 25 kg
The recommended dose of BIKTARVY is one tablet taken orally once daily with or without food.

Pediatrics (weighing < 25 kg)
BIKTARVY is not indicated for use in pediatric patients weighing < 25 kg

Geriatrics (≥ 65 years of age)
No dose adjustment of BIKTARVY is required for elderly patients. No differences in safety or efficacy have been observed between elderly patients and those < 65 years of age.

Renal Impairment
No dose adjustment of BIKTARVY is required in adult patients with estimated CrCl ≥ 30 mL/minute or in adult patients with end stage renal disease (ESRD; estimated CrCl < 15 mL/minute) who are receiving chronic hemodialysis. On days of hemodialysis, administer the daily dose of BIKTARVY after completion of hemodialysis treatment. BIKTARVY is not recommended in patients with estimated CrCl ≥ 15 and < 30 mL per minute, or < 15 mL/minute who are not receiving chronic hemodialysis, as the safety of BIKTARVY has not been

established in these populations.

No data are available to make dose recommendations in pediatric patients with renal impairment.

Hepatic Impairment
BIKTARVY is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) because it has not been studied in these patients. No dose adjustment of BIKTARVY is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment (see **10 CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions**).

4.3 Administration

The recommended dose of BIKTARVY is one tablet taken orally once daily with or without food in adults and pediatric patients weighing ≥ 25 kg.

4.4 Missed Dose

If a patient misses a dose of BIKTARVY within 18 hours of the time it is usually taken, the patient should take BIKTARVY as soon as possible, and then take the next dose of BIKTARVY at the regularly scheduled time. If a patient misses a dose of BIKTARVY by more than 18 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

5 OVERDOSAGE

No data are available on overdose of BIKTARVY in patients. If overdose occurs, the patient must be monitored for evidence of toxicity. Treatment of overdose with BIKTARVY consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

There is no specific antidote for overdose with BIKTARVY. As BIC is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis. FTC can be removed by hemodialysis, which removes approximately 30% of the FTC dose over a 3 hour dialysis period starting within 1.5 hours of FTC dosing. It is not known whether FTC can be removed by peritoneal dialysis.
Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Each tablet contains 50 mg of BIC (equivalent to 52.5 mg of bictegravir sodium), 200 mg of FTC, and 25 mg of TAF (equivalent to 28.0 mg of tenofovir alafenamide hemifumarate).	Croscarmellose Sodium, Iron Oxide Black, Iron Oxide Red, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Polyvinyl Alcohol, Talc, Titanium-Dioxide

BIKTARVY tablets are purplish brown, capsule-shaped, film-coated, and debossed with “GSI” on one side and “9883” on the other side.

BIKTARVY tablets are packaged in white, high density polyethylene (HDPE) bottles and enclosed with a polypropylene continuous thread child resistant cap, lined with an induction activated aluminum foil liner. Each bottle contains 7 or 30 tablets, silica gel desiccant, and polyester coil.

BIKTARVY tablets are also packaged in blister packaging which consists of a clear laminated blister film sealed to an aluminum lidding material. Each individual blister cavity contains a tablet and a die-cut desiccant film (Activ-Film™), which is heat staked to the lidding material. Each blister card is fitted between 2 paperboard cards, which are sealed together. There are 4 blister cards containing 7 tablets and 1 card containing 2 tablets placed inside a paperboard carton for a total of 30 tablets per pack.

7 WARNINGS AND PRECAUTIONS

Please see the **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

General
BIKTARVY should not be coadministered with any other antiretroviral products including products containing BIC, FTC, or TAF (ATRIPLA®, COMPLERA®, DESCOVY®, EMTRIVA®, GENVOYA®, ODEFSEY®, Symtuza™, STRIBILD®, TRUVADA®, VEMLIDY®); or with products containing lamivudine or tenofovir disoproxil fumarate (3TC®, ATRIPLA, Combivir®, COMPLERA, Delstrigo®, Dovato®, Heptovir®, Kivexa®, STRIBILD, Triumeq®, Trizivir®, TRUVADA, VIREAD®). BIKTARVY should not be administered with adefovir dipivoxil (HEPSERA®).

The safety and efficacy of BIKTARVY have not been established in patients who have failed treatment with an antiretroviral therapy regimen and are currently not virologically suppressed.

Driving and Operating Machinery
No studies on the effects of BIKTARVY on the ability to drive and use machines have been performed.

Endocrine and Metabolism

Serum Lipids and Blood Glucose
Serum lipid and blood glucose levels may increase during antiretroviral therapy (ART). Disease control and life style changes may also be contributing factors. Consideration should be given to the measurement of serum lipids and blood glucose. Lipid disorders and blood glucose elevations should be managed as clinically appropriate.

Hepatic/Biliary/Pancreatic

Lactic acidosis and severe hepatomegaly with steatosis
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogs, including FTC, a component of BIKTARVY, and TDF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with BIKTARVY should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Hepatic Impairment
Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at increased risk for severe hepatic adverse events (see **7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations**).

Immune

Immune Reconstitution Inflammatory Syndrome
Immune reconstitution inflammatory syndrome has been reported in patients treated with combination antiretroviral therapy, including FTC, a component of BIKTARVY. During the initial

phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution; however, the reported time to onset is more variable, and can occur many months after initiation of treatment.

Renal

Renal impairment
Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir prodrugs in both animal toxicology studies and human trials. In clinical trials with BIKTARVY, there have been no cases of Fanconi syndrome or proximal renal tubulopathy (PRT).

Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

BIKTARVY is not recommended in patients with estimated CrCl ≥ 15 and < 30 mL/min, or in patients with estimated CrCl < 15 mL/min who are not receiving chronic hemodialysis.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well controlled studies of BIKTARVY or its components in pregnant women. Dolutegravir (DTG), another integrase inhibitor, has been associated with neural tube defects (NTDs). There are insufficient human data on the use of BIKTARVY during pregnancy to inform a drug-associated risk of birth defects and miscarriage. BIKTARVY should not be used during pregnancy unless the potential benefits outweigh the potential risks to the fetus.

Bictegravir
Data from an observational study in Botswana showed that DTG, another integrase inhibitor, was associated with increased risk of neural tube defects when administered at the time of conception and in early pregnancy. Data available to date from other sources including the Antiretroviral Pregnancy Registry (APR), clinical trials, and postmarketing data are insufficient to address this risk with BIC.

Embryo-fetal development toxicity studies of BIC conducted in pregnant rats and rabbits revealed no evidence of adverse developmental effects at maternal exposures that were approximately 36 and 0.6 times, respectively, the human exposure at the recommended human dose. In rabbits, abortions and decreased fetal body weight were noted at maternally toxic exposures that were approximately 1.4 times the human exposure at the recommended human dose.

Emtricitabine
Reproductive studies were conducted in rats, mice, and rabbits. Animal studies (performed at 60- to 120-fold human exposure) did not indicate harmful effects of FTC with respect to fertility, pregnancy, fetal parameters, parturition or postnatal development.

Tenofovir Alafenamide
Embryonic fetal development studies performed in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus. The embryo-fetal NOAELs in rats and rabbits occurred at TAF exposures approximately 2 and 78 times higher than, respectively, the exposure in humans at the recommended daily dose of BIKTARVY. TAF is rapidly converted to tenofovir; the observed tenofovir exposure in rats and rabbits were 55 and 86 times higher, respectively, than human tenofovir exposures at the recommended human dose.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to ART (antiretroviral therapy), including BIKTARVY, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients:

http://www.apregistry.com
Telephone: (800) 258-4263
Fax: (800) 800-1052

7.1.2 Breast-feeding

In animal studies, BIC was detected in the plasma of nursing rat pups likely due to the presence of BIC in milk, without effects on nursing pups. In animal studies, it has been shown that tenofovir is secreted into milk. It is not known whether BIC or TAF are secreted in human milk. In humans, samples of breast milk obtained from five HIV-1 infected mothers given TRUVADA (FTC/TDF) show that FTC is secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the FTC IC_{50} but 3 to 12 times lower than the C_{min} achieved from oral administration of FTC. Breastfeeding infants whose mothers are being treated with FTC may be at risk for developing viral resistance to FTC. Other FTC-associated risks in infants breastfed by mothers being treated with FTC are unknown.

7.1.3 Pediatrics

Safety and effectiveness of BIKTARVY in pediatric patients weighing < 25 kg have not been established.

7.1.4 Geriatrics

Clinical studies included 111 patients aged 65 years and over who received BIKTARVY. No differences in safety or efficacy have been observed between elderly patients and those less than 65 years of age.

7.1.5 Patients Co-infected with HIV and HBV

Prior to or when initiating BIKTARVY, test for hepatitis B virus infection (see **4 DOSAGE AND ADMINISTRATION**).

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing FTC and/or TDF, and may occur with discontinuation of BIKTARVY. Therefore, patients co-infected with HIV-1 and HBV who discontinue BIKTARVY should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in HBV co-infected patients with advanced liver disease or cirrhosis since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following adverse drug reactions are discussed in other sections of the labeling:

- Severe Acute Exacerbations of Hepatitis B (See **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**)
- Immune Reconstitution Inflammatory Syndrome (See **7 WARNINGS AND PRECAUTIONS**)
- Lactic Acidosis/Severe Hepatomegaly with Steatosis (See **7 WARNINGS AND PRECAUTIONS**)

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Clinical Trials in Treatment-Naïve Adults

The primary safety assessment of BIKTARVY was based on Weeks 48, 96, and 144 pooled data from 1274 patients in two randomized, double-blind, active-controlled trials, Study 1489 and Study 1490, in antiretroviral treatment-naïve HIV-1 infected adult patients. A total of 634 patients received one tablet of BIKTARVY once daily (See **14 CLINICAL TRIALS**).

The most common adverse reactions (all Grades) reported in at least 5% of patients in the BIKTARVY group in Study 1489 were diarrhea, nausea, and headache. No adverse reactions were reported in at least 5% in the BIKTARVY group in Study 1490. The proportion of patients who discontinued treatment with BIKTARVY, abacavir [ABC]/DTG/lamivudine [3TC]), or DTG + FTC/TAF, due to adverse events, regardless of severity, was 0.9%, 1.6%, and 1.8% through Week 144, respectively. Table 2 and Table 3 display the frequency of adverse reactions (all Grades) greater than or equal to 2% in the BIKTARVY group in Study 1489 and Study 1490, respectively. The safety profile of BIKTARVY was consistent through Week 144 in both studies.

Table 2 **Adverse Reactions[a] (All Grades) Reported in ≥ 2% of HIV-1 Infected Treatment-Naïve Adults Receiving BIKTARVY in Study 1489 (Week 48 and 144 analysis)**

	Week 48		Week 144	
Adverse Reactions	**BIKTARVY** N=314 (%)	**ABC/DTG/3TC** N=315 (%)	**BIKTARVY** N=314 (%)	**ABC/DTG/3TC** N=315 (%)
GASTROINTESTINAL DISORDERS				
Diarrhea	6	4	6	4
Nausea	5	17	6	18
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Fatigue	3	3	3	3
NERVOUS SYSTEM DISORDERS				
Headache	5	5	5	5
Dizziness	2	3	2	3
PSYCHIATRIC DISORDERS				
Insomnia	2	3	2	3
Abnormal dreams	3	3	3	3

a. Frequencies of adverse reactions are based on all adverse events attributed to study drugs by the investigator. No adverse reactions of Grade 2 or higher occurred in ≥1% of patients treated with BIKTARVY in Study 1489.

Table 3 **Adverse Reactions[a] (All Grades) Reported in ≥ 2% of HIV-1 Infected Treatment-Naïve Adults Receiving BIKTARVY in Study 1490 (Week 48 and 144 analysis)**

	Week 48		Week 144	
Adverse Reactions	**BIKTARVY** N=320 (%)	**DTG + FTC/TAF** N=325 (%)	**BIKTARVY** N=320 (%)	**DTG + FTC/TAF** N=325 (%)
GASTROINTESTINAL DISORDERS				
Diarrhea	3	3	3	3
Nausea	3	5	3	5
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Fatigue	2	2	2	2
NERVOUS SYSTEM DISORDERS				
Headache	4	3	4	3
Dizziness	2	1	2	1
PSYCHIATRIC DISORDERS				
Insomnia	2	<1	2	<1

a. Frequencies of adverse reactions are based on all adverse events attributed to study drugs by the investigator. No adverse reactions of Grade 2 or higher occurred in ≥1% of patients treated with BIKTARVY in Study 1490.

