PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr BIKTARVY®

(bictegravir/emtricitabine/tenofovir alafenamide) tablets
Oral

50 mg bictegravir*
200 mg emtricitabine
25 mg tenofovir alafenamide**

*as 52.5 mg bictegravir sodium
**as 28.0 mg tenofovir alafenamide hemifumarate

Antiretroviral Agent

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RECENT MAJOR LABEL CHANGES

Warnings and Precautions (7), Immune Reconstitution Syndrome	05/2019

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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 with no known substitution associated with resistance to the individual components of BIKTARVY.

1.1 Pediatrics

Pediatrics (< 18 yrs. of age): Safety and efficacy of BIKTARVY in pediatric patients less than 18 years of age have not been established.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Clinical studies of BIKTARVY did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from patients less than 65 years of age.

2 CONTRAINDICATIONS

BIKTARVY is contraindicated in patients who are hypersensitive to bictegravir, emtricitabine (FTC), tenofovir alafenamide (TAF) or to any ingredient in the formulation or component of the container. For a complete listing, see **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 **DRUG INTERACTIONS**).
- rifampin due to decreased bictegravir plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to BIKTARVY (see **DRUG INTERACTIONS**).
- St. John's wort due to the effect of St. John's wort on the bictegravir component of BIKTARVY. This may result in loss of therapeutic effect and development of resistance (see **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 emtricitabine (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 **WARNINGS AND PRECAUTIONS, Special Populations**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

BIKTARVY is a three-drug fixed dose combination product containing 50 mg of bictegravir, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide.

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, 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
The recommended dose of BIKTARVY is one tablet taken orally once daily with or without food.

Pediatrics
Safety and efficacy of BIKTARVY in pediatric patients less than 18 years of age have not been established. Therefore, it is not recommended for pediatric patients.

Geriatrics (≥ 65 years of age)
Clinical trials of BIKTARVY did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients (see **ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics, Special Populations and Conditions**).

Renal Impairment
BIKTARVY is not recommended in patients with estimated creatinine clearance below 30 mL per minute.

No dose adjustment of BIKTARVY is required in patients with estimated creatinine clearance greater than or equal to 30 mL per minute.

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 **ACTION AND 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.

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 bictegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis. Emtricitabine can be removed by hemodialysis, which removes approximately 30% of the emtricitabine dose over a 3 hour dialysis period starting within 1.5 hours of emtricitabine dosing. It is not known whether emtricitabine 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 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). The 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 30 tablets, silica gel desiccant, and polyester coil.	Tablet Core: Microcrystalline Cellulose, Croscarmellose Sodium, Magnesium Stearate Film-Coating: Iron Oxide Black, Iron Oxide Red, Polyethylene Glycol, Polyvinyl Alcohol, Talc, Titanium Dioxide

7 WARNINGS AND PRECAUTIONS

Please see the **SERIOUS WARNINGS AND PRECAUTIONS BOX** at the beginning of Part I: Health Professional Information.

General

BIKTARVY should not be coadministered with any other antiretroviral products including products containing bictegravir, emtricitabine, or tenofovir alafenamide (ATRIPLA®, COMPLERA®, DESCOVY®, EMTRIVA®, GENVOYA®, ODEFSEY®, STRIBILD®, Symtuza™, TRUVADA®, TYBOST®, VEMLIDY™); or with products containing lamivudine or tenofovir disoproxil fumarate (3TC®, ATRIPLA, Combivir®, COMPLERA, 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.

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 emtricitabine, a component of BIKTARVY, and tenofovir disoproxil fumarate, 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 **WARNINGS AND PRECAUTIONS**, **Special Populations**).

Immune Reconstitution Inflammatory Syndrome
Immune reconstitution inflammatory syndrome has been reported in patients treated with combination antiretroviral therapy, including emtricitabine, 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.

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. BIKTARVY should not be used during pregnancy unless the potential benefits outweigh

the potential risks to the foetus.

Bictegravir
Embryo-fetal development toxicity studies 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 140-fold human exposure) did not indicate harmful effects of emtricitabine 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 tenofovir alafenamide exposures approximately 2 and 78 times higher than, respectively, the exposure in humans at the recommended daily dose of BIKTARVY. Tenofovir alafenamide 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, bictegravir was detected in the plasma of nursing rat pups likely due to the presence of bictegravir 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 bictegravir or TAF are secreted in human milk. In humans, samples of breast milk obtained from five HIV-1 infected mothers given TRUVADA (emtricitabine (FTC)/tenofovir disoproxil fumarate (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 less than 18 years of age have not been established.

