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

ODEFSEY® (emtricitabine, rilpivirine, and tenofovir alafenamide) tablets, for oral use
Initial U.S. Approval: 2016

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B
See full prescribing information for complete boxed warning.

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs. (5.1)**
- **ODEFSEY is not approved for the treatment of chronic hepatitis B virus (HBV) infection. 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 ODEFSEY. Hepatic function should be monitored closely in these patients. If appropriate, initiation of anti-hepatitis B therapy may be warranted. (5.2)**

----------INDICATIONS AND USAGE----------
ODEFSEY is a three-drug combination of emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV nucleoside analog reverse transcriptase inhibitors (NRTIs), and rilpivirine (RPV), a non-nucleoside reverse transcriptase inhibitor (NNRTI), and is indicated as a complete regimen for the treatment of HIV-1 infection in patients 12 years of age and older as initial therapy in those with no antiretroviral treatment history with HIV-1 RNA less than or equal to 100,000 copies per mL; or to replace a stable antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) for at least six months with no history of treatment failure and no known substitutions associated with resistance to the individual components of ODEFSEY. (1)

----------DOSAGE AND ADMINISTRATION----------
- Testing: prior to initiation of ODEFSEY, patients should be tested for hepatitis B virus infection, and estimated creatinine clearance, urine glucose, and urine protein should be obtained. (2.1)
- Recommended dosage: one tablet taken orally once daily with a meal. (2.2)
- After initiation of ODEFSEY, additional monitoring of HIV-1 RNA and regimen tolerability is recommended after replacing therapy to assess for potential virologic failure or rebound. (2.3)
- Renal impairment: ODEFSEY is not recommended in patients with estimated creatinine clearance below 30 mL per minute. (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------
Tablets: 200 mg of FTC, 25 mg of RPV and 25 mg of TAF. (3)

----------CONTRAINDICATIONS----------
ODEFSEY is contraindicated when coadministered with drugs where significant decreases in RPV plasma concentrations may occur, which may result in loss of virologic response and possible resistance and cross-resistance. (4)

---------- WARNINGS AND PRECAUTIONS----------
- Skin and Hypersensitivity Reactions: Severe skin and hypersensitivity reactions have been reported during postmarketing experience with RPV-containing regimens, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Immediately discontinue treatment if hypersensitivity or rash with systemic symptoms or elevations in hepatic serum biochemistries develops and closely monitor clinical status, including hepatic serum biochemistries. (5.3)
- Concomitant use of ODEFSEY with other drugs that may reduce the exposure of RPV may lead to loss of therapeutic effect of ODEFSEY and possible development of resistance. (5.4)
- Concomitant use of ODEFSEY with drugs with a known risk to prolong the QTc interval of the electrocardiogram may increase the risk of Torsade de Pointes. (5.5)
- Depressive disorders: Severe depressive disorders have been reported. Immediate medical evaluation is recommended for severe depressive disorders. (5.6)
- Hepatotoxicity: Hepatic adverse events have been reported in patients receiving an RPV-containing regimen. Monitor liver-associated tests before and during treatment with ODEFSEY in patients with underlying hepatic disease or marked elevations in liver-associated tests. Also consider monitoring liver-associated tests in patients without risk factors. (5.7)
- Redistribution/accumulation of body fat: Observed in patients receiving antiretroviral therapy. (5.8)
- Immune reconstitution syndrome: May necessitate further evaluation and treatment. (5.9)
- New onset or worsening renal impairment: Assess creatinine clearance, urine glucose, and urine protein in all patients before initiating ODEFSEY therapy and monitor during therapy. Monitor serum phosphorus in patients with chronic kidney disease. (5.10)
- Bone loss and mineralization defects: Consider monitoring BMD in patients with a history of pathologic fracture or other risk factors of osteoporosis or bone loss. (5.11)

---------- ADVERSE REACTIONS ----------
Rilpivirine: Most common adverse reactions to RPV (incidence greater than or equal to 2%, Grades 2–4) are depressive disorders, insomnia, and headache. (6.1)
Emtricitabine & Tenofovir Alafenamide: Most common adverse reaction (incidence greater than or equal to 10%, all grades) is nausea. (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----------
- CYP3A4 inducers or inhibitors: Drugs that induce or inhibit CYP3A4 may affect the plasma concentrations of RPV. (7.1)
- P-glycoprotein (P-gp) inducers or inhibitors: Drugs that strongly affect P-gp activity may lead to changes in TAF absorption. (7.1)
- Drugs that increase gastric pH: Drugs that increase gastric pH may decrease plasma concentrations of RPV. (7.1)

---------- 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 less than 12 years of age or weighing less than 35 kg. (8.4)

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

Revised: 03/2016

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs in combination with other antiretrovirals *[see Warnings and Precautions (5.1)]*.

ODEFSEY is not approved for the treatment of chronic hepatitis B virus (HBV) infection, and the safety and efficacy of ODEFSEY have not been established in patients coinfected with human immunodeficiency virus-1 (HIV-1) and HBV. 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 ODEFSEY.

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 ODEFSEY. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

ODEFSEY is indicated as a complete regimen for the treatment of HIV-1 infection in patients 12 years of age and older as initial therapy in those with no antiretroviral treatment history with HIV-1 RNA less than or equal to 100,000 copies per mL; or to replace a stable antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) for at least six months with no history of treatment failure and no known substitutions associated with resistance to the individual components of ODEFSEY *[see Microbiology (12.4) and Clinical Studies (14)].*

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of ODEFSEY

Prior to initiation of ODEFSEY, patients should be tested for hepatitis B virus infection *[see Warnings and Precautions (5.2)]*.