Clinical Trials in Virologically Suppressed Adults

The safety of BIKTARVY in virologically suppressed adults was based on Week 48 data from 282 patients in a randomized, double-blind, active-controlled trial (Study 1844) in which virologically suppressed patients were switched from either DTG + ABC/3TC or ABC/DTG/3TC to BIKTARVY; and Week 48 data from 290 patients in an open-label, active-controlled trial in which virologically suppressed patients were switched from a regimen containing atazanavir (ATV) (given with cobicistat or ritonavir) or darunavir (DRV) (given with cobicistat or ritonavir) plus either FTC/TDF or ABC/3TC, to BIKTARVY (Study 1878). Overall, the safety profile in virologically suppressed adult patients in Studies 1844 and 1878 was similar to that in treatment-naïve patients.

Clinical Trials in Adults with Renal Impairment

The safety of FTC + TAF (components of BIKTARVY) was evaluated in a single arm, open-label clinical trial (GS-US-292-1825 [Study 1825]), in which 55 virologically-suppressed HIV-1 infected patients with ESRD (eGFR by Cockcroft-Gault method < 15 mL/min) on chronic hemodialysis received FTC+TAF in combination with elvitegravir (EVG) + cobicistat (COBI) as a fixed-dose combination tablet for 96 weeks. In an extension phase of Study 1825, 10 patients switched to BIKTARVY for 48 weeks. The safety profile of FTC + TAF in patients with ESRD on chronic hemodialysis was similar to that in patients with normal renal function, and no additional adverse reactions were identified in patients administered BIKTARVY in this study.

Clinical Trials in Geriatric Patients (≥ 65 years of age)

The safety of switching from a stable antiretroviral regimen to BIKTARVY was evaluated in an open-label, single arm trial of virologically suppressed HIV-1 infected adults aged 65 years and over (N=86), Study GS-US-380-4449 (Study 4449). No additional adverse drug reactions were identified through Week 48 in virologically suppressed patients aged ≥ 65 years administered BIKTARVY in this study.

Adverse Reactions from Clinical Trials of the Components of BIKTARVY

For information on the safety profiles of FTC or TAF, consult the Product Monographs for EMTRIVA®, VEMLIDY® or DESCOVY®.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The safety of BIKTARVY was evaluated in 50 HIV-1 infected virologically suppressed patients between the ages of 12 to < 18 years (weighing ≥ 35 kg) through Week 48 and in 50 virologically suppressed patients between the ages of 6 to < 12 years (weighing ≥ 25 kg) through Week 24 in an open label clinical study, GS-US-380-1474 (Study 1474). In Study 1474, the safety profile of BIKTARVY was similar to that in adults. Adverse reactions were reported in 10% of pediatric patients. No Grade 3 or 4 adverse reactions were reported. One patient (1%) had Grade 2 adverse reactions of insomnia and anxiety that led to discontinuation of BIKTARVY. The other adverse reactions that occurred in single patients were similar to those seen in adults.

8.3 Less Common Clinical Trial Adverse Reactions

Additional adverse reactions (all Grades) occurring in less than 2% of patients administered

BIKTARVY in Studies 1489 and 1490:

Gastrointestinal disorders: abdominal pain, dyspepsia, flatulence, vomiting
Psychiatric Disorders: depression
Skin and subcutaneous tissue disorders: rash

Suicidal ideation or suicide attempt (in patients with a pre-existing history of depression or psychiatric illness) occurred in < 1% of patients administered BIKTARVY.

The majority of adverse reactions were Grade 1.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

The frequency of laboratory abnormalities (Grades 3–4) occurring in at least 2% of patients receiving BIKTARVY in Studies 1489 and 1490 are presented in Table 4 and Table 5, respectively.

Table 4 Laboratory Abnormalities (Grades 3–4) Reported in ≥ 2% of Patients Receiving BIKTARVY in Study 1489 (Week 48 and 144 analysis)

	Week 48		Week 144	
Laboratory Parameter Abnormality[a]	**BIKTARVY** N=314 (%)	**ABC/DTG/3TC** N=315 (%)	**BIKTARVY** N=314 (%)	**ABC/DTG/3TC** N=315 (%)
Amylase (>2.0 x ULN)	2	2	3	4
ALT (>5.0 x ULN)	1	1	2	2
AST (>5.0 × ULN)	2	1	5	3
Creatine Kinase (≥10.0 × ULN)	4	3	8	8
Neutrophils (<750 mm^3)	2	3	3	4
LDL-cholesterol (fasted) (>190 mg/dL)	2	3	4	5

ULN = Upper limit of normal
a. Frequencies are based on treatment-emergent laboratory abnormalities.

Table 5 Laboratory Abnormalities (Grades 3–4) Reported in ≥ 2% of Patients Receiving BIKTARVY in Study 1490 (Week 48 and 144 analysis)

	Week 48		Week 144	
Laboratory Parameter Abnormality[a]	**BIKTARVY** N=320 (%)	**DTG + FTC/TAF** N=325 (%)	**BIKTARVY** N=320 (%)	**DTG + FTC/TAF** N=325 (%)
Amylase (>2.0 x ULN)	2	2	3	4
ALT (>5.0 x ULN)	2	1	3	1
AST (>5.0 × ULN)	1	3	2	3
Creatine Kinase (≥10.0 × ULN)	4	2	6	4
Neutrophils (<750 mm^3)	2	1	3	2
LDL-cholesterol (fasted) (>190 mg/dL)	3	4	4	6

ULN = Upper limit of normal

a. Frequencies are based on treatment-emergent laboratory abnormalities.

***Changes in Serum Creatinine*:** Bictegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function (see **10 CLINICAL PHARMACOLOGY**). Increases in serum creatinine occurred by Week 4 of treatment and remained stable through Week 144. In Studies 1489 and 1490, median (Q1, Q3) serum creatinine increased by 0.11 (0.03, 0.19) mg per dL, 0.11 (0.04, 0.19) mg per dL, and 0.12 (0.06, 0.21) mg per dL from baseline to Week 144 in the BIKTARVY, ABC/DTG/3TC, and DTG+FTC/TAF groups, respectively. There were no discontinuations due to renal adverse events through Week 144 in patients administered BIKTARVY in clinical studies.

***Changes in Bilirubin*:** In Studies 1489 and 1490, total bilirubin increases were observed in 17% of patients administered BIKTARVY through Week 144. Increases were primarily Grade 1 (12%) and Grade 2 (4%) (≥1.0 to 2.5 x ULN) and were not associated with hepatic adverse reactions or other liver related laboratory abnormalities. Five patients administered BIKTARVY (1%) had Grade 3 bilirubin increases that were not considered related to study drug. There were no discontinuations due to hepatic adverse events through Week 144 in BIKTARVY clinical studies.

8.5 Post-Market Adverse Reactions

In addition to the adverse reaction reports from clinical trials, the following possible adverse reactions have been identified during post-approval use of BIKTARVY or products containing FTC or TAF. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been considered possible adverse reactions due to a combination of their seriousness, frequency of reporting or potential causal relationship with treatment. No additional adverse reactions have been identified during post-approval use of other components of BIKTARVY.

BIKTARVY (BIC/FTC/TAF)

Skin and subcutaneous tissue disorders:	Stevens-Johnson syndrome/toxic epidermal necrolysis

Emtricitabine

The following adverse experiences have been reported in post-marketing experience without regard to causality; some events represent a single report.

Blood and lymphatic system disorders:	Thrombocytopenia
Gastrointestinal disorders:	Pancreatitis
General disorders and administrative site conditions:	Pyrexia
Metabolism and nutrition disorders:	Lactic acidosis

Tenofovir Alafenamide

Skin and subcutaneous tissue disorders:	Angioedema, urticaria

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

Coadministration of BIKTARVY is contraindicated with:

- Dofetilide* due to the potential for increased dofetilide plasma concentrations and associated serious and/or life-threatening events (see **9.4 Drug-Drug Interactions**)
- Rifampin due to decreased bictegravir plasma concentrations, which may result in the loss of therapeutic effect and development of resistance of BIKTARVY (see **9.4 Drug-Drug Interactions**)
- St. John's wort due to the effect of St. John's wort on the bictegravir component of BIKTARVY which may result in loss of therapeutic effect and development of resistance (see **9.4 Drug-Drug Interactions**).

*Product not marketed in Canada

9.2 Drug Interactions Overview

The drug interactions described in Table 6 are based on studies conducted with BIKTARVY, or the components of BIKTARVY (BIC, FTC, or TAF) as individual components and/or in combination, or are potential drug interactions that may occur with BIKTARVY. The table is not

comprehensive.

Potential for BIKTARVY to Affect Other Drugs

Bictegravir inhibits organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1) *in vitro*. Coadministration of BIKTARVY with the OCT2 and MATE1 substrate metformin did not result in a clinically significant increase in metformin exposure. BIKTARVY may be coadministered with substrates of OCT2 and MATE1 except dofetilide*, which is contraindicated due to the potential for increased dofetilide plasma concentrations and associated serious and/or life-threatening events (see **2 CONTRAINDICATIONS**).
*Product not marketed in Canada

Bictegravir is not an inhibitor or inducer of CYP3A *in vivo*.

Emtricitabine
In vitro and clinical pharmacokinetic drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving FTC with other medicinal products is low.

FTC is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of FTC with drugs that are eliminated by active tubular secretion may increase concentrations of FTC, and/or the coadministered drug.

Drugs that decrease renal function may increase concentrations of FTC.

Tenofovir Alafenamide
TAF is a substrate of P-gp and BCRP. Drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption.

TAF is not an inhibitor or inducer of CYP3A *in vivo*.

Potential for Other Drugs to Affect One or More Components of BIKTARVY
Bictegravir, a component of BIKTARVY, is a substrate of CYP3A and UGT1A1. Coadministration of BIC and drugs that potently induce both CYP3A and UGT1A1 may significantly decrease plasma concentrations of BIC, which may result in loss of therapeutic effect of BIKTARVY and development of resistance. Coadministration of BIC with drugs that potently inhibit both CYP3A and UGT1A1 may significantly increase plasma concentrations of BIC.

TAF, a component of BIKTARVY, is a substrate of P-gp and BCRP. Drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption (see Table 6). Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect of BIKTARVY and development of resistance. Coadministration of BIKTARVY with other drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of TAF (see Table 9).

9.3 Drug-Behavioural Interactions

Interactions of BIKTARVY with individual behavioural risks have not been established.

9.4 Drug-Drug Interactions

Drug-drug interaction studies were conducted with BIKTARVY or various combinations of the components of BIKTARVY (BIC, FTC or TAF).

BIKTARVY should not be coadministered with atazanavir due to a potential drug interaction. As BIKTARVY is a complete regimen, comprehensive information regarding drug-drug interactions with other antiretrovirals agents is not provided.

Drug interaction information for BIKTARVY with potential concomitant drugs is summarized in Table 6. The drug interactions described are based on studies conducted with either BIKTARVY, the components of BIKTARVY (BIC, FTC, and TAF) as individual agents, or are predicted drug interactions that may occur with BIKTARVY. For contraindicated drugs, see **2 CONTRAINDICATIONS**. For magnitude of interaction, see **Drug Interaction Studies**.

The table is not all-inclusive.