7.1.4 Geriatrics

Clinical studies of BIKTARVY did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

7.1.5 Patients Co-infected with HIV and HBV

Prior to or when initiating BIKTARVY, test for hepatitis B virus infection [see **DOSAGE AND ADMINISTRATION (4.1)**].

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 **SERIOUS WARNINGS AND PRECAUTIONS BOX**]
- Immune Reconstitution Inflammatory Syndrome [See **WARNINGS AND PRECAUTIONS**].
- Lactic Acidosis/Severe Hepatomegaly with Steatosis [See **WARNINGS AND PRECAUTIONS**]

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials 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 is useful for identifying drug-related adverse events and for approximating rates.

Clinical Trials in Treatment-Naïve Adults

The primary safety assessment of BIKTARVY was based on Week 48 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 **Clinical Studies (14.2)**].

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]/dolutegravir [DTG]/lamivudine [3TC]), or DTG + emtricitabine (FTC)/tenofovir alafenamide (TAF), due to adverse events,

regardless of severity, was 0.8%, 1.3%, and 0.3%, respectively. Table 2 displays the frequency of adverse reactions (all Grades) greater than or equal to 2% in the BIKTARVY group in either Study 1489 or Study 1490.

Table 2 Adverse Reactions[a] (All Grades) Reported in ≥ 2% of HIV-1 Infected Treatment-Naïve Adults Receiving BIKTARVY in Studies 1489 or 1490 (Week 48 analysis)

	Study 1489		Study 1490	
Adverse Reactions	**BIKTARVY** N=314 (%)	**ABC/DTG/3TC** N=315 (%)	**BIKTARVY** N=320 (%)	**DTG+ FTC/TAF** N=325 (%)
GASTROINTESTINAL DISORDERS				
Diarrhea	6	4	3	3
Nausea	5	17	3	5
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Fatigue	3	3	2	2
NERVOUS SYSTEM DISORDERS				
Headache	5	5	4	3
Dizziness	2	3	2	1
PSYCHIATRIC DISORDERS				
Insomnia	2	3	2	<1
Abnormal dreams	3	3	<1	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 either study.

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 subjects administered BIKTARVY.

The majority of adverse reactions were Grade 1.

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.

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

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 3.

Table 3 Laboratory Abnormalities (Grades 3–4) Reported in ≥ 2% of Patients Receiving BIKTARVY in Studies 1489 and 1490 (Week 48 analysis)

	Study 1489		Study 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)	2	2	2	2
ALT (>5.0 x ULN)	1	1	2	1
AST (>5.0 × ULN)	2	1	1	3
Creatine Kinase (≥10.0 × ULN)	4	3	4	2
Neutrophils (<750 mm^3)	2	3	2	1
LDL-cholesterol (fasted) (>190 mg/dL)	2	3	3	3

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* **ACTION AND CLINICAL PHARMACOLOGY**]. Increases in serum creatinine occurred by Week 4 of treatment and remained stable through Week 48. In Studies 1489 and 1490, median (Q1, Q3) serum creatinine increased by 0.10 (0.03, 0.17) mg per dL, 0.11 (0.03, 0.18) mg per dL, and 0.11 (0.04, 0.19) mg per dL from baseline to Week 48 in the BIKTARVY, ABC/DTG/3TC, and DTG+FTC/TAF groups, respectively. There were no discontinuations due to renal adverse events through Week 48 in BIKTARVY clinical studies.

Changes in Bilirubin: In Studies 1489 and 1490, total bilirubin increases were observed in 12% of patients administered BIKTARVY through Week 48. Increases were primarily Grade 1 (9%) and Grade 2 (3%) (1.0 to 2.5 x ULN) and were not associated with hepatic adverse reactions or other liver related laboratory abnormalities. There were no discontinuations due to hepatic adverse events through Week 48 in BIKTARVY clinical studies.

Adverse Reactions from Clinical Trials of the Components of BIKTARVY
For information on the safety profiles of emtricitabine or tenofovir alafenamide, consult the Product Monographs for EMTRIVA®, VEMLIDY® or DESCOVY®.

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 products containing emtricitabine or tenofovir alafenamide. 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.

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 Overview

The drug interactions described in Table 4 are based on studies conducted with BIKTARVY, or the components of BIKTARVY (bictegravir, emtricitabine, or tenofovir alafenamide) 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 **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 bictegravir and drugs that potently induce both CYP3A and UGT1A1 may significantly decrease plasma concentrations of bictegravir, which may result in loss of therapeutic effect of BIKTARVY and development of resistance. Coadministration of bictegravir with drugs that potently inhibit both CYP3A and UGT1A1 may significantly increase plasma concentrations of bictegravir (see Table 4).