Estimated creatinine clearance, urine glucose, and urine protein should be assessed before initiating ODEFSEY therapy and should be monitored during therapy in all patients *[see Warnings and Precautions (5.10)].*

2.2 Recommended Dosage

ODEFSEY is a 3-drug fixed dose combination product containing 200 mg of emtricitabine (FTC), 25 mg of rilpivirine (RPV), and 25 mg of tenofovir alafenamide (TAF). The recommended dosage of ODEFSEY is one tablet taken orally once daily with a meal in the following patient population: adults and in pediatric patients 12 years of age and older with body weight greater than or equal to 35 kg and a creatinine clearance greater than or equal to 30 mL per minute [*see Clinical Pharmacology (12.3)].*

2.3 Testing After Initiation of ODEFSEY

In virologically-suppressed patients, additional monitoring of HIV-1 RNA and regimen tolerability is recommended after replacing therapy to assess for potential virologic failure or rebound [*see Clinical Studies (14)]*.

2.4 Not Recommended in Patients with Severe Renal Impairment

ODEFSEY is not recommended in patients with estimated creatinine clearance below 30 mL per minute *[see Warnings and Precautions (5.10) and Use in Specific Populations (8.6)].*

3 DOSAGE FORMS AND STRENGTHS

Each ODEFSEY tablet contains 200 mg of emtricitabine (FTC), 25 mg of rilpivirine (RPV) (equivalent to 27.5 mg of rilpivirine hydrochloride), and 25 mg of tenofovir alafenamide (TAF) (equivalent to 28 mg of tenofovir alafenamide fumarate).

The tablets are gray, capsule-shaped, film-coated and debossed with “GSI” on one side and “255” on the other side.

4 CONTRAINDICATIONS

ODEFSEY is contraindicated when coadministered with the following drugs, as significant decreases in RPV plasma concentrations may occur due to cytochrome P450 (CYP) 3A enzyme induction or gastric pH increase, which may result in loss of virologic response and possible resistance to ODEFSEY or to the class of NNRTIs *[see Warnings and Precautions (5.4), Drug Interactions (7) and Clinical Pharmacology (12.3)]*:

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the antimycobacterials rifampin and rifapentine
- proton pump inhibitors, such as dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
- the glucocorticoid systemic dexamethasone (more than a single dose)
- St. John’s wort (*Hypericum perforatum*)

5 WARNINGS AND PRECAUTIONS

5.1 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 in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Given that ODEFSEY contains two nucleos(t)ide analogs (i.e., FTC and TAF), ODEFSEY should be discontinued 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).

5.2 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 hepatitis B virus (HBV) before initiating antiretroviral therapy *[see Dosage and Administration (2.1)]*. ODEFSEY is not approved for the treatment of chronic HBV infection, and the safety and efficacy of ODEFSEY have not been established in patients coinfected with HIV-1 and HBV.

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 TDF, and may occur with discontinuation of ODEFSEY. Patients coinfected with HIV-1 and HBV who discontinue ODEFSEY should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, initiation of antihepatitis 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.

5.3 Skin and Hypersensitivity Reactions

Severe skin and hypersensitivity reactions, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), have been reported during postmarketing experience with RPV-containing regimens. While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunction, including elevations in hepatic serum biochemistries. During Phase 3 clinical trials of RPV, treatment-related rashes with at least Grade 2 severity were reported in 1% of subjects. Overall, most rashes were Grade 1 or 2 and occurred in the first four to six weeks of therapy *[see Adverse Reactions (6.2)]*.

Discontinue ODEFSEY immediately if signs or symptoms of severe skin or hypersensitivity reactions develop, including but not limited to, severe rash or rash accompanied by fever, blisters, mucosal involvement, conjunctivitis, facial edema,

angioedema, hepatitis, or eosinophilia. Clinical status including laboratory parameters should be monitored and appropriate therapy should be initiated.

5.4 Loss of Virologic Response Due to Drug Interactions

The concomitant use of ODEFSEY and other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of ODEFSEY and possible development of resistance due to reduced exposure of RPV.

See Table 1 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Contraindications (4) and Drug Interactions (7)].* Consider the potential for drug interactions prior to and during ODEFSEY therapy; review concomitant medications during ODEFSEY therapy; and monitor for the adverse reactions associated with the concomitant drugs.

5.5 Prolongation of QTc Interval with Higher Than Recommended Dosages

In healthy subjects, higher than recommended doses of RPV (75 mg once daily and 300 mg once daily – 3 and 12 times the recommended dosages, respectively) have been shown to prolong the QTc interval of the electrocardiogram *[see Drug Interactions (7.2) and Clinical Pharmacology (12.2)]*. Consider alternatives to ODEFSEY when coadministered with a drug with a known risk of Torsade de Pointes or when administered to patients at higher risk of Torsades de Pointes.

5.6 Depressive Disorders

Depressive disorders (including depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) have been reported with RPV. Promptly evaluate patients with severe depressive symptoms to assess whether the symptoms are related to ODEFSEY, and to determine whether the risks of continued therapy outweigh the benefits.

In Phase 3 trials of RPV in adult subjects (N=1368) through 96 weeks, the incidence of depressive disorders (regardless of causality, severity) reported among RPV-treated subjects (n=686) was 9%. Most events were mild or moderate in severity. In RPV-treated subjects, the incidence of Grades 3 and 4 depressive disorders (regardless of causality) was 1%, the incidence of discontinuation due to depressive disorders was 1%, and suicidal ideation and suicide attempt was reported in 4 and 2 subjects, respectively.