Table 6 Established or Potential[a] Drug-Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Anticonvulsants: carbamazepine[c] oxcarbazepine phenobarbital phenytoin	↓ BIC ↓ TAF	Coadministration of carbamazepine, oxcarbazepine, phenobarbital, or phenytoin may decrease BIC and TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Therefore, it is not recommended. Alternative anticonvulsants should be considered.
Antimycobacterials: rifabutin[c] rifampin[c,d] rifapentine	↓ BIC ↓ TAF	Coadministration of rifabutin, rifampin, or rifapentine may decrease BIC and TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of BIKTARVY with rifampin is contraindicated due to the effect of rifampin on the BIC component of BIKTARVY (see **2 CONTRAINDICATIONS**). Coadministration of BIKTARVY with rifabutin or rifapentine is not recommended.
HIV-1 Antiviral Agent: atazanavir[c,e]	↑ BIC	Coadministration of BIKTARVY with atazanavir is not recommended.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓ BIC ↓ TAF	Coadministration of BIKTARVY with St. John's wort is contraindicated.
Medications or oral supplements containing polyvalent cations (e.g. Mg, Al, Ca, Fe): Calcium or iron supplements[c] Cation-containing antacids or laxatives[c] Sucralfate Buffered medications	↓ BIC	Administer BIKTARVY 2 hours before or 2 hours after taking medications or oral supplements containing polyvalent cations. Alternatively, BIKTARVY and medications or oral supplements containing polyvalent cations can be taken together with food.

a. Table is not all inclusive
b. ↑ = increase, ↓ = decrease
c. Drug-drug interaction study was conducted.
d. Potent inducer of both CYP3A and UGT1A1.
e. Potent inhibitor of both CYP3A and UGT1A1.

Drug Interaction Studies

Drug-drug interaction studies were conducted with BIKTARVY or various combinations of BIKTARVY components (BIC, FTC or TAF).

The effects of coadministered drugs on the exposure of BIC are shown in Table 7 . The effects of coadministered drugs on the exposure of TAF are shown in Table 8. The effects of BIC and /or TAF on the exposure of coadministered drugs are shown in Table 9.

Drugs without Clinically Significant Interactions with BIKTARVY

Based on drug interaction studies conducted with BIKTARVY or the components of BIKTARVY, no clinically significant drug interactions have been either observed or are expected when BIKTARVY is combined with the following drugs: amlodipine, atorvastatin, buprenorphine, drospirenone, ethinyl estradiol, famciclovir, famotidine, fluticasone, itraconazole, ketoconazole, ledipasvir/sofosbuvir, metformin, methadone, midazolam, naloxone, norbuprenorphine, norgestimate, omeprazole, sertraline, sofosbuvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir.

Table 7 **Drug Interactions: Changes in Pharmacokinetic Parameters for Bictegravir in the Presence of the Coadministered Drug[a]**

Coadministered Drug	Dose of Coadministered Drug (mg)	Bictegravir (mg)	N	Mean % Change of Bictegravir Pharmacokinetic Parameters (90% CI)[b]		
				C_{max}	AUC	C_{min}
Atazanavir[c] (fed)	300+150 cobicistat once daily	75 single dose	15	↔	↑ 306% (↑276%, ↑337%)	NA
Atazanavir[d] (fed)	400 once daily	75 single dose	15	↔	↑ 315% (↑281%, ↑351%)	NA
Darunavir[e] (fed)	800+150 cobicistat once daily	75 once daily	13	↑ 52% (↑40%, ↑64%)	↑ 74% (↑62%, ↑87%)	↑ 111% (↑95%, ↑129%)
Ledipasvir/ Sofosbuvir (fed)	90/400 once daily	75 once daily	30	↔	↔	↔
Rifabutin (fasted)	300 once daily	75 once daily	13	↓ 20% (↓33%, ↓3%)	↓ 38% (↓47%, ↓28%)	↓ 56% (↓63%, ↓48%)
Rifampin (fed)	600 once daily	75 single dose	15	↓ 28% (↓33%, ↓22%)	↓ 75% (↓78%, ↓73%)	NA
Sofosbuvir/ velpatasvir/ voxilaprevir (fed)	400/100/100+100 voxilaprevir[f] once daily	50 once daily	30	↔	↔	↔
Voriconazole[e] (fasted)	300 twice daily	75 single dose	15	↔	↑ 61% (↑41%, ↑84%)	NA
Medications or Oral Supplements Containing Polyvalent Cations						
Maximum strength antacid (simultaneous administration, fasted)	20 mL[g] single dose (oral)	50 single dose	14	↓ 80% (↓84%, ↓76%)	↓ 79% (↓82%, ↓74%)	NA
Maximum strength antacid (2 h after BIKTARVY fasted)	20 mL[g] single dose (oral)	50 single dose	13	↔	↔	NA
Maximum strength antacid (2 h before BIKTARVY fasted)	20 mL[g] single dose (oral)	50 single dose	13	↓ 58% (↓67%, ↓48%)	↓ 52% (↓62%, ↓41%)	NA
Maximum strength antacid (simultaneous administration, fed[h])	20 mL[g] single dose (oral)	50 single dose	14	↓ 49% (↓57%, ↓38%)	↓ 47% (↓56%, ↓36%)	NA

Coadministered Drug	Dose of Coadministered Drug (mg)	Bictegravir (mg)	N	Mean % Change of Bictegravir Pharmacokinetic Parameters (90% CI)[b]		
				C_{max}	AUC	C_{min}
Calcium carbonate (simultaneous administration, fasted)	1200 single dose	50 single dose	14	↓ 42% (↓49%, ↓33%)	↓ 33% (↓43%, ↓22%)	NA
Calcium carbonate (simultaneous administration, fed[h])	1200 single dose	50 single dose	14	↔	↔	NA
Ferrous fumarate (simultaneous administration, fasted)	324 single dose	50 single dose	14	↓ 71% (↓74%, ↓67%)	↓ 63% (↓67%, ↓58%)	NA
Ferrous fumarate (simultaneous administration, fed[h])	324 single dose	50 single dose	14	↓ 25% (↓35%, ↓13%)	↔	NA

NA = Not Available / Not Applicable; 90% CIs of the GLSM ratio were within (↔), extended above (↑), or extended below (↓) the predetermined No Effect Boundaries.

a. All interaction studies conducted in healthy volunteers.
b. All No Effect Boundaries are 70% -143%.
c. Evaluated as a potent inhibitor of CYP3A, UGT1A1, and an inhibitor of P-gp.
d. Evaluated as a potent inhibitor of CYP3A and UGT1A1.
e. Evaluated as a potent inhibitor of CYP3A.
f. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.
g. Maximum strength antacid contained 80 mg aluminum hydroxide, 80 mg magnesium hydroxide, and 8 mg simethicone, per mL.
h. Reference treatment administered under fasted conditions.

Table 8 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir Alafenamide in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Tenofovir Alafenamide (mg)	N	Mean % Change of Tenofovir Alafenamide Pharmacokinetic Parameters (90% CI)[b]		
				C_{max}	AUC	C_{min}
Carbamazepine	300 twice daily	25 single dose[c]	22	↓57% (↓64%, ↓49%)	↓54% (↓60%, ↓46%)	NA
Ledipasvir/sofosbuvir	90/400 once daily	25 once daily	30	↔	↔	NA
Sofosbuvir/ velpastasvir/ voxilaprevir	400/100/100+100 voxilaprevir[d] once daily	25 once daily	30	↑28% (↑9%, ↑51%)	↑57% (↑44%, ↑71%)	NA

NA= Not Available / Not Applicable; 90% CIs of the GLSM ratio were within (↔), extended above (↑), or extended below (↓) the predetermined No Effect Boundaries

a. All interaction studies conducted in healthy volunteers.
b. All No Effect Boundaries are 70% -143% unless otherwise specified.
c. Study conducted with DESCOVY (FTC/TAF).
d. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Table 9 **Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of the Individual Components of BIKTARVY [a]**

Coadministered Drug	Dose of Coadministered Drug (mg)	Bictegravir (mg)	Tenofovir Alafenamide (mg)	N	Mean % Change of Coadministered Drug Pharmacokinetic Parameters (90% CI)[b]		
					C_{max}	AUC	C_{min}
Ledipasvir	90/400 once daily	75 once daily	25 once daily	30	↔	↔	↔
Sofosbuvir					↔	↔	NA
GS-331007[c]					↔	↔	↔
Metformin	500 twice daily	50 once daily	25 once daily	30	↔	↑39% (↑31%, ↑48%)	↑36% (↑21%, ↑53%)
Midazolam	2 single dose	50 once daily	25 once daily	14	↔	↔	NA
Norelgestromin	norgestimate 0.180/0.215/0.250 once daily / ethinyl estradiol 0.025 once daily	75 once daily	-	15	↔	↔	↔
Norgestrel					↔	↔	↔
Ethinyl estradiol					↔	↔	↔
Norelgestromin	norgestimate 0.180/0.215/0.250 once daily / ethinyl estradiol 0.025 once daily	-	25 once daily[d]	14	↔	↔	↔
Norgestrel					↔	↔	↔
Ethinyl estradiol					↔	↔	↔
Sertraline	50 single dose	-	10 once daily[e]	19	↔	↔	NA
Sofosbuvir	400//100/100 + 100[f] once daily	50 once daily	25 once daily	30	↔	↔	NA
GS-331007[c]					↔	↔	↔
Velpatasvir					↔	↔	↔
Voxilaprevir					↔	↔	↔

NA = Not Available / Not Applicable; 90% CIs of the GLSM ratio were within (↔), extended above (↑), or extended below (↓) the predetermined No Effect Boundaries
a. All interaction studies conducted in healthy volunteers.
b. All No Effect Boundaries are 70% -143% unless otherwise specified.
c. The predominant circulating nucleoside metabolite of sofosbuvir.
d. Study conducted with DESCOVY (FTC/TAF).
e. Study conducted with GENVOYA (EVG/COBI/FTC/TAF).
f. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

9.5 Drug-Food Interactions

The effect of food on the components of the BIKTARVY was evaluated with a high (~800 calories, 50% from fat) or moderate fat (600 calories, 27% from fat) meal relative to fasted conditions.

Relative to fasting conditions, the administration of BIKTARVY with a moderate or high fat meal resulted in a 24% increase in BIC exposure. The alterations in mean systemic exposures of BIC were not clinically significant.

Relative to fasting conditions, the exposure to FTC was similar following administration of BIKTARVY with a moderate or high fat meal.

Relative to fasting conditions, the administration of BIKTARVY with a moderate or high fat meal resulted in a 48% and 63% increase in TAF exposures, respectively. The alterations in mean systemic exposures of TAF were not clinically significant.

BIKTARVY may be administered without regard to food.

9.6 Drug-Herb Interactions

Coadministration of St. John's wort may significantly decrease BIC and TAF plasma concentrations, which may result in loss of therapeutic effect and development of resistance.

Coadministration of BIKTARVY with St. John's wort is contraindicated.

9.7 Drug-Laboratory Test Interactions

Interactions of BIKTARVY with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

BIKTARVY is a fixed-dose combination, single tablet regimen of the antiviral drugs BIC, FTC and TAF.

Bictegravir
Bictegravir is an integrase strand transfer inhibitor (INSTI) that binds to the integrase active site and blocks the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

Bictegravir has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2).

Emtricitabine
FTC is a nucleoside analogue of 2'-deoxycytidine. FTC is phosphorylated by cellular enzymes to form FTC triphosphate. FTC triphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

FTC has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus.

FTC triphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

Tenofovir Alafenamide
TAF is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). TAF is permeable into cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, TAF is more efficient than TDF in loading tenofovir into peripheral blood mononuclear cells (PBMCs) (including lymphocytes and other HIV target cells) and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

Tenofovir has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus. *In vitro* studies have shown that both FTC and tenofovir can be fully phosphorylated when combined in cells. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of mitochondrial toxicity *in vitro* based on several assays including mitochondrial DNA analyses.

10.2 Pharmacodynamics

Effects on Electrocardiogram
Bictegravir
In a thorough QT/QTc study in 48 healthy subjects, BIC at supratherapeutic doses of 1.5 and 6 times the recommended therapeutic dose did not affect the QT/QTc interval and did not prolong the PR interval.

Tenofovir Alafenamide
In a thorough QT/QTc study in 48 healthy subjects, TAF at the therapeutic dose or at a supratherapeutic dose approximately 5 times the recommended therapeutic dose did not affect the QT/QTc interval and did not prolong the PR interval.