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 4). 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 7).

9.2 Drug-Drug Interactions

Drug-drug interaction studies were conducted with BIKTARVY or various combinations of the components of BIKTARVY (bictegravir, 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 4. The drug interactions described are based on studies conducted with either BIKTARVY, the components of BIKTARVY (bictegravir, FTC, and TAF) as individual agents, or are predicted drug interactions that may occur with BIKTARVY. For contraindicated drugs, see **CONTRAINDICATIONS**. For magnitude of interaction, see **DRUG INTERACTIONS STUDIES**.

The table is not all-inclusive.

Table 4 Established or Potential[a] Drug-Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Anticonvulsants: carbamazepine[c] oxcarbazepine phenobarbital phenytoin	↓ bictegravir ↓ TAF	Coadministration of carbamazepine, oxcarbazepine, phenobarbital, or phenytoin may decrease bictegravir 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	↓ bictegravir ↓ TAF	Coadministration of rifabutin, rifampin, or rifapentine may decrease bictegravir 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 bictegravir component of BIKTARVY *[see **CONTRAINDICATIONS**]*. Coadministration of BIKTARVY with rifabutin or rifapentine is not recommended.
HIV-1 Antiviral Agent: atazanavir[c,e]	↑ bictegravir	Coadministration of BIKTARVY with atazanavir is not recommended.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓ bictegravir ↓ 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	↓ bictegravir	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 This 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.

9.3 Drug Interaction Studies

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

The effects of coadministered drugs on the exposure of bictegravir are shown in Table 5. The effects of coadministered drugs on the exposure of tenofovir alafenamide (TAF) are shown in Table 6. The effects of bictegravir and /or TAF on the exposure of coadministered drugs are shown in Table 7.

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 5 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 6 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 (emtricitabine/tenofovir alafenamide).
d Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

Table 7 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 (emtricitabine/tenofovir alafenamide).
e. Study conducted with GENVOYA (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide).
f. Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

9.4 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 bictegravir exposure. The alterations in mean systemic exposures of bictegravir were not clinically significant.

Relative to fasting conditions, the exposure to emtricitabine 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.

9.5 Drug-Herb Interactions

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

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

9.6 Drug-Laboratory Test Interactions

Interactions of BIKTARVY with laboratory tests have not been established.

9.7 Drug-Lifestyle Interactions

Interactions of BIKTARVY with lifestyle have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

BIKTARVY is a fixed-dose combination, single tablet regimen of the antiviral drugs bictegravir, emtricitabine (FTC) and tenofovir alafenamide (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, bictegravir 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 bictegravir on renal function was evaluated in a randomized, blinded, parallel,

placebo-controlled trial in 40 healthy subjects who received bictegravir 75 mg (n = 20) or placebo (n = 20) once daily with food for 14 days. Mean change from baseline in serum creatinine in the bictegravir group was 0.1 mg per dL on Days 7 and 14. Bictegravir 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 8. The multiple dose PK parameters of the components of BIKTARVY are provided in Table 9.

Table 8 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: bictegravir (single dose administration of [^{14}C] bictegravir); FTC (single dose administration of [^{14}C] emtricitabine after multiple dosing of emtricitabine for ten days); TAF (single dose administration of [^{14}C] tenofovir alafenamide).

Table 9 Multiple Dose PK Parameters of bictegravir, 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 bictegravir 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

Geriatrics: The pharmacokinetics of bictegravir, 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 bictegravir 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 bictegravir were not observed in subjects with moderate (Child-Pugh Class B) hepatic impairment.

Emtricitabine

The pharmacokinetics of emtricitabine have not been studied in subjects with hepatic impairment; however, emtricitabine 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 tenofovir alafenamide or its metabolite tenofovir were not observed in subjects with mild, moderate, or severe (Child-Pugh Class A, B and C) hepatic impairment; no tenofovir alafenamide dose adjustment is required in subjects with hepatic impairment.

Renal Insufficiency:
No clinically relevant differences in bictegravir, tenofovir alafenamide, or tenofovir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment (estimated creatinine clearance less than 30 mL per minute). There are no pharmacokinetic data on bictegravir or tenofovir alafenamide in patients with creatinine clearance less than 15 mL per minute.

Hepatitis B and/or Hepatitis C Virus Coinfection
Pharmacokinetics of bictegravir, emtricitabine, and tenofovir alafenamide have not been fully evaluated in patients coinfected with hepatitis B and/or C virus.

11 STORAGE, STABILITY AND DISPOSAL

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.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

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

Each tablet contains 50 mg of bictegravir (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.