During the Phase 2 trial in RPV-treated pediatric subjects 12 to less than 18 years of age (N=36), the incidence of depressive disorders (regardless of causality, severity) was 19% (7/36) through 48 weeks. Most events were mild or moderate in severity. The incidence of Grade 3 and 4 depressive disorders (regardless of causality) was 6% (2/36). None of the subjects discontinued due to depressive disorders. Suicidal ideation and suicide attempt were reported in 1 subject.

5.7 Hepatotoxicity

Hepatic adverse events have been reported in patients receiving an RPV-containing regimen. Patients with underlying hepatitis B or C, or marked elevations in liver-associated tests prior to treatment, may be at increased risk for worsening or development of liver-associated test elevations with use of ODEFSEY. A few cases of hepatic toxicity have been reported in adult patients receiving a RPV-containing regimen who had no preexisting hepatic disease or other identifiable risk factors. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with ODEFSEY is recommended in patients with underlying hepatic disease such as hepatitis B or C, or in patients with marked elevations in liver-associated tests prior to treatment initiation. Liver-associated test monitoring should also be considered for patients without preexisting hepatic dysfunction or other risk factors.

5.8 Fat Redistribution

Redistribution or accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.9 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including FTC and RPV, both components of ODEFSEY. 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, and Guillain-Barré syndrome) 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.

5.10 New Onset or Worsening 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 of FTC+TAF with EVG+COBI, there have been no cases of Fanconi syndrome or proximal renal tubulopathy (PRT). In clinical trials of FTC+TAF with EVG+COBI in treatment-naïve subjects and in virally suppressed subjects switched to FTC+TAF with EVG+COBI with eGFRs greater than 50 mL per minute, renal serious adverse events or

discontinuations due to renal adverse reactions were encountered in less than 1% of participants treated with FTC+TAF with EVG+COBI. In a study of virally suppressed subjects with baseline eGFRs between 30 and 69 mL per minute treated with FTC+TAF with EVG+COBI for a median duration of 43 weeks, FTC+TAF with EVG+COBI was permanently discontinued due to worsening renal function in two of 80 (3%) subjects with a baseline eGFR between 30 and 50 mL per minute [*see Adverse Reactions (6.1)]*. ODEFSEY is not recommended in patients with estimated creatinine clearance below 30 mL per minute because data in this population are insufficient.

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

Estimated creatinine clearance, urine glucose and urine protein should be assessed before initiating ODEFSEY therapy and should be monitored during therapy in all patients. Serum phosphorus should be monitored in patients with chronic kidney disease because these patients are at greater risk of developing Fanconi syndrome on tenofovir prodrugs. Discontinue ODEFSEY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

5.11 Bone Loss and Mineralization Defects

Decrease in Bone Mineral Density (BMD):

In animal toxicology studies and human clinical trials, TAF and tenofovir have been associated with decreases in BMD and increases in biochemical markers of bone metabolism suggestive of increased bone turnover. In clinical trials in HIV-1 infected treatment-naïve adults, a significant decline in BMD was observed in 15% of subjects treated with FTC+TAF with EVG+COBI *[see Adverse Reactions (6.1)]*. The long-term clinical significance of these changes has not been established.

Assessment of BMD should be considered for adults and pediatric patients treated with ODEFSEY who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Calcium and vitamin D supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Mineralization Defects:

Cases of osteomalacia associated with proximal renal tubulopathy (PRT), manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of TDF-containing products. Hypophosphatemia and osteomalacia secondary to PRT have occurred in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing TDF *[see Warnings and Precautions (5.10)]*. While not observed in clinical studies of FTC+TAF with EVG+COBI, the risk of osteomalacia with ODEFSEY is not known.

6 ADVERSE REACTIONS

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

- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[See Boxed Warning and Warnings and Precautions (5.1)]*
- Severe Acute Exacerbations of Hepatitis B *[See Boxed Warning and Warnings and Precautions (5.2)]*
- Skin and Hypersensitivity Reactions *[See Warnings and Precautions (5.3)]*
- Depressive Disorders *[See Warnings and Precautions (5.6)]*
- Hepatotoxicity *[See Warnings and Precautions (5.7)]*
- Immune Reconstitution Syndrome *[See Warnings and Precautions (5.9)]*
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.10)]*
- Bone Loss and Mineralization Defects *[see Warnings and Precautions (5.11)]*

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 (or a drug given in various combinations with other concomitant therapy) cannot be directly compared to rates in the clinical trials of another drug (or drug given in the same or different combination therapy) and may not reflect the rates observed in practice.

Adverse Reactions in Clinical Trials of RPV-Containing Regimens in Adult Subjects with HIV-1 Infection

In pooled 96-week trials of antiretroviral treatment-naïve HIV-1 infected adult subjects, the most common adverse reactions in subjects treated with RPV+FTC/TDF (N=550) (incidence greater than or equal to 2%, Grades 2–4) were headache, depressive disorders, and insomnia. The proportion of subjects who discontinued treatment with RPV+FTC/TDF due to adverse reactions, regardless of severity, was 2%. The most common adverse reactions that led to discontinuation in this treatment group were psychiatric disorders (1.6%) and rash (0.2%). Although the safety profile was similar in virologically-suppressed adults with HIV-1 infection who were switched to RPV and other antiretroviral drugs, the frequency of adverse events increased by 20% (N=317).