Emtricitabine
The effect of FTC on the QT interval is not known.

Effects on Serum Creatinine
The effect of BIC on renal function was evaluated in a randomized, blinded, parallel, placebo-

controlled trial in 40 healthy subjects who received BIC 75 mg (n=20) or placebo (n=20) once daily with food for 14 days. Mean change from baseline in serum creatinine in the BIC group was 0.1 mg per dL on Days 7 and 14. BIC did not have a significant effect on the estimated glomerular filtration rate or on the actual glomerular filtration rate (determined by the clearance of probe drug, iohexol) compared with placebo.

10.3 Pharmacokinetics

The pharmacokinetic (PK) properties of the components of BIKTARVY are provided in Table 10. The multiple dose PK parameters of the components of BIKTARVY are provided in Table 11.

Table 10 Pharmacokinetic Properties of the Components of BIKTARVY

	Bictegravir	Emtricitabine	Tenofovir Alafenamide
Absorption			
T_{max} (h)[a]	2.0-4.0	1.5-2.0	0.5-2.0
Effect of high fat meal (relative to fasting)[b]	AUC ratio = 1.24 (1.16, 1.33) C_{max} Ratio = 1.13 (1.06, 1.20)	AUC Ratio = 0.96 (0.93, 0.99) C_{max} Ratio = 0.86 (0.78, 0.93)	AUC Ratio = 1.63 (1.43, 1.85) C_{max} Ratio= 0.92 (0.73, 1.14)
Distribution			
% Bound to human plasma proteins	>99	<4	~80
Source of protein binding data	*In vitro*	*In vitro*	*Ex vivo*
Blood-to-plasma ratio	0.64	0.6	1.0
Metabolism			
Metabolism	CYP3A UGT1A1	Not significantly metabolized	Cathepsin A[c] (PBMCs) CES1 (hepatocytes)
Elimination			
Major route of elimination	Metabolism	Glomerular filtration and active tubular secretion	Metabolism
$t_{1/2}$ (h)[d]	17.3	10	0.51[d]
% Of dose excreted in urine[d]	35	70	<1
% Of dose excreted in feces[e]	60.3	13.7	31.7

PBMCs = peripheral blood mononuclear cells; CES1 = carboxylesterase 1

a. Values reflect administration of BIKTARVY with or without food.

b. Values refer to geometric mean ratio [High-fat meal/fasting] in PK parameters and (90% confidence interval). High-calorie/high-fat meal = ~800 kcal, 50% fat.

c. *In vivo*, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. *In vitro* studies have shown that TAF is metabolized to tenofovir by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes.

d. $t_{1/2}$ values refer to median terminal plasma half-life. Note that the pharmacologically active metabolite of TAF, tenofovir diphosphate, has a half-life of 150-180 hours within PBMCs.

e. Dosing in mass balance studies: BIC (single dose administration of [^{14}C] BIC); FTC (single dose administration of [^{14}C] FTC after multiple dosing of FTC for ten days); TAF (single dose administration of [^{14}C] TAF).

Table 11 Multiple Dose PK Parameters of BIC, FTC, and TAF Following Oral Administration With or Without Food in HIV-Infected Adults

Parameter	Bictegravir[a] Mean (CV%)	Emtricitabine[b] Mean (CV%)	Tenofovir Alafenamide[c] Mean (CV%)
C_{max} (µg per mL)	6.15 (22.9)	2.13 (34.7)	0.121 (15.4)
AUC_{tau} (µg•h per mL)	102 (26.9)	12.3 (29.2)	0.142 (17.3)
C_{trough} (µg per mL)	2.61 (35.2)	0.096 (37.4)	NA

CV = Coefficient of Variation; NA = Not Applicable
a. From Population PK analysis in Studies 1489, 1490, 1844, and 1878; N=1193.
b. From Intensive PK analysis in Studies 1489, 1490, 1844, and 1878; N=77.
c. From Population PK analysis in Studies 1489 and 1490; N=486.

Linearity/Non-linearity

Bictegravir

The multiple dose pharmacokinetics of BIC are dose proportional over the dose range of 25 to 100 mg.

Emtricitabine

The multiple dose pharmacokinetics of FTC are dose proportional over the dose range of 25 to 200 mg.

Tenofovir Alafenamide

TAF exposures are dose proportional over the dose range of 8 mg to 125 mg.

Special Populations and Conditions

- **Pediatrics:** Mean BIC C_{trough} was lower in 50 pediatric patients aged 12 to < 18 years (≥ 35 kg) who received BIKTARVY in Study 1474 relative to adults following administration of BIKTARVY, but was not considered clinically significant based on exposure-response relationships; exposures of FTC and TAF in these pediatric patients were similar to those in adults (Table 12).

Table 12 Multiple Dose PK Parameters of BIC, FTC, and TAF Following Oral Administration of BIKTARVY in HIV-Infected Pediatric Patients Aged 12 to < 18 years and Weighing ≥ 35 kg (Adolescents)

Parameter	Bictegravir[a] Mean (CV%)	Emtricitabine[b] Mean (CV%)	Tenofovir Alafenamide[a] Mean (CV%)
C_{max} (µg per mL)	6.24 (27.1)	2.69 (34.0)	0.133 (70.2)
AUC_{tau} (µg•h per mL)	89.1 (31.0)	13.6 (21.7)	0.196 (50.3)
C_{trough} (µg per mL)	1.78 (44.4)	0.064 (25.0)	NA

CV=Coefficient of Variation; NA=Not Applicable
a. From Population PK analysis of Cohort 1 of Trial 1474 (n=50 for BIC; n=49 for TAF).
b. From Intensive PK analysis of Cohort 1 of Trial 1474 (n=24).

Mean BIC C_{max}, and exposures of FTC and TAF (AUC_{tau} and C_{max}) achieved in 50 pediatric patients between the ages of 6 to < 12 years and weighing ≥ 25 kg who received BIKTARVY in Study 1474 were higher than exposures in adults; however, the increase was not considered clinically significant as the safety profiles were similar in adult and pediatric patients (Table 13).

Table 13 Multiple Dose PK Parameters of BIC, FTC, and TAF Following Oral Administration of BIKTARVY in HIV-Infected Pediatric Patients Aged 6 to < 12 years and Weighing ≥ 25 kg (Children)

Parameter	Bictegravir[a] Mean (CV%)	Emtricitabine[b] Mean (CV%)	Tenofovir Alafenamide[a] Mean (CV%)
C_{max} (µg per mL)	9.46 (24.3)	3.89 (31.0)	0.205 (44.6)
AUC_{tau} (µg•h per mL)	128 (27.8)	17.6 (36.9)	0.278 (40.3)
C_{trough} (µg per mL)	2.36 (39.0)	0.227 (323)	NA

CV=Coefficient of Variation; NA=Not Applicable
a. From Population PK analysis of Cohort 2 of Trial 1474 (n=50 for BIC; n=47 for TAF).
b. From Intensive PK analysis of Cohort 2 of Trial 1474 (n=25 except n=24 for C_{trough}).

- **Geriatrics:** The pharmacokinetics of BIC, FTC, and TAF have not been fully evaluated in the elderly (65 years of age and older). Population pharmacokinetics analysis of HIV-infected patients in Phase 3 trials of BIKTARVY showed that age did not have a clinically relevant effect on exposures of BIC and TAF up to 74 years of age.

- **Sex:** Based on population pharmacokinetic analyses, no dosage adjustment for BIKTARVY is recommended based on gender.

- **Ethnic origin:** Based on population pharmacokinetic analyses, no dosage adjustment for BIKTARVY is recommended based on race.

- **Hepatic Insufficiency:**

  Bictegravir
  Clinically relevant changes in the pharmacokinetics of BIC were not observed in subjects with moderate (Child-Pugh Class B) hepatic impairment.

  Emtricitabine
  The pharmacokinetics of FTC have not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes; therefore, the impact of liver impairment should be limited.

  Tenofovir Alafenamide
  Clinically relevant changes in the pharmacokinetics of TAF or its metabolite tenofovir were not observed in subjects with mild, moderate, or severe (Child-Pugh Class A, B and C) hepatic impairment; no TAF dose adjustment is required in subjects with hepatic impairment.

- **Renal Insufficiency:**

  Severe Renal Impairment (estimated CrCl ≥ 15 and < 30 mL/minute)

  No clinically relevant differences in BIC, TAF, or tenofovir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment (estimated CrCl ≥ 15 and < 30 mL/minute) in Phase 1 studies. In a separate Phase 1 study of FTC alone, FTC exposures were increased in patients with severe renal impairment. The safety of BIKTARVY has not been established in patients with estimated CrCl ≥ 15 mL and < 30 mL/min.

  End Stage Renal Disease (estimated CrCl < 15 mL/minute)

  Exposures of FTC and tenofovir in 12 patients with ESRD (estimated CrCl < 15 mL/minute) on chronic hemodialysis who received FTC+TAF in combination with EVG+COBI as a fixed-dose combination tablet in Study 1825 were significantly higher than in patients with normal renal function. However, the safety profile of FTC+TAF in patients with ESRD on chronic hemodialysis who received FTC+TAF in combination with EVG+COBI was similar to that in patients with normal renal function. No clinically relevant differences in TAF pharmacokinetics were observed in patients with ESRD as compared to those with normal renal function.

  In the extension phase of Study 1825, a lower BIC C_{trough} was observed in patients with ESRD who received BIKTARVY compared to patients with normal renal function, but this difference was not considered clinically relevant.

  There are no pharmacokinetic data on BIC, FTC or TAF in patients with creatinine clearance < 15 mL/minute not on chronic hemodialysis.

- **Hepatitis B and/or Hepatitis C Virus Coinfection**
  Pharmacokinetics of BIC, FTC, and TAF have not been fully evaluated in patients coinfected with hepatitis B and/or C virus.

11 STORAGE, STABILITY AND DISPOSAL

Bottle
Dispense only in original container. Keep the bottle tightly closed. Do not use if seal over bottle opening is broken or missing. Store below 30°C.

Blister Pack
Dispense only in original container. Do not use if the foil over the blister or the seal around the blister card is broken. Store BIKTARVY between 15-30 °C (59-86 °F).

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

BIKTARVY (BIC, FTC, and TAF) is a fixed dose combination, single tablet regimen containing BIC, FTC, and TAF for oral administration.

Each tablet contains 50 mg of BIC (equivalent to 52.5 mg of bictegravir sodium), 200 mg of FTC, and 25 mg of TAF (equivalent to 28.0 mg of tenofovir alafenamide fumarate) and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Bictegravir

Drug Substance

Common Name: bictegravir sodium (USAN)

Chemical Name: Sodium (2R,5S,13aR)-7,9-dioxo-10-[(2,4,6-trifluorobenzyl)carbamoyl]-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate

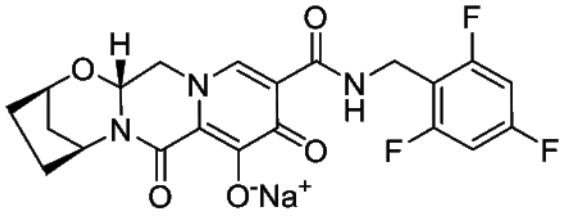
Empirical formula: $C_{21}H_{17}F_3N_3NaO_5$

$C_{21}H_{18}F_3N_3O_5$ (bictegravir free acid)

Molecular Weight: 471.4

449.4 (bictegravir free acid)

Structural formula:



Physicochemical Properties:

Description: Bictegravir sodium is an off-white to yellow solid.

Solubility: The solubility is approximately 0.1 mg per mL in water at 20°C. The partition coefficient (log P) is 1.45 and the pKa is 8.6.