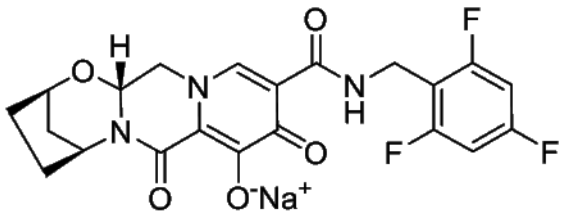
Bictegravir

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: $C_{21}H_{17}F_3N_3NaO_5$
Molecular Weight: 471.4
Structural formula:



Physicochemical Properties:

Description: Bictegravir is a white to 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

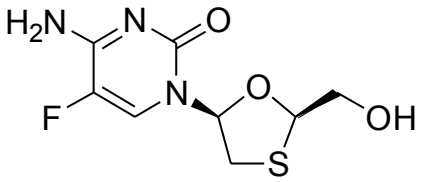
Common Name: emtricitabine (USAN)

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: Emtricitabine 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

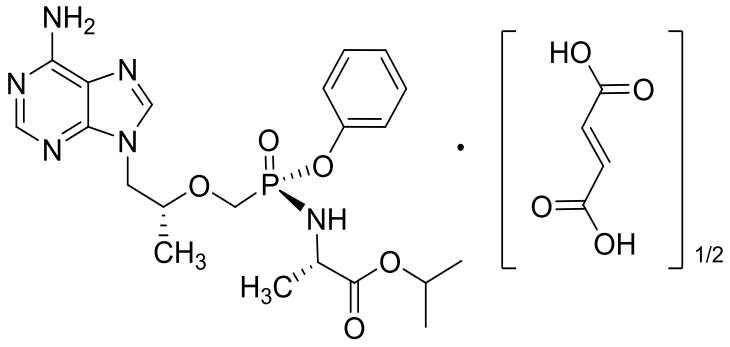
Common Name: Tenofovir alafenamide hemifumarate
Tenofovir alafenamide fumarate (USAN)

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: $C_{21}H_{29}O_5N_6P \bullet 1/2(C_4H_4O_4)$

Molecular Weight: 534.5

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 10.

14.1 Trial Design and Study Demographics

Table 10 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)	48
Study 1490[a]		BIKTARVY (320) DTG + FTC/TAF(325)	48
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

a. Randomized, double blind, active controlled trial.
b. Randomized, open label, active controlled trial.
c. HIV-1 RNA less than 50 copies per mL at screening.

Treatment-Naïve HIV-1 Infected Patients
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% percent 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 11.

Table 11 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)

	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 (%)**
HIV disease status						
Asymptomatic	286 (91)	286 (91)	572 (91)	286 (89)	288 (89)	574 (89)
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						
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.

14.2 Study Results

Clinical Trial Results in Treatment-Naïve HIV-1 Infected Patients

Treatment outcomes of Studies 1489 and 1490 through Week 48 are presented in Table 12.

Table 12 Virologic Outcomes of Randomized Treatment in Studies 1489 and 1490 at Week 48[a] in Treatment-Naïve Patients

	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	92%	93%	89%	93%
Treatment Difference (95% CI) BIKTARVY vs. Comparator	-0.6% (-4.8% to 3.6%)		-3.5% (-7.9% to 1.0%)	
HIV-1 RNA ≥ 50 copies/mL[b]	1%	3%	4%	1%

	Trial 1489		Trial 1490	
	BIKTARVY (N=314)	**ABC/DTG/3TC** (N=315)	**BIKTARVY** (N=320)	**DTG + FTC/TAF** (N=325)
No Virologic Data at Week 48 Window	7%	4%	6%	6%
Discontinued Study Drug Due to AE or Death[c]	0	1%	1%	1%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL[d]	5%	3%	3%	4%
Missing Data During Window but on Study Drug	2%	<1%	2%	1%

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 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 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.

d. 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 Week 48 when compared to ABC/DTG/3TC and DTG+FTC/TAF, respectively. Treatment outcomes were similar among treatment groups, across subgroups by age, sex, race, baseline viral load, and baseline CD4+ cell count.

In Study 1489, the mean increase from baseline in CD4+ count at Week 48 was 233 and 229 cells per mm^3 in the BIKTARVY and ABC/DTG/3TC groups, respectively. In Study 1490, the mean increase from baseline in CD4+ count at Week 48 was 180 and 201 cells per mm^3 in the BIKTARVY and DTG+FTC/TAF groups, respectively.

Clinical Trial Results in 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 13.

Table 13 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.