Adverse Reactions in Clinical Trials of FTC+TAF with EVG+COBI in Adult Subjects with HIV-1 Infection

In pooled 48-week trials of antiretroviral treatment-naïve HIV-1 infected adult subjects, the most common adverse reaction in subjects treated with FTC+TAF with EVG+COBI (N=866) (incidence greater than or equal to 10%, all grades) was nausea (10%). In this treatment group, 0.9% of subjects discontinued FTC+TAF with EVG+COBI due to adverse event *[see Clinical Studies (14)]*. The safety profile was similar in virologically-suppressed adults with HIV-1 infection who were switched to FTC+TAF with EVG+COBI (N=799). Antiretroviral treatment-naïve adult subjects treated with FTC+TAF with EVG+COBI experienced mean increases of 30 mg/dL of total cholesterol, 15 mg/dL of LDL cholesterol, 7 mg/dL of HDL cholesterol and 29 mg/dL of triglycerides after 48 weeks of use.

Renal Laboratory Tests

In two 48-week trials in antiretroviral treatment-naïve HIV-1 infected adults treated with FTC+TAF with EVG+COBI (N=866) with a median baseline eGFR of 115 mL per minute, mean serum creatinine increased by 0.1 mg per dL from baseline to Week 48. Median urine protein-to-creatinine ratio (UPCR) was 44 mg per gram at baseline and at Week 48. In a 48-week trial in virologically-suppressed TDF-treated adults who switched to FTC+TAF with EVG+COBI (N=959) with a mean baseline eGFR of 112 mL per minute, mean serum creatinine was similar to baseline and median UPCR was 61 mg per gram at baseline and 46 mg per gram at Week 48. In a 24-week trial in adults with renal impairment (baseline eGFR 30 to 69 mL per minute) who received FTC+TAF with EVG+COBI (N=248), mean serum creatinine was 1.5 mg per dL at both baseline and Week 24. Median UPCR was 161 mg per gram at baseline and 93 mg per gram at Week 24.

Bone Mineral Density Effects

In the pooled analysis of two 48-week trials of antiretroviral treatment-naïve HIV-1 infected adult subjects, bone mineral density (BMD) from baseline to Week 48 was

assessed by dual-energy X-ray absorptiometry (DXA). Mean BMD decreased from baseline to Week 48 by −1.30% with FTC+TAF with EVG+COBI at the lumbar spine and -0.66% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 10% of FTC+TAF with EVG+COBI subjects. BMD declines of 7% or greater at the femoral neck were experienced by 7% of FTC+TAF with EVG+COBI subjects. The long-term clinical significance of these BMD changes is not known. Fractures (excluding fingers and toes) were reported in 7 (0.8%) subjects in the FTC+TAF with EVG+COBI group.

In 799 virologically-suppressed TDF-treated adult subjects that switched to FTC+TAF with EVG+COBI, at Week 48 mean BMD increased (1.86% lumbar spine, 1.95% total hip). BMD declines of 5% or greater at the lumbar spine were experienced by 1% of FTC+TAF with EVG+COBI subjects. BMD declines of 7% or greater at the femoral neck were experienced by 1% of FTC+TAF with EVG+COBI subjects.

Adverse Reactions in Clinical Trials in Pediatric Subjects with HIV-1 Infection
In an open-label 48-week trial of 36 antiretroviral treatment-naïve HIV-1 infected pediatric subjects 12 to less than 18 years old (weighing at least 32 kg) treated with 25 mg per day of RPV and other antiretrovirals, the most common adverse reactions were headache (19%), depression (19%), somnolence (14%), nausea (11%), dizziness (8%), abdominal pain (8%), vomiting (6%) and rash (6%).

In a 24-week, open-label trial of 23 antiretroviral treatment-naïve HIV-1 infected pediatric subjects aged 12 to less than 18 years old (weighing at least 35 kg) who received FTC+TAF with EVG+COBI, the safety of this combination was similar to that of adults. Among these pediatric subjects, mean BMD increased from baseline to Week 24, +1.7% at the lumbar spine and +0.8% for the total body less head. Mean changes from baseline BMD Z-scores were -0.10 for lumbar spine and -0.11 for total body less head at Week 24. Two subjects had significant (greater than 4%) lumbar spine BMD loss at Week 24.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing experience in patients receiving RPV-containing regimens. Because these reactions 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.

Metabolism and Nutrition Disorders
Weight increased

Skin and Subcutaneous Tissue Disorders
Severe skin and hypersensitivity reactions including DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)

Renal and Urinary Disorders
Nephrotic syndrome

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect One or More Components of ODEFSEY

Drugs that Induce or Inhibit CYP3A Enzymes

RPV is primarily metabolized by CYP3A, and drugs that induce or inhibit CYP3A may thus affect the clearance of RPV *[see Contraindications (4) and Clinical Pharmacology (12.3)]*. Coadministration of RPV and drugs that induce CYP3A may result in decreased plasma concentrations of RPV and loss of virologic response and possible resistance to RPV or to the class of NNRTIs. Coadministration of RPV and drugs that inhibit CYP3A may result in increased plasma concentrations of RPV and possible adverse events.

Drugs that Induce or Inhibit P-glycoprotein

TAF, a component of ODEFSEY, is a substrate of P-gp, BCRP, OATP1B1, and OATP1B3. Drugs that strongly affect P-gp activity (e.g., cyclosporine) may lead to changes in TAF absorption *(see Table 1)*. 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 ODEFSEY and development of resistance. Coadministration of ODEFSEY with other drugs that inhibit P-gp may result in increased absorption and plasma concentrations of TAF and possible adverse events.