Emtricitabine

Drug Substance

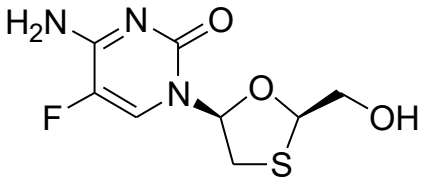
Common Name: emtricitabine (USAN)

Chemical Name: 5-fluoro-1-(2R,5S)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine

Empirical Formula: $C_8H_{10}FN_3O_3S$

Molecular Weight: 247.24

Structural Formula:



Physicochemical Properties:

Description: FTC is a white to off-white crystalline powder.

Solubility: The solubility is approximately 112 mg/mL in water at 25 °C. The partition coefficient (log P) is −0.43 and the pKa is 2.65.

Tenofovir alafenamide

Drug Substance

Common Name: Tenofovir alafenamide hemifumarate
Tenofovir alafenamide fumarate (USAN)

Chemical Name: Propan-2-yl N-[(S)-({[(2R)-1-(6-amino-9H-purin-9-yl)propan-2-yl]-oxy}methyl)(phenoxy)phosphoryl]-l-alaninate, (2E)-but-2-enedioate (2:1)

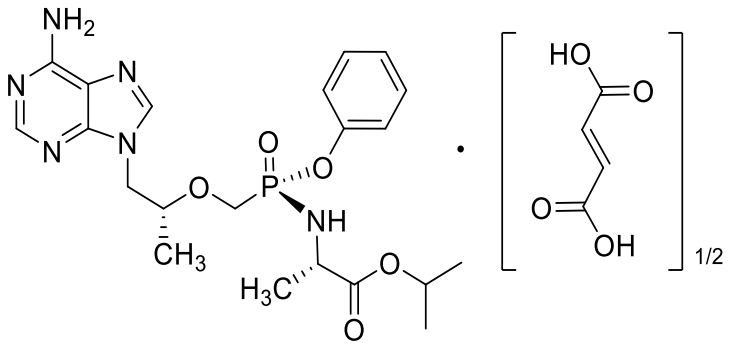
Empirical Formula: $C_{21}H_{29}O_5N_6P \cdot 1/2(C_4H_4O_4)$

$C_{21}H_{29}O_5N_6P$ (tenofovir alafenamide free base)

Molecular Weight: 534.5

476.5 (tenofovir alafenamide free base)

Structural Formula:



Physicochemical Properties:

Description: TAF hemifumarate is a white to off-white or tan powder.

Solubility: The solubility of TAF hemifumarate in water, pH 8.0 (50 mM phosphate buffer) at 20 °C is 4.86 mg/mL. The partition coefficient (log P) is 1.6 and the pKa is 3.96.

14 CLINICAL TRIALS

The efficacy and safety of BIKTARVY were evaluated in the studies summarized in Table 14.

14.1 Trial Design and Study Demographics

Table 14 Trials Conducted with BIKTARVY in Patients with HIV-1 Infection

Trial	Population	Study Arms (N)	Timepoint (Week)
Study 1489[a]	Treatment-naïve adults	BIKTARVY (314) ABC/DTG/3TC (315)	144
Study 1490[a]		BIKTARVY (320) DTG + FTC/TAF(325)	144
Study 1844[a]	Virologically-suppressed[c] adults	BIKTARVY (282) ABC/DTG/3TC (281)	48
Study 1878[b]		BIKTARVY (290) ATV or DRV (with cobicistat or ritonavir) plus either FTC/TDF or ABC/3TC (287)	48
Study 1474[d] Cohort 1	Virologically-suppressed[c] adolescents (Cohort 1: 12 to < 18 years of age; weight ≥ 35 kg	BIKTARVY (50)	48
Study 1474[d] Cohort 2	Virologically-suppressed[c] children (Cohort 2: 6 to < 12 years of age; weight ≥ 25 kg	BIKTARVY (50)	24
Study 1825	Virologically suppressed[c] adults with ESRD[e] receiving chronic hemodialysis	FTC+TAF in combination with EVG and COBI as a fixed-dose combination (55). In an extension phase of Study 1825, 10 virologically suppressed patients switched to BIKTARVY.	48[f]
Study 4449	Virologically suppressed[c] adults aged 65 years and over	BIKTARVY (86)	48

a. Randomized, double blind, active controlled trial.
b. Randomized, open label, active controlled trial.
c. HIV-1 RNA less than 50 copies per mL.
d. Open label trial
e. End stage renal disease (estimated CrCl of less than 15 mL per minute by Cockcroft-Gault method).
f. Patients received FTC+TAF in combination with elvitegravir and cobicistat for 96 weeks, followed by an extension phase in which 10 patients received BIKTARVY for 48 weeks.

Treatment-Naïve HIV-1 Infected Patients

The efficacy and safety of Biktarvy in HIV-1 infected, treatment-naïve adults are based on 48-week data from two randomized, double-blind, active-controlled studies, GS-US- 380-1489 (N=629) and GS-US-380-1490 (N=645).

In Study 1489, patients were randomized in a 1:1 ratio to receive either BIKTARVY (N=314) or ABC/DTG/3TC (600/50/300 mg) (N=315) once daily. In Study 1490, patients were randomized in a 1:1 ratio to receive either BIKTARVY (N=320) or DTG + FTC/TAF (50+200/25 mg) (N=325) once daily.

In Study 1489, the mean age was 34 years (range 18–71), 90% were male, 57% were White, 36% were Black, and 3% were Asian. 22% of patients identified as Hispanic or Latino. The mean baseline plasma HIV-1 RNA was 4.4 $\log_{10}$ copies/mL (range 1.3-6.5). The mean baseline CD4+ cell count was 464 cells per mm^3 (range 0-1424) and 11% had CD4+ cell counts less than 200 cells per mm^3. 16% of patients had baseline viral loads greater than 100,000 copies per mL.

In Study 1489, 0.6% of patients had HIV/HCV coinfection at baseline. In Study 1490, the mean age was 37 years (range 18-77), 88% were male, 59% were White, 31% were Black, and 3% were Asian. 25% of patients identified as Hispanic or Latino. The mean baseline plasma HIV-1 RNA was 4.4 $\log_{10}$ copies/mL (range 2.3-6.6). The mean baseline CD4+ cell count was 456 cells per mm^3 (range 2-1636), and 12% had CD4+ cell counts less than 200 cells per mm^3. 19% of patients had baseline viral loads greater than 100,000 copies per mL. In Study 1490, 2% of patients had HIV/HBV coinfection and 2% had HIV/HCV coinfection at baseline.

In both studies, patients were stratified by baseline HIV-1 RNA (less than or equal to 100,000 copies/mL, greater than 100,000 copies per mL to less than or equal to 400,000 copies per mL, or greater than 400,000 copies/mL), by CD4 count (less than 50 cells/µL, 50-199 cells/µL, or greater than or equal to 200 cells/µL), and by region (US or ex-US).

For demographic and baseline characteristics for Study 1489 and 1490, see Table 15.

Table 15 **Demographic and Baseline Characteristics of Treatment-Naïve Patients in Studies 1489 and 1490**

	Study 1489			Study 1490		
	BIKTARVY N = 314 n (%)	**ABC/DTG/3TC N = 315 n (%)**	**Total N = 629 n (%)**	**BIKTARVY N=320 n (%)**	**DTG + F/TAF N=325 n (%)**	**Total N=645 n (%)**
Demographic characteristics						
Median age, years (range)	31 (18-71)	32 (18-68)	32 (18-71)	33 (18-71)	34 (18-77)	34 (18-77)
Sex						
Male	285 (91)	282 (90)	567 (90)	280 (88)	288 (89)	568 (88)
Female	29 (9)	33 (10)	62 (10)	40 (13)	37 (11)	77 (12)
Race						
American Indian or Alaska Native	2 (0.6)	4 (1)	6 (1)	1 (0.3)	1 (0.3)	2 (0.3)
Asian	6 (2)	10 (3)	16 (3)	7 (2)	10 (3)	17 (3)
Black	114 (37)	112 (36)	226 (36)	97 (30)	100 (31)	197 (31)
Native Hawaiian or Pacific Islander	1 (0.3)	2 (0.6)	3 (0.5)	1 (0.3)	0	1 (0.2)
White	180 (58)	179 (57)	359 (57)	183 (57)	195 (60)	378 (59)
Other	9 (3)	8 (3)	17 (3)	31 (10)	19 (6)	50 (8)
Not Permitted[a]	2	0	2	-	-	-
Baseline disease characteristics						
Median baseline HIV-1 RNA log_{10} copies/mL (range)	4.42 (2.23-6.52)	4.51 (1.28-6.19)	4.47 (1.28-6.52)	4.43 (2.29-6.58)	4.45 (2.76-6.15)	4.44 (2.29-6.58)
Patients with viral load ≤ 100,000 copies/mL	261 (83)	265 (84)	526 (84)	254 (79)	271 (83)	525 (81)
Patients with viral load > 100,000 copies/mL	53 (17)	50 (16)	103 (16)	66 (21)	54 (17)	120 (19)
Patients with CD4+ cell counts < 200 cells/mm^3	36 (11)	32 (10)	68 (11)	44 (14)	34 (10)	78 (12)
HIV disease status						
Asymptomatic	286 (91)	286 (91)	572 (91)	286 (89)	288 (89)	574 (89)

	Study 1489			Study 1490		
	BIKTARVY N = 314 n (%)	ABC/DTG/3TC N = 315 n (%)	Total N = 629 n (%)	BIKTARVY N=320 n (%)	DTG + F/TAF N=325 n (%)	Total N=645 n (%)
Symptomatic HIV infection	16 (5)	14 (4)	30 (5)	10 (3)	11 (3)	21 (3)
AIDS	12 (4)	15 (5)	27 (4)	24 (8)	26 (8)	50 (8)
$eGFR_{CG}$ (mL/min), median (Q1, Q3)	125.9 (107.7, 146.3)	123.0 (107.0, 144.3)	124.8 (107.6, 145.2)	120.4 (100.8, 141.8)	120.6 (102.8, 145.1)	120.6 (102.1, 143.3)
HIV/HBV Coinfection Status[b]						
Yes	0	0	0	8 (3)	6 (2)	14 (2)
No	313 (100)	312 (100)	625 (100)	310 (97)	318 (98)	628 (98)
Missing	1	3	4	2	1	3
HIV/HCV Coinfection Status[b]						
Yes	0	4 (1)	4 (0.6)	5 (2)	5 (2)	10 (2)
No	313 (100)	311 (99)	624 (99)	315 (98)	320 (98)	635 (98)
Missing	1	0	1	-	-	-

a. Not Permitted = Local regulators did not allow collection of race or ethnicity information.
For race and ethnicity, patients who reported "Not Permitted" were excluded from the percentage and p-value calculation.

b. HIV/HBV and HIV/HCV coinfection status were missing when test was not done at screening.

HIV-1 Virologically-Suppressed Patients Who Switched to BIKTARVY

In Study 1844, the efficacy and safety of switching from a regimen of DTG + ABC/3TC or ABC/DTG/3TC to BIKTARVY were evaluated in a randomized, double-blind study of virologically-suppressed (HIV-1 RNA less than 50 copies per mL) HIV-1 infected adults (N=563). Patients must have been stably suppressed (HIV-1 RNA less than 50 copies per mL) on their baseline regimen for at least 3 months prior to study entry. Patients were randomized in a 1:1 ratio to either switch to BIKTARVY at baseline (N=282), or stay on their baseline antiretroviral regimen as the FDC of ABC/DTG/3TC (N=281). Patients had a mean age of 45 years (range 20–71), 89% were male, 73% were White, and 22% were Black. 17% of patients identified as Hispanic/Latino. The mean baseline CD4+ cell count was 723 cells per mm^3 (range 124–2444). At baseline, one patient had HIV/HCV coinfection.

In Study 1878, the efficacy and safety of switching from either ABC/3TC or FTC/TDF (200/300 mg) plus ATV or DRV (given with either cobicistat or ritonavir) to BIKTARVY were evaluated in a randomized, open-label study of virologically-suppressed HIV-1 infected adults (N=577). Patients must have been stably suppressed on their baseline regimen for at least 6 months and must not have been previously treated with any INSTI. Patients were randomized in a 1:1 ratio to either switch to BIKTARVY (N=290) or stay on their baseline antiretroviral regimen (N=287).