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

Table 14 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%

	Study 1844		Study 1878	
	BIKTARVY (N=282)	**ABC/DTG/3TC (N=281)**	**BIKTARVY (N=290)**	**ATV- or DRV-based regimen (N=287)**
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%)	
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 48 was assessed by dual-energy X-ray absorptiometry (DXA). In patients who had both baseline and Week 48 hip and lumbar spine BMD measurements (n=257 and 267 in the BIKTARVY group and n=270 and 274 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 (−0.8% vs. −1.0%) and lumbar spine (−0.8% vs.−0.6%).

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.

15 MICROBIOLOGY

Antiviral Activity in Cell Culture

The triple combination of bictegravir, FTC, and TAF demonstrated synergistic antiviral activity in cell culture.

Bictegravir: The antiviral activity of bictegravir 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 bictegravir were in the range of <0.05 to 6.6 nM. The protein-adjusted EC_{95} of bictegravir 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 bictegravir 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 bictegravir have been selected in cell culture. In one selection, amino acid substitutions M50I and R263K emerged and phenotypic susceptibility to bictegravir 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 bictegravir 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 bictegravir, FTC, or TAF in the resistance analysis population (n = 8 with HIV-1 RNA ≥ 200 copies/mL at the time of confirmed virologic failure, Week 48, or early study drug discontinuation) in a pooled analysis of 634 antiretroviral-naïve patients through Week 48 (Studies 1489 and 1490).

In Virologically Suppressed Patients:

No patients receiving BIKTARVY had HIV-1 with treatment emergent genotypic or phenotypic resistance to bictegravir, 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 bictegravir, 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: The susceptibility of bictegravir was tested against 64 INSTI-resistant clinical isolates (20 with single substitutions and 44 with 2 or more substitutions). Fifty of the 64 INSTI-resistant clinical isolates had ≤ 2.5-fold phenotypic change to bictegravir and were assessed as sensitive. All single and double mutants of these isolates lacking Q148H/K/R, and 10 of 24 Q148H/K/R + G140A/C/S containing isolates with or without additional INSTI resistance associated substitutions also had ≤ 2.5-fold reduced susceptibility to bictegravir. Reduced susceptibility to bictegravir of >2.5-fold was found for 14 of the 24 isolates that contained G140A/C/S and Q148H/R/K substitutions in integrase. Of those, 9 of the 14 isolates had additional mutations at L74M, T97A, or E138A/K. In addition, site-directed mutants with G118R and T97A+G118R had 3.4- and 2.8-fold reduced susceptibility to bictegravir, respectively.

Reverse Transcriptase Inhibitor- and Protease Inhibitor-resistant Strains: bictegravir 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, emtricitabine, 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

Bictegravir

Bictegravir was not mutagenic or clastogenic in conventional genotoxicity assays.

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 to 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

FTC was not mutagenic or clastogenic in conventional genotoxicity assays.
Long-term carcinogenicity studies of FTC in rats and mice did not show any carcinogenicity potential.

Tenofovir Alafenamide
Nonclinical studies in rats and dogs revealed bone and kidney as the primary target organs of toxicity.

TAF was not mutagenic or clastogenic in conventional genotoxicity assays.

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.

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.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

BIKTARVY®
(bictegravir*/emtricitabine/tenofovir alafenamide**) tablets
*as bictegravir sodium **as tenofovir alafenamide hemifumarate

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. **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, magnesium stearate, microcrystalline cellulose.

Each tablet is covered with the following ingredients that are not medicines: iron oxide black, iron oxide red, 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.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Drugs that should not be taken with Biktarvy:

- Any other medicines that contain tenofovir (ATRIPLA®, COMPLERA®, DESCOVY®, GENVOYA®, ODEFSEY®, STRIBILD®, Symtuza™, TRUVADA®, VEMLIDY™, VIREAD®).
- Any other medicines that contain emtricitabine or lamivudine (ATRIPLA, COMPLERA, DESCOVY, EMTRIVA®, GENVOYA, ODEFSEY, STRIBILD, Symtuza, TRUVADA, 3TC, Combivir®, Heptovir®, Kivexa®, Triumeq®, Trizivir®).

The following may interact with Biktarvy:
- Medicines used for treating HIV, containing:
  - atazanavir
- Antibiotics, used to treat bacterial infections including tuberculosis, containing:
  - rifabutin and rifapentine
- Anticonvulsants, used to treat epilepsy, such as:
  - carbamazepine, oxcarbazepine, phenobarbital and 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: Take one tablet each day with or without food. Try to take the tablet at the same time each day.

Overdose:

If you think you 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) and 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		✓	

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	
• Fast or irregular heartbeat		✓	
• Fast and deep breathing		✓	
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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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:
- 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 carton and bottle 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 (http://hc-sc.gc.ca/index-eng.php); 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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