Drugs that Increase Gastric pH

Coadministration of RPV with drugs that increase gastric pH (e.g., famotidine) may decrease plasma concentrations of RPV and lead to loss of virologic response and possible resistance to RPV or to the class of NNRTIs *(see Table 1).*

7.2 QT Prolonging Drugs

There is limited information available on the potential for a pharmacodynamic interaction between RPV and drugs that prolong the QTc interval. In a study of healthy subjects, higher than recommended doses of RPV, 75 mg once daily and 300 mg once daily (3 times and 12 times recommended daily dose in ODEFSEY) prolonged the QTc interval *[see Warnings and Precautions (5.5) and Clinical Pharmacology (12.2)]*. Consider alternative medications to ODEFSEY in patients taking a drug with a known risk of Torsade de Pointes.

7.3 Drugs that Affect Renal Function

Because FTC and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of ODEFSEY 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 (5.10)]*.

7.4 Established and Other Potentially Significant Drug Interactions

Table 1 provides a listing of established or potentially clinically significant drug interactions with recommended steps to prevent or manage the drug interaction (the table is not all inclusive). The drug interactions described are based on studies conducted with either ODEFSEY, the components of ODEFSEY (FTC, RPV and TAF) as individual agents, or are predicted drug interactions that may occur with ODEFSEY. For pharmacokinetic data, see Tables 5–8 *[see Clinical Pharmacology (12.3)]*.

Table 1 Established and Other Potentially Significant[a] Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antacids: antacids (e.g., aluminum, magnesium hydroxide, or calcium carbonate)	↔ RPV (antacids taken at least 2 hours before or at least 4 hours after RPV) ↓ RPV (concomitant intake)	Administer antacids at least 2 hours before or at least 4 hours after ODEFSEY.
Antimycobacterials: rifabutin	↓ RPV[c] ↓ TAF	Coadministration of ODEFSEY with rifabutin is not recommended.
Azole Antifungal Agents: fluconazole itraconazole ketoconazole posaconazole voriconazole	↑ RPV[c,d] ↑ TAF ↓ ketoconazole[c,d]	No dosage adjustment is required when ODEFSEY is coadministered with azole antifungal agents. Clinically monitor for breakthrough fungal infections when azole antifungals are coadministered with ODEFSEY.
H_2-Receptor Antagonists: cimetidine famotidine nizatidine ranitidine	↔ RPV[c,d] (famotidine taken 12 hours before RPV or 4 hours after RPV) ↓ RPV[c,d] (famotidine taken 2 hours before RPV)	Administer H_2-receptor antagonists at least 12 hours before or at least 4 hours after ODEFSEY.
Macrolide or Ketolide Antibiotics: clarithromycin erythromycin telithromycin	↑ RPV ↔ clarithromycin ↔ erythromycin ↔ telithromycin	Where possible, alternatives such as azithromycin should be considered.

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Narcotic Analgesics: methadone	↓ R(–) methadone[c] ↓ S(+) methadone[c] ↔ RPV[c] ↔ methadone[c] (when used with tenofovir)	No dosage adjustments are required when initiating coadministration of methadone with ODEFSEY. However, clinical monitoring is recommended, as methadone maintenance therapy may need to be adjusted in some patients.

a. This table is not all inclusive.
b. Increase=↑; Decrease=↓; No Effect=↔
c. The interaction was evaluated in a clinical study. All other drug interactions shown are predicted.
d. This interaction study has been performed with a dose higher than the recommended dose for RPV. The dosing recommendation is applicable to the recommended dose of RPV 25 mg once daily.

7.5 Drugs Without Clinically Significant Interactions with ODEFSEY

Based on drug interaction studies conducted with the fixed dose combination or components of ODEFSEY, no clinically significant drug interactions have been either observed or expected when ODEFSEY is combined with the following drugs: acetaminophen, atorvastatin, buprenorphine, chlorzoxazone, digoxin, ethinyl estradiol, ledipasvir, lorazepam, metformin, midazolam, naloxone, norbuprenorphine, norethindrone, norgestimate/ethinyl estradiol, sildenafil, simeprevir and sofosbuvir.

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 ODEFSEY 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 ODEFSEY during pregnancy to inform a drug-associated risk of birth defects and miscarriage. Tenofovir alafenamide (TAF) and rilpivirine (RPV) use in women during pregnancy have not been evaluated; however, emtricitabine (FTC) use during pregnancy has been evaluated in a limited number of women reported to the Antiretroviral Pregnancy Registry. Available data from the APR show no difference in the risk of overall major birth defects for FTC (2.4%) compared with the background rate for major birth defects of 2.7% in a US reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15-20%. In animal studies, no adverse developmental effects were observed when the components of ODEFSEY were administered separately during the period of

organogenesis at exposures up to 60 and 108 times (mice and rabbits, respectively; FTC), 15 and 70 times (rats and rabbits, respectively; RPV) and equal to and 53 times (rats and rabbits, respectively; TAF) the exposure at the recommended daily dose of these components in ODEFSEY *[see Data (8.1)]*. Likewise, no adverse developmental effects were seen when FTC was administered to mice and RPV was administered to rats through lactation at exposures up to approximately 60 and 63 times, respectively, the exposure at the recommended daily dose of these components in ODEFSEY. No adverse effects were observed in the offspring when TDF was administered through lactation at tenofovir exposures of approximately 14 times the exposure at the recommended daily dosage of ODEFSEY.