Patients had a mean age of 46 years (range 20–79), 83% were male, 66% were White, and 26% were Black. 19% of patients identified as Hispanic/Latino. The mean baseline CD4+ cell count was 663 cells per mm^3 (range 62–2582). Patients were stratified by prior treatment regimen (ie, TDF-containing regimen vs non-TDF containing regimen). At screening, 15% of patients were receiving ABC/3TC plus ATV or DRV (given with either cobicistat or ritonavir) and 85% of patients were receiving FTC/TDF plus ATV or DRV (given with either cobicistat or ritonavir). At baseline, 2% of patients had HIV/HBV coinfection and 2% had HIV/HCV coinfection.

For demographic and baseline characteristics for Studies 1844 and 1878, see Table 16.

Table 16 Demographic and Baseline Characteristics of Virologically Suppressed Patients in Studies 1844 and 1878

	Study 1844			Study 1878		
	BIKTARVY N = 282 n (%)	**ABC/DTG/3TC N = 281 n (%)**	**Total N = 563 n (%)**	**BIKTARVY N=290 n (%)**	**SBR N=287 n (%)**	**Total N=577 n (%)**
Demographic characteristics						
Median age, years (range)	47 (21-71)	45 (20-70)	46 (20-71)	48 (20-74)	47 (21-79)	48 (20-79)
Sex						
Male	247 (88)	252 (90)	499 (89)	243 (84)	234 (82)	477 (83)
Female	35 (12)	29 (10)	64 (11)	47 (16)	53 (18)	100 (17)
Race						
American Indian or Alaska Native	2 (0.7)	2 (0.7)	4 (0.7)	3 (1)	3 (1)	6 (1)
Asian	9 (3)	9 (3)	18 (3)	6 (2)	10 (3)	16 (3)
Black	59 (21)	62 (22)	121 (22)	79 (27)	72 (25)	151 (26)
Native Hawaiian or Pacific Islander	3 (1)	0	3 (0.5)	0	0	0
White	206 (73)	202 (73)	408 (73)	188 (65)	190 (66)	378 (66)
Other	3 (1)	3 (1)	6 (1)	14 (5)	12 (4)	26 (5)
Not Permitted[a]	0	3	3	-	-	-
Baseline disease characteristics						
Patients with CD4+ cell counts < 200 cells/mm^3	6 (2)	4 (1)	10 (2)	4 (1)	8 (3)	12 (2)

	Study 1844			Study 1878		
	BIKTARVY N = 282 n (%)	**ABC/DTG/3TC N = 281 n (%)**	**Total N = 563 n (%)**	**BIKTARVY N=290 n (%)**	**SBR N=287 n (%)**	**Total N=577 n (%)**
CD4 cell count (cells/mm^3), median (range)	732 (124-2444)	661 (125-1570)	695 (124-2444)	617 (147-2582)	626 (62-1684)	624 (62-2582)
HIV disease status						
Asymptomatic	243 (86)	245 (87)	488 (87)	240 (83)	234 (82)	474 (82)
Symptomatic HIV infection	9 (3)	9 (3)	18 (3)	16 (6)	20 (7)	36 (6)
AIDS	30 (11)	27 (10)	57 (10)	34 (12)	33 (11)	67 (12)
$eGFR_{CG}$ (mL/min), median (Q1, Q3)	100.5 (84.5, 119.0)	100.7 (84.9, 122.4)	100.7 (84.6, 120.1)	106.7 (87.0, 124.2)	104.9 (87.1, 125.3)	105.6 (87.1, 124.8)
HIV/HBV Coinfection Status[b]						
Yes	0	0	0	8 (3)	6 (2)	14 (2)
No	282 (100)	281 (100)	563 (100)	278 (97)	280 (98)	558 (98)
Missing	-	-	-	4	1	5
HIV/HCV Coinfection Status[b]						
Yes	0	1 (0.4)	1 (0.2)	5 (2)	5 (2)	10 (2)
No	282 (100)	280 (100)	562 (100)	283 (98)	282 (98)	565 (98)
Missing	-	-	-	2	0	2

a. Not Permitted = Local regulators did not allow collection of race or ethnicity information.
For race and ethnicity, patients who reported "Not Permitted" were excluded from the percentage and p-value calculation.

b. HIV/HBV and HIV/HCV coinfection status were missing when test was not done at screening.

Pediatric Patients

In Study 1474, an open-label, single arm trial the efficacy, safety, and pharmacokinetics of BIKTARVY in HIV-1 infected pediatric patients were evaluated in virologically-suppressed adolescents between the ages of 12 to less than 18 years weighing at least 35 kg (N=50) and in virologically-suppressed children between the ages of 6 to less than 12 years weighing at least 25 kg (N=50). Demographics and baseline characteristics for patients in the 2 study cohorts (Cohort 1: virologically suppressed adolescents [12 to < 18 years; ≥ 35 kg]; Cohort 2: virologically suppressed children [6 to < 12 years; ≥ 25 kg]) are presented in Table 17.

Table 17 Demographic and Baseline Characteristics of Virologically Suppressed Pediatric Patients in Study 1474 (Cohort 1 and Cohort 2)

	Study 1474	
	Cohort 1 12 to < 18 years of age (N=50)	**Cohort 2 6 to < 12 years of age (N=50)**
Demographic characteristics		
Median age, years (range)	15 (12-17)	10 (6-11)
Sex		
Male	18	23
Female	32	27
Race		
Asian	13	11
Black	32	36
Baseline BMI (kg/m^2), median (Q1, Q3)	19.1 (17.8, 22.4)	16.7 (15.6, 18.7)
Baseline disease characteristics		
HIV-1 RNA Category (copies/mL)		
< 50	50	50
≥ 50	0	0
CD4 cell count (cells/µL), median (Q1, Q3)	750 (586, 926)	898 (707, 1121)
eGFR by Schwartz formula (mL/min/1.73 m^2), median (Q1, Q3)	145.0 (134.0, 170.0)	153.5 (144.0, 173.0)

14.2 Study Results

Clinical Trial Results in Treatment-Naïve HIV-1 Infected Patients

Treatment outcomes of Studies 1489 and 1490 through 48 and 144 weeks are presented in Table 18.

Table 18 **Virologic Outcomes of Randomized Treatment in Studies 1489 and 1490 at Weeks 48[a] and 144[b] in Treatment-Naïve Patients**

	Week 48				Week 144			
	Trial 1489		Trial 1490		Trial 1489		Trial 1490	
	BIKTARVY (N=314)	ABC/DTG/ 3TC (N=315)	BIKTARVY (N=320)	DTG + FTC/TAF (N=325)	BIKTARVY (N=314)	ABC/DTG/ 3TC (N=315)	BIKTARVY (N=320)	DTG + FTC/TAF (N=325)
HIV-1 RNA < 50 copies/mL	92%	93%	89%	93%	82%	84%	82%	84%
Treatment Difference (95% CI) BIKTARVY vs. Comparator	-0.6% (-4.8% to 3.6%)		-3.5% (-7.9% to 1.0%)		−2.6% (−8.5% to 3.4%)		−1.9% (−7.8% to 3.9%)	
HIV-1 RNA ≥ 50 copies/mL[c]	1%	3%	4%	1%	<1%	3%	5%	3%
No Virologic Data at Week 48 or Week 144 Window	7%	4%	6%	6%	18%	13%	13%	13%
Discontinued Study Drug Due to AE or Death[d]	0	1%	1%	1%	<1%	2%	3%	3%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL[e]	5%	3%	3%	4%	16%	11%	11%	9%
Missing Data During Window but on Study Drug	2%	<1%	2%	1%	1%	<1%	0	1%

a Week 48 window was between Day 295 and 378 (inclusive).
b. Week 144 window was between Day 967 and 1050 (inclusive).
c. Includes patients who had ≥ 50 copies/mL in the Week 48 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
d. Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
e. Includes patients who discontinued for reasons other than an AE, death, or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc

BIKTARVY was noninferior in achieving HIV-1 RNA less than 50 copies per mL at Weeks 48, 96 and 144 when compared to ABC/DTG/3TC and to DTG+FTC/TAF, respectively. In Study 1489, 88% of patients who received BIKTARVY versus 90% of patients who received ABC/DTG/3TC, had HIV RNA <50 copies/mL at Week 96. At Week 96, 1% of patients who received BIKTARVY had HIV-1 RNA ≥50 copies/mL versus 2% in those who received ABC/DTG/3TC. The percentage of patients with no virologic data at the Week 96 window was 12% and 8% for those who received BIKTARVY and ABC/DTG/3TC, respectively. In Study 1490, 84% of patients who received BIKTARVY versus 87% of patients who received DTG+FTC/TAF, had HIV RNA <50 copies/mL at Week 96. At Week 96, 4% of patients who received BIKTARVY had HIV-1 RNA ≥50 copies/mL versus 3% in those who received DTG+FTC/TAF. The percentage of patients with no virologic data at the Week 96 window was 12% and 11% for those who received BIKTARVY and DTG+FTC/TAF, respectively. Treatment outcomes between treatment groups were similar across subgroups by age, sex, race, baseline viral load, and baseline CD4+ cell count up to Week 144 in both studies.

In Study 1489, the mean increase from baseline in CD4+ was 233 and 229 cells per mm^3, at Week 48, 287 and 288 cells per mm^3 at Week 96, and 299 and 317 cells per mm^3 at Week 144, in the BIKTARVY and ABC/DTG/3TC groups, respectively. In Study 1490, the mean increase from baseline in CD4+ count was 180 and 201 cells per mm^3 at Week 48, 237 and 281 cells per mm^3 at Week 96, and 278 and 289 cells per mm^3 at Week 144, in the BIKTARVY and DTG+FTC/TAF groups, respectively.

HIV-1 Virologically-Suppressed Patients Who Switched to BIKTARVY

Treatment outcomes of Studies 1844 and 1878 through Week 48 are presented in Table 19.

Table 19 Virologic Outcomes of Studies 1844 and 1878 at Week 48 [a] in Virologically-Suppressed Patients who Switched to BIKTARVY

	Study 1844		Study 1878	
	BIKTARVY (N=282)	**ABC/DTG/3TC (N=281)**	**BIKTARVY (N=290)**	**ATV- or DRV-based regimen (N=287)**
HIV-1 RNA ≥ 50 copies/mL [b]	1%	<1%	2%	2%
Treatment Difference (95% CI)	0.7% (-1.0% to 2.8%)		0.0% (-2.5% to 2.5%)	
HIV-1 RNA < 50 copies/mL	94%	95%	92%	89%
Treatment Difference (95% CI)	-1.4% (-5.5% to 2.6%)		3.2% (-1.6% to 8.2%)	

	Study 1844		Study 1878	
	BIKTARVY (N=282)	**ABC/DTG/3TC (N=281)**	**BIKTARVY (N=290)**	**ATV- or DRV-based regimen (N=287)**
No Virologic Data at Week 48 Window	5%	5%	6%	9%
Discontinued Study Drug Due to AE or Death and Last Available HIV-1 RNA < 50 copies/mL	2%	1%	1%	1%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[c]	2%	3%	3%	7%
Missing Data During Window but on Study Drug	2%	1%	2%	2%

a. Week 48 window was between Day 295 and 378 (inclusive).

b. Includes patients who had ≥ 50 copies/mL in the Week 48 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

c. Includes patients who discontinued for reasons other than an AE, death, or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

In Study 1844, at Week 48, switching to BIKTARVY was noninferior to remaining on ABC/DTG/3TC with respect to the percentage of patients with HIV-1 RNA ≥ 50 copies/mL and the percentage of patients who maintained HIV-1 RNA < 50 copies/mL. Treatment outcomes between treatment groups were similar across subgroups by age, sex, race, and region. The mean change from baseline in CD4+ count at Week 48 was -31 cells/mm^3 in patients who switched to BIKTARVY and 4 cells/mm^3 in patients who stayed on their baseline antiretroviral regimen as the FDC ABC/DTG/3TC.