Data

Human Data

Emtricitabine: Based on prospective reports to the APR through July 2015 of 2933 exposures to FTC-containing regimens during pregnancy (including 1984 exposed in the first trimester and 949 exposed in the second/third trimester), there was no difference between FTC and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 2.4% (95% CI: 1.7% to 3.1%) with first trimester exposure to FTC-containing regimens and 2.1% (95% CI: 1.3% to 3.2%) with the second/third trimester exposure to FTC-containing regimens.

Animal Data

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 FTC in mice at exposures (AUC) approximately 60 times higher and in rabbits at approximately 108 times higher than human exposures at the recommended daily dose. 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-fold higher than human exposures at the recommended daily dose.

Rilpivirine: RPV was administered orally to pregnant rats (40, 120, or 400 mg/kg/day) and rabbits (5, 10, or 20 mg/kg/day) through organogenesis (on gestation days 6 through 17, and 6 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with RPV in rats and rabbits at exposures 15 (rats) and 70 (rabbits) times higher than the exposure in humans at the recommended dose of 25 mg once daily. In a pre/postnatal development study with RPV, where rats were administered up to 400 mg/kg/day through lactation, no significant adverse effects directly related to drug were noted in the offspring.

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 similar to (rats) and approximately 53 (rabbits) times higher than the exposure in humans at the recommended daily dose of ODEFSEY. TAF is rapidly converted to tenofovir; the observed tenofovir exposure in rats and rabbits were 59 (rats) and 93 (rabbits) times higher than human tenofovir exposures at the recommended daily doses. Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to tenofovir disoproxil fumarate (TDF, another prodrug for tenofovir) 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 14 [21] times higher than the exposures in humans at the recommended daily dose of ODEFSEY.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants, to avoid risking postnatal transmission of HIV.

FTC has been shown to be present in human breast milk; it is unknown if RPV and TAF are present in human breast milk. RPV is present in rat milk and tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF *[see Data (8.2)].* It is unknown if TAF is present in animal milk.

It is not known if ODEFSEY affects milk production or has effects on the breastfed infant. 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 ODEFSEY.

Data

Human Data

Emtricitabine: Samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is present in human milk. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown.

Animal Data

Rilpivirine: In animals, no studies have been conducted to assess the excretion of rilpivirine directly; however RPV was measured in rat pups which were exposed through the milk of treated dams (dosed up to 400 mg/kg/day).

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 *[see Data (8.1)].* 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 efficacy and safety of ODEFSEY as a complete regimen for the treatment of HIV-1 infection was established in pediatric patients 12 years of age and older with body weight greater than or equal to 35 kg *[see Dosage and Administration (2.2)].* Use of ODEFSEY in this age group is supported by adequate and well-controlled studies of RPV+FTC+TDF in adults with HIV-1 infection, adequate and well-controlled studies of FTC+TAF with EVG+COBI in adults with HIV-1 infection, and by the following pediatric studies *[see Clinical Studies (14)]:*

- 48-week open-label trial of 36 antiretroviral treatment-naïve HIV-1 infected pediatric subjects 12 to less than 18 years old weighing at least 32 kg treated with 25 mg per day of RPV and other antiretrovirals. The safety and efficacy of RPV and other antiretrovirals was similar to that of antiretroviral treatment-naïve HIV-1 infected adults on this regimen.
- 24-week open-label trial of 23 antiretroviral treatment-naïve HIV-1 infected pediatric subjects 12 to less than 18 years old (weighing at least 35 kg) treated with FTC+TAF with EVG+COBI. The safety and efficacy of FTC+TAF with EVG+COBI was similar to that of antiretroviral treatment-naïve HIV-1 infected adults on this regimen.

Because it is a fixed-dose combination tablet, the dose of ODEFSEY cannot be adjusted for patients of lower age and weight. The safety and efficacy of ODEFSEY have not been established in pediatric patients less than 12 years of age or weighing less than 35 kg *[see Clinical Pharmacology (12.3)]*.

8.5 Geriatric Use

In clinical trials, 80 of the 97 subjects enrolled aged 65 years and over received FTC+TAF with EVG+COBI. No differences in safety or efficacy have been observed between elderly subjects and those between 12 and less than 65 years of age. Clinical trials of RPV did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects *[see Clinical Pharmacology (12.3)].*

8.6 Renal Impairment

ODEFSEY is not recommended in patients with severe renal impairment (estimated creatinine clearance below 30 mL per minute). No dosage adjustment of ODEFSEY is recommended in patients with estimated creatinine clearance greater than or equal to 30 mL per minute *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3) and Clinical Studies (14)].*

8.7 Hepatic Impairment

No dosage adjustment of ODEFSEY is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. ODEFSEY has not been studied in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

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

Emtricitabine (FTC): Limited clinical experience is available at doses higher than the recommended dosage of FTC in ODEFSEY. In one clinical pharmacology study, single doses of FTC 1200 mg (6 times the dose in ODEFSEY) were administered to 11 subjects. No severe adverse reactions were reported. The effects of higher doses are not known.

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 per minute and a dialysate flow rate of 600 mL per minute). It is not known whether FTC can be removed by peritoneal dialysis.

Rilpivirine (RPV): Human experience of overdose with RPV is limited. There is no specific antidote for overdose with RPV. Since RPV is highly bound to plasma protein, dialysis is unlikely to result in significant removal of RPV.

Administration of activated charcoal may be used to aid in removal of unabsorbed active substance.

Tenofovir Alafenamide (TAF): Limited clinical experience is available at doses higher than the recommended dosage of TAF in ODEFSEY. A single dose of 125 mg TAF (5 times the dose of TAF in ODEFSEY) was administered to 48 healthy subjects; no serious adverse reactions were reported. The effects of higher doses are unknown. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

11 DESCRIPTION

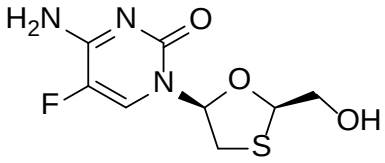
ODEFSEY (emtricitabine, rilpivirine, and tenofovir alafenamide) is a fixed-dose combination tablet containing emtricitabine (FTC), rilpivirine (RPV), and tenofovir alafenamide (TAF) for oral administration.

- FTC, a synthetic nucleoside analog of cytidine, is an HIV-1 nucleoside analog reverse transcriptase inhibitor (HIV-1 NRTI).
- RPV is an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI).
- TAF, an HIV-1 NRTI, is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

Each tablet contains 200 mg of FTC, 25 mg of RPV (equivalent to 27.5 of rilpivirine hydrochloride) and 25 mg of TAF (equivalent to 28 mg of tenofovir alafenamide fumarate) and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 20, and povidone. The tablets are film-coated with a coating material containing iron oxide black, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

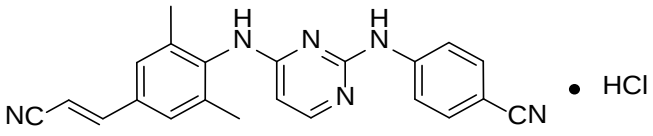
Emtricitabine: The chemical name of FTC is 4-amino-5-fluoro-1-(2*R*-hydroxymethyl-1,3-oxathiolan-5*S*-yl)-(1*H*)-pyrimidin-2-one. FTC is the (-)enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5 position.

FTC has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24 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.

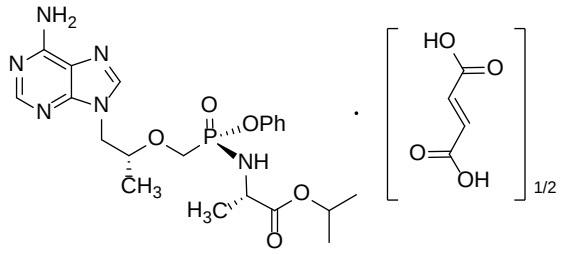
Rilpivirine: The chemical name of rilpivirine hydrochloride drug substance is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile monohydrochloride. Its molecular formula is $C_{22}H_{18}N_6 \bullet HCl$ and its molecular weight is 402.88. Rilpivirine hydrochloride has the following structural formula:



Rilpivirine hydrochloride is a white to almost white powder. Rilpivirine hydrochloride is practically insoluble in water over a wide pH range.

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 $C_{21}H_{29}O_5N_6P \bullet ½(C_4H_4O_4)$ and a formula weight of 534.50 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

ODEFSEY is a fixed dose combination of antiretroviral drugs emtricitabine, rilpivirine, and tenofovir alafenamide *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

When higher than recommended RPV doses of 75 mg (3 times the recommended dosage in ODEFSEY) once daily and 300 mg (12 times the recommended dosage in ODEFSEY) once daily were studied in healthy adults, the maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline correction were 10.7 (15.3) and 23.3 (28.4) milliseconds, respectively. Steady-state administration of RPV 75 mg once daily and 300 mg once daily resulted in a mean steady-state C_{max} approximately 2.6 times and 6.7 times, respectively, higher than the mean C_{max} observed with the recommended 25 mg once daily dose of RPV *[see Warnings and Precautions (5.5)]*.

The effect of RPV at the recommended dose of 25 mg once daily on the QTcF interval was evaluated in a randomized, placebo-, and active- (moxifloxacin 400 mg once daily) controlled crossover study in 60 healthy adults, with 13 measurements over 24 hours at steady state. The maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline correction was 2 (5) milliseconds (i.e., below the threshold of clinical concern).

In a thorough QT/QTc study in 48 healthy subjects, TAF at the recommended dose and at a dose approximately 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.

12.3 Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetic properties of the components of ODEFSEY are provided in Table 2. The multiple dose pharmacokinetic parameters of FTC, RPV and TAF and its metabolite tenofovir are provided in Table 3.

Table 2 Pharmacokinetic Properties of the Components of ODEFSEY

	Rilpivirine	Emtricitabine	Tenofovir Alafenamide
Absorption			
T_{max} (h)	4	3	1
Effect of moderate fat meal (relative to fasting)[a]	AUC Ratio = 1.13 (1.03, 1.23)	AUC Ratio = 0.91 (0.89, 0.93)	AUC Ratio = 1.45 (1.33, 1.58)
Effect of high fat meal (relative to fasting)[a]	AUC Ratio = 1.72 (1.49, 1.99)	AUC Ratio = 0.88 (0.85, 0.90)	AUC Ratio = 1.53 (1.39, 1.69)
Distribution			
% Bound to human plasma proteins	~99	<4	~80
Source of protein binding data	In vitro	In vitro	Ex vivo
Blood-to-plasma ratio	0.7	0.6	1.0
Metabolism			
Metabolism	CYP3A	Not significantly metabolized	Cathepsin A[b] (PBMCs) CES1 (hepatocytes) CYP3A (minimal)
Elimination			
Major route of elimination	Metabolism	Glomerular filtration and active tubular secretion	Metabolism (>80% of oral dose)
$t_{1/2}$ (h)[c]	50	10	0.51
% Of dose excreted in urine[d]	6	70	<1
% Of dose excreted in feces[d]	85	13.7	31.7

PBMCs = peripheral blood mononuclear cells; CES1 = carboxylesterase 1.

a. Values refer to geometric mean ratio [fed/ fasted] in PK parameters and (90% confidence interval). High-calorie/high-fat meal = ~800 kcal, 50% fat. Moderate-fat meal = ~600 kcal, 27% fat.

b. 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. Upon coadministration with the moderate CYP3A inducer probe efavirenz, TAF exposure was unaffected.