In Study 1878, at Week 48, switching to BIKTARVY was noninferior to remaining on an ATV- or DRV-based regimen with respect to the percentage of patients with HIV-1 RNA ≥ 50 copies/mL and the percentage of patients who maintained HIV-1 RNA < 50 copies/mL. Treatment outcomes between treatment groups were similar across subgroups by age, sex, race, and region. The mean change from baseline in CD4+ count at Week 48 was 25 cells/mm^3 in patients who switched to BIKTARVY and 0 cells/mm^3 in patients who stayed on their baseline regimen.

Bone Mineral Density:
In Study 1489, bone mineral density (BMD) change from baseline to Week 144 was assessed by dual-energy X-ray absorptiometry (DXA). In patients who had both baseline and Week 144 hip and lumbar spine BMD measurements (n=236 and 243 in the BIKTARVY group and n=240 and 258 in the ABC/DTG/3TC group, for hip and lumbar spine, respectively), mean percentage changes in BMD were similar in the BIKTARVY group compared to the ABC/DTG/3TC group for hip (−1.0% vs. −1.3%) and lumbar spine (−0.4% vs.−0.04%).

In Study 1844, BMD change from baseline to Week 48 was assessed by DXA. In patients who had both baseline and Week 48 hip and lumbar spine BMD measurements (N=229 and 233 in

the BIKTARVY group and N=242 and 244 in the ABC/DTG/3TC group, for hip and lumbar spine, respectively), mean percentage increases in BMD were similar in the BIKTARVY group compared to the ABC/DTG/3TC group for hip (0.2% vs. 0.3%) and lumbar spine (0.7% vs.0.4%).

Effects on Renal Parameters
No patients receiving BIKTARVY in the Phase 3 studies developed proximal tubulopathy (including Fanconi Syndrome) or discontinued study drugs due to a renal and urinary disorder or associated investigation AE.

Pediatric Patients

Cohort 1: Virologically suppressed adolescents (12 to < 18 years; ≥ 35 kg):

After switching to BIKTARVY, 98% (49/50) of patients in Cohort 1 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 48. The mean change from baseline in CD4+ cell count at Week 48 was -22 cells/mm^3. Two of 50 patients met the criteria for inclusion in the resistance analysis population through Week 48. No emergent resistance to BIKTARVY was detected through Week 48.

Cohort 2: Virologically suppressed children (6 to < 12 years; ≥ 25 kg):

After switching to BIKTARVY, 100% (50/50) of patients in Cohort 2 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 24. The mean change from baseline in CD4+ cell count at Week 24 was -24 cells/mm^3. No patient qualified for resistance analysis through Week 24.

Clinical Trial Results HIV-1 Infected Patients with Renal Impairment

In Study 1825, an open-label single arm study, the efficacy, safety, and pharmacokinetics of FTC and TAF (components of BIKTARVY) were evaluated in virologically suppressed adults with ESRD (estimated CrCl of less than 15 mL/min) on chronic hemodialysis treated with FTC + TAF in combination with EVG and COBI as a fixed-dose combination tablet for 96 weeks (N = 55). In an extension phase of Study 1825, 10 virologically suppressed patients switched to BIKTARVY and all patients remained virologically suppressed (HIV-1 RNA < 50 copies/mL) for 48 weeks.

Clinical Trial in HIV-infected Adults over 65 years of age

In Study 4449, the efficacy and safety of switching from a stable antiretroviral regimen to BIKTARVY were evaluated in an open-label, single arm study of virologically suppressed (HIV-1 RNA less than 50 copies per mL) HIV-1 infected adults aged 65 years and over (N = 86). Patients treated with BIKTARVY had a mean age of 70 years (range: 65 to 80). No patients had HIV RNA > 50 copies/mL at Weeks 24 and 48. Ninety-eight percent (84/86) and 91% (78/86) of patients remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 24 and Week 48, respectively. Two and 8 patients did not have virologic data due to discontinuation or missing data at the Week 24 and Week 48 timepoints, respectively.

15 MICROBIOLOGY

Antiviral Activity in Cell Culture

The triple combination of BIC, FTC, and TAF demonstrated synergistic antiviral activity in cell culture.

Bictegravir: The antiviral activity of BIC against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells, and CD4+ T-lymphocytes. The EC_{50} values for BIC were in the range of <0.05 to 6.6 nM. The protein-adjusted EC_{95} of BIC was 361 nM (0.162 micrograms per mL) for wild type HIV-1 virus. Bictegravir displayed antiviral activity in cell culture against HIV-1 groups (M, N, O), including subtypes A, B, C, D, E, F and G (EC_{50} values ranged from <0.05 and 1.71 nM), and activity against HIV-2 (EC_{50} = 1.1 nM).

In a study of BIC with representatives from the major classes of approved anti-HIV agents (NRTIs [nucleoside reverse transcriptase inhibitors], NNRTIs [non-nucleoside reverse transcriptase inhibitors], INSTIs, and PIs [protease inhibitors]), additive to synergistic antiviral effects were observed. No antagonism was observed for these combinations.

Emtricitabine: The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, the MAGI-CCR5 cell line, and primary peripheral blood mononuclear cells. The EC_{50} values for FTC were in the range of 0.0013–0.64 µM.

FTC displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007–0.075 µM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007–1.5 µM).

In two-drug combination studies of FTC with NRTIs, NNRTIs, protease inhibitors (PIs), and INSTIs, additive to synergistic effects were observed. No antagonism was observed for these combinations.

Tenofovir Alafenamide: The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4-T lymphocytes. The EC_{50} values for TAF ranged from 2.0 to 14.7 nM.

TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to 12.0 nM) and strain specific activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM).

In a study of TAF with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, NNRTIs, INSTIs, and PIs), additive to synergistic effects were observed. No antagonism was observed for these combinations.

Resistance

In Cell Culture

Bictegravir: HIV-1 isolates with reduced susceptibility to BIC have been selected in cell culture. In one selection, amino acid substitutions M50I and R263K emerged and phenotypic susceptibility to BIC was reduced 1.3-, 2.2-, and 2.9-fold for M50I, R263K, and M50I+R263K, respectively. In a second selection, amino acid substitutions T66I and S153F emerged and

phenotypic susceptibility to BIC was shifted 0.4-, 1.9-, and 0.5-fold for T66I, S153F, and T66I+S153F, respectively.

Emtricitabine: HIV-1 isolates with reduced susceptibility to FTC were selected in cell culture. Reduced susceptibility to FTC was associated with M184V or I substitutions in HIV-1 RT.

Tenofovir Alafenamide: HIV-1 isolates with reduced susceptibility to TAF have been selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R substitution in HIV-1 RT; in addition, a K70E mutation in HIV-1 RT has been transiently observed. HIV-1 isolates with the K65R mutation have low level reduced susceptibility to abacavir, FTC, tenofovir, and lamivudine. *In vitro* drug resistance selection studies with TAF have shown no development of resistance increases above 2.5-fold after 6 months in culture.

In Clinical Trials

In Treatment-Naïve Patients:

No patients receiving BIKTARVY had HIV-1 with treatment emergent genotypic or phenotypic resistance to BIC, FTC, or TAF in the final resistance analysis population (n=8 with HIV-1 RNA ≥ 200 copies/mL at the time of confirmed virologic failure, Week 48, Week 96, Week 144, or early study drug discontinuation) in a pooled analysis of 634 antiretroviral-naïve patients through Week 144 (Studies 1489 and 1490).

In Virologically Suppressed Patients:

No patients receiving BIKTARVY had HIV-1 with treatment emergent genotypic or phenotypic resistance to BIC, FTC, or TAF in the resistance analysis population (n=2 with HIV-1 RNA ≥ 200 copies/mL at the time of confirmed virologic failure, Week 48, or early study drug discontinuation) of 282 virologically-suppressed patients who switched from DTG + ABC/3TC or ABC/DTG/3TC to BIKTARVY (Study 1844).

No patients receiving BIKTARVY had HIV-1 with treatment emergent genotypic or phenotypic resistance to BIC, FTC, or TAF in the resistance analysis population (n=1 with HIV-1 RNA ≥ 200 copies/mL at the time of confirmed virologic failure, Week 48, or early study drug discontinuation) of 290 virologically-suppressed patients who switched from regimens of ATV or DRV (given with cobicistat or ritonavir), plus either FTC/TDF or ABC/3TC, to BIKTARVY (Study 1878).

Cross-Resistance

Bictegravir:

Integrase Strand Transfer Inhibitor-resistant Mutant HIV-1 Strains: Cross-resistance has been observed among INSTIs. The susceptibility of BIC was tested against 64 clinical isolates expressing known INSTI resistance-associated substitutions listed by IAS-USA (20 with single substitutions and 44 with 2 or more substitutions). Isolates with a single INSTI-resistance substitution including E92Q, T97A, Y143C/R, Q148R, and N155H showed less than 2-fold reduced susceptibility to BIC. All isolates (n=14) with more than 2.5-fold reduced susceptibility to BIC (above the biological cutoff for BIC) contained G140A/C/S and Q148H/R/K substitutions; the majority (64.3%, 9/14) had a complex INSTI resistance pattern with an additional INSTI-resistance substitution L74M, T97A, or E138A/K. Of those evaluated isolates containing G140A/C/S and Q148H/R/K substitutions in the absence of additional INSTI-resistance substitutions, 38.5% (5/13) showed more than 2.5-fold reduction. In addition, site-directed

mutant viruses with G118R (DTG and raltegravir treatment-emergent substitution) and G118R+T97A had 3.4- and 2.8-fold reduced susceptibility to BIC, respectively.

Reverse Transcriptase Inhibitor- and Protease Inhibitor-resistant Strains: BIC demonstrated equivalent antiviral activity against 5 NNRTI-resistant, 3 NRTI-resistant, and 4 PI-resistant HIV-1 mutant clones compared with the wild-type strain.

Emtricitabine:

FTC-resistant viruses with the M184V or I substitution were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir, and zidovudine.

Viruses harboring substitutions conferring reduced susceptibility to stavudine and zidovudine - thymidine analog substitutions – TAMS (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to FTC. HIV-1 containing the K103N substitution or other substitutions associated with resistance to NNRTIs was susceptible to FTC.

Tenofovir Alafenamide:

Tenofovir resistance substitutions K65R and K70E result in reduced susceptibility to abacavir, didanosine, FTC, lamivudine, and tenofovir, but retain sensitivity to zidovudine.

Multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M substitution complex including K65R, showed reduced susceptibility to TAF in cell culture.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Tenofovir Alafenamide
Nonclinical studies in rats and dogs revealed bone and kidney as the primary target organs of toxicity.

Carcinogenicity:

Bictegravir
Bictegravir was not carcinogenic in a 6-month rasH2 transgenic mouse study at doses of up to 100 and 300 mg/kg/day in males and females [approximately 15 and 23 times the exposure in humans at the recommended human dose], respectively, or in a 2-year rat study at doses of up to 300 mg/kg/day [approximately 31 times the exposure in humans at the recommended human dose].

Emtricitabine
Long-term carcinogenicity studies of FTC in rats and mice did not show any carcinogenicity potential.

Tenofovir Alafenamide
Because there is a lower tenofovir exposure in rats and mice after TAF administration compared to TDF, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 10 times

(mice) and 4 times (rats) those observed in humans at the 300 mg therapeutic dose of TDF for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at tenofovir exposures 10 times (300 mg TDF) and 151 times (BIKTARVY) that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 4 times that observed in humans at the therapeutic dose.

Genotoxicity:

Bictegravir
Bictegravir was not mutagenic or clastogenic in conventional genotoxicity assays.

Emtricitabine
FTC was not mutagenic or clastogenic in conventional genotoxicity assays.

Tenofovir Alafenamide
TAF was not mutagenic or clastogenic in conventional genotoxicity assays.

17 SUPPORTING PRODUCT MONOGRAPHS

GENVOYA (elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg) tablets, Control No. 195789, Product Monograph, Gilead Sciences Canada, Inc. May 24, 2017.