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

d. Dosing in mass balance studies: 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 3 Multiple Dose Pharmacokinetic Parameters of Emtricitabine, Rilpivirine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration with a Meal in HIV-Infected Adults

Parameter Mean (CV%)	Emtricitabine[a]	Rilpivirine[b]	Tenofovir Alafenamide[c]	Tenofovir[d]
C_{max} (microgram per mL)	2.1 (20.2)	NA	0.16 (51.1)	0.02 (26.1)
AUC_{tau} (microgram•hour per mL)	11.7 (16.6)	2.2 (38.1)	0.21 (71.8)	0.29 (27.4)
C_{trough} (microgram per mL)	0.10 (46.7)	0.08 (44.3)	NA	0.01 (28.5)

CV = Coefficient of Variation; NA = Not Applicable
a. From Intensive PK analysis in a phase 2 trial in HIV infected adults treated with FTC+TAF with EVG+COBI (n=19).
b. From Population PK analysis in a trial of treatment-naïve adults with HIV-1 infection treated with RPV (n=679).
c. From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated within EVG+COBI+FTC+TAF (n=539).
d. From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated with EVG+COBI+FTC+TAF (n=841).

Specific Populations

Patients with Renal Impairment

Rilpivirine: Population pharmacokinetic analysis indicated that RPV exposure was similar in HIV-1 infected subjects with eGFR 60 to 89 mL per minute by Cockcroft-Gault method relative to HIV-1 infected subjects with normal renal function. There is limited or no information regarding the pharmacokinetics of RPV in patients with moderate or severe renal impairment or in patients with end-stage renal disease *[see Use in Specific Populations (8.6)]*.

Tenofovir Alafenamide: The pharmacokinetics of FTC+TAF with EVG+COBI in HIV-1 infected subjects with renal impairment (eGFR 30 to 69 mL per minute by Cockcroft-Gault method) were evaluated within a subset of virologically-suppressed subjects in an open-label trial (Table 4).

Table 4 Pharmacokinetics of the FTC, TAF, and a Metabolite of TAF (Tenofovir) in HIV-Infected Adults with Renal Impairment as Compared to Subjects with Normal Renal Function

	AUC_{tau} (microgram-hour per mL) Mean (CV%)		
Creatinine Clearance	**≥90 mL per minute (N=18)[a]**	**60–89 mL per minute (N=11)[b]**	**30–59 mL per minute (N=18)**
Emtricitabine	11.4 (11.9)	17.6 (18.2)	23.0 (23.6)
Tenofovir Alafenamide*	0.23 (47.2)	0.24 (45.6)	0.26 (58.8)
Tenofovir	0.32 (14.9)	0.46 (31.5)	0.61 (28.4)

*AUC_{last}
a. From a phase 2 trial in HIV-infected adults with normal renal function treated with FTC+TAF with EVG+COBI.
b. These subjects had an eGFR ranging from 60 to 69 mL per minute.

Patients with 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, so the impact of hepatic impairment should be limited.

Rilpivirine: In a study comparing 8 subjects with mild hepatic impairment (Child-Pugh score A) to 8 matched controls and 8 subjects with moderate hepatic impairment (Child-Pugh score B) to 8 matched controls, the multiple-dose exposure of RPV was 47% higher in subjects with mild hepatic impairment and 5% higher in subjects with moderate hepatic impairment *[see Use in Specific Populations (8.7)]*.

Tenofovir Alafenamide: Clinically relevant changes in tenofovir pharmacokinetics in subjects with hepatic impairment were not observed in subjects with mild to 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 FTC and TAF have not been fully evaluated in subjects coinfected with hepatitis B and/or C virus. Population pharmacokinetic analysis indicated that hepatitis B and/or C virus coinfection had no clinically relevant effect on the exposure of RPV.

Pediatric Patients

Exposures of TAF in 24 pediatric subjects with HIV-1 infection aged 12 to less than 18 years who received FTC+TAF with EVG+COBI were decreased (23% for TAF AUC) compared to exposures achieved in treatment-naïve adults following administration of FTC+TAF with EVG+COBI. These exposure differences are not thought to be clinically significant based on exposure-response relationships.

FTC exposures were similar in adolescents compared to treatment-naïve adults. The PK of RPV in antiretroviral HIV-1-infected pediatric subjects 12 to less than 18 years of age who received RPV 25 mg once daily were comparable to those in HIV-1 infected adults. As in adults, there was no impact of body weight on RPV PK in pediatric subjects *[see Use In Specific Populations (8.4)]*.

Geriatric Patients

The pharmacokinetics of 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 2 and Phase 3 trials of FTC+TAF with EVG+COBI showed that age did not have a clinically relevant effect on exposures of TAF up to 75 years of age.

The pharmacokinetics of RPV have not been fully evaluated in the elderly (65 years of age and older) *[see Use in Specific Populations (8.5)].*

Race

Based on population pharmacokinetic analyses, no dosage adjustment is recommended based on race.

Gender

Based on population pharmacokinetic analyses, no dosage adjustment is recommended based on gender.

Drug Interaction Studies

Rilpivirine: RPV is primarily metabolized by CYP3A, and drugs that induce or inhibit CYP3A may thus affect the clearance of