VEMLIDY (tenofovir alafenamide 25 mg) tablets, Control No. 193066, Product Monograph, Gilead Sciences Canada, Inc. May 17, 2017.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

BIKTARVY®
bictegravir/emtricitabine/tenofovir alafenamide tablets

Read this carefully before you start taking **Biktarvy** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Biktarvy**.

Serious Warnings and Precautions

- You may experience a "Flare-up" of Hepatitis B Virus infection if you also have hepatitis B and stop taking Biktarvy. This may result in your Hepatitis B infection becoming worse than before. Do not stop taking Biktarvy without your doctor's advice. If you stop taking Biktarvy, tell your doctor immediately about any new, unusual or worsening symptoms that you notice after stopping treatment. After you stop taking Biktarvy, your doctor will still need to check your health and take blood tests regularly to check your liver.

What is Biktarvy used for?
Biktarvy is a single tablet for the treatment of human immunodeficiency virus 1 (HIV-1) infection in adults and children who weigh at least 25 kg (55 lbs). **Biktarvy** is for people who do not have an HIV virus that is resistant to the components in **Biktarvy**.

How does Biktarvy work?
Biktarvy reduces the amount of HIV in your body and keeps it at a low level. **Biktarvy** also increases the CD4+ (T) cell count in your blood. CD4 cells are white blood cells that are important in helping your body to fight infection.

What are the ingredients in Biktarvy?
Each tablet has the following medicines: bictegravir (as bictegravir sodium), emtricitabine, tenofovir alafenamide (as tenofovir alafenamide hemifumarate)

Each tablet has the following ingredients that are not medicines: croscarmellose sodium, iron oxide black, iron oxide red, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide.

Biktarvy comes in the following dosage forms:
Biktarvy is available as purplish brown capsule-shaped tablets. Each tablet has 50 mg of bictegravir (equivalent to 52.5 mg of bictegravir sodium), 200 mg of emtricitabine and 25 mg of tenofovir alafenamide (equivalent to 28.0 mg of tenofovir alafenamide hemifumarate).

Do not take Biktarvy if:
- You are allergic to bictegravir, emtricitabine, tenofovir alafenamide or any of the other ingredients of this medicine (Read "What are the ingredients in **Biktarvy**?" above).

- You are currently taking dofetilide* (Tikosyn®)
- You are currently taking rifampin (Rifadin®, Rifamate®, Rifater®, Rimactane®)
- You are currently taking St. John's wort (*Hypericum perforatum*), an herbal remedy used to treat depression and anxiety

*Not available in Canada

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Biktarvy. Talk about any health conditions or problems you may have, including if you:

- Have liver problems or a history of liver disease, including hepatitis B virus infection (see Serious Warnings and Precautions box and Serious Side Effects table).
- Have kidney problems. Kidney problems, including kidney failure, have occurred in patients taking tenofovir. If you have kidney problems and are taking **Biktarvy** along with certain medicines such as non-steroidal anti-inflammatory drugs, your kidney problems could get worse.
- Have lactic acidosis (high levels of acid in the blood). See the Serious Side Effects table for symptoms and contact your doctor right away if you get these symptoms.

Other warnings you should know about:

If you are pregnant or plan to become pregnant:
It is not known if **Biktarvy** can harm your unborn child. Tell your healthcare provider if you become pregnant while taking **Biktarvy**.

Pregnancy Registry: There is a pregnancy registry for women who take antiviral medicines during pregnancy. This registry collects information about your health and your baby's health. If you become pregnant while taking **Biktarvy**, talk with your doctor about taking part in this registry.

If you are breast-feeding or plan to breast-feed:
Do not breast-feed if you have HIV because of the chance of passing the HIV virus to your baby. One of the ingredients of **Biktarvy**, emtricitabine, can be passed to your baby in your breast milk and may cause harm to your baby. It is not known if the other components can be passed to your baby in breast milk. If you are a woman who has or will have a baby, talk with your doctor about the best way to feed your baby.

Blood Sugar and Fat Levels:
Your blood sugar levels (glucose) or levels of fats (lipids) in your blood may increase with HIV treatment. Your doctor may order blood tests for you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Do not take Biktarvy if:
- You are currently taking dofetilide* (Tikosyn®).
- You are currently taking rifampin (Rifadin®, Rifamate®, Rifater®, Rimactane®).
- You are currently taking St. John's wort (*Hypericum perforatum*), an herbal remedy used to treat depression and anxiety.

*Not available in Canada

Drugs that should not be taken with Biktarvy:
- Any other medicines that contain tenofovir (ATRIPLA®, COMPLERA®, DESCOVY®, Delstrigo®, GENVOYA®, ODEFSEY®, STRIBILD®, Symtuza™, TRUVADA®, VEMLIDY®, VIREAD®).
- Any other medicines that contain emtricitabine or lamivudine (ATRIPLA, COMPLERA, DESCOVY, Delstrigo®, Dovato®, EMTRIVA®, GENVOYA, ODEFSEY, STRIBILD, Symtuza, TRUVADA, 3TC, Combivir®, Heptovir®, Kivexa®, Triumeq®, Trizivir®).
- Adefovir dipivoxil (HEPSERA®).

The following may interact with Biktarvy:
- Medicines used for treating HIV, containing:
  - atazanavir
- Antibiotics, used to treat bacterial infections including tuberculosis, containing:
  - rifabutin or rifapentine
- Anticonvulsants, used to treat epilepsy, such as:
  - carbamazepine, oxcarbazepine, phenobarbital or phenytoin
- Antacids for stomach ulcers, heartburn or acid reflux such as:
  - aluminium/magnesium hydroxide or calcium carbonate
- Mineral supplements and vitamins, containing:
  - calcium or iron
- Ulcer-healing medication, such as:
  - sucralfate

If you are taking an antacid, a mineral supplement or vitamin containing **calcium or iron,** or an **ulcer healing medication,** take it at least 2 hours before or at least 2 hours after **Biktarvy**, or take it with **Biktarvy** together with food.

How to take Biktarvy:
- Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
- Do not run out of **Biktarvy**. Refill your prescription or talk to your doctor before your **Biktarvy** is all gone.
- Do not stop taking **Biktarvy** without first talking to your doctor.

Usual dose:
Adults and children who weigh at least 25 kg (55 lbs): Take one tablet each day with or without food. Try to take the tablet at the same time each day.

Adults on Dialysis:

- If you are on dialysis, take your daily dose of Biktarvy following dialysis.

Overdose:

If you think you, or a person you are caring for, have taken too much Biktarvy, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed dose:
It is important not to miss a dose of **Biktarvy**.

- **If you miss a dose of Biktarvy** and you notice **within 18 hours** of the time you usually take **Biktarvy**, take the tablet as soon as you can. Then take the next dose as usual.
- **If you miss a dose of Biktarvy** and you notice **after 18 hours**, wait and take the next dose at your usual time. Do NOT take a double dose (two doses close together).

What are possible side effects from using Biktarvy?

Like all medicines, **Biktarvy** can have side effects. When treating HIV infection, it is not always possible to tell whether some of the undesirable effects that occur are caused by **Biktarvy**, by other medicines you are taking at the same time or by the HIV infection. For this reason it is very important that you inform your doctor about any changes in your health.

Common side effects of **Biktarvy** are:

- Diarrhea.
- Headache.
- Nausea.
- Tiredness.
- Dizziness.
- Trouble sleeping.
- Abnormal dreams.

Less common side effects are indigestion, gas, depression, rash and thoughts of suicide.

Other side effects may include swelling in the face, lips, tongue, or throat (angioedema); hives (urticaria).

These are not all the possible side effects you may feel when taking **Biktarvy**.
If you experience any side effects not listed here, contact your healthcare professional.

Changes to your immune system (Immune Reconstitution Inflammatory Syndrome) can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time.

- Autoimmune disorders (when the immune system attacks healthy body tissue) may also occur after you start taking medicines for HIV infection. Examples of this include: Grave's disease (which affects the thyroid gland), Guillain-Barré syndrome (which affects the

nervous system), polymyositis (which affects the muscles), or autoimmune hepatitis (which affects the liver). Autoimmune disorders may occur many months after the start of treatment. Look for any other symptoms such as:

- high temperature (fever), redness, rash or swelling
- joint or muscle pain
- numbness or weakness beginning in the hands and feet and moving up towards the trunk of the body
- palpitations (chest pain) or rapid heart rate

If you notice these or any symptoms of inflammation or infection, tell your doctor immediately.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE Effect: Lactic acidosis Symptoms:			
• Feeling very weak or tired		✓	
• Unusual muscle pain		✓	
• Stomach pain with nausea and vomiting		✓	
• Feeling unusually cold, especially in arms and legs		✓	
• Feeling dizzy or lightheaded		✓	
• Fast or irregular heartbeat		✓	
• Fast and deep breathing		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE Effect: Severe skin rash (Stevens-Johnson syndrome/toxic epidermal necrolysis) Symptoms: • Blisters or peeling of the skin • Blisters or peeling of the mouth, lips and throat • Fever and general ill feeling.			✓ ✓ ✓
VERY RARE Effect: Flare-ups of hepatitis B virus infection following drug discontinuation Symptoms: • Jaundice (skin or the white part of eyes turns yellow) • Urine turns dark • Bowel movements (stools) turn light in color • Loss of appetite for several days or longer • Feeling sick to your stomach (nausea) • Lower stomach pain		✓ ✓ ✓ ✓ ✓ ✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Bottles

- Store **Biktarvy** below 30 °C (86 °F).

- Keep **Biktarvy** in its original container and keep the container tightly closed.
- Do not use **Biktarvy** if the seal over the bottle opening is broken or missing.
- Keep this medicine out of reach and sight of children.
- Do not use this medicine after the expiry date which is stated on the bottle after {EXP}. The expiry date refers to the last day of that month.

Blister Pack
- Store **Biktarvy** between 15-30 °C (59-86 °F).
- Keep **Biktarvy** in its original container.
- Do not use **Biktarvy** if the foil over the blister or the seal around the blister card is broken or missing.
- Keep this medicine out of reach and sight of children.
- Do not use this medicine after the expiry date which is stated on the carton and blister card after {EXP}. The expiry date refers to the last day of that month.

If you want more information about Biktarvy:
- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); the manufacturer's website www.gilead.ca, or by calling 1-866-207-4267.

This leaflet was prepared by Gilead Sciences Canada, Inc.

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Marketing Status in United States

Drug Databases (https://www.fda.gov/Drugs/InformationOnDrugs/)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home (index.cfm?resetfields=1) | Back to Search Results

Product Details for NDA 210251

Collapse All

BIKTARVY (BICTEGRAVIR SODIUM; EMTRICITABINE; TENOFOVIR ALAFENAMIDE FUMARATE)
EQ 30MG BASE;120MG;EQ 15MG BASE
Marketing Status: Prescription

Active Ingredient: BICTEGRAVIR SODIUM; EMTRICITABINE; TENOFOVIR ALAFENAMIDE FUMARATE
Proprietary Name: BIKTARVY
Dosage Form; Route of Administration: TABLET; ORAL
Strength: EQ 30MG BASE;120MG;EQ 15MG BASE
Reference Listed Drug: Yes
Reference Standard: No
TE Code:
Application Number: N210251
Product Number: 002
Approval Date: Oct 7, 2021
Applicant Holder Full Name: GILEAD SCIENCES INC
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=002&Appl_No=210251&Appl_type=N)

BIKTARVY (BICTEGRAVIR SODIUM; EMTRICITABINE; TENOFOVIR ALAFENAMIDE FUMARATE)
EQ 50MG BASE;200MG;EQ 25MG BASE
Marketing Status: Prescription

Active Ingredient: BICTEGRAVIR SODIUM; EMTRICITABINE; TENOFOVIR ALAFENAMIDE FUMARATE

Proprietary Name: BIKTARVY
Dosage Form; Route of Administration: TABLET; ORAL
Strength: EQ 50MG BASE;200MG;EQ 25MG BASE
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N210251
Product Number: 001
Approval Date: Feb 7, 2018
Applicant Holder Full Name: GILEAD SCIENCES INC
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=001&Appl_No=210251&Appl_type=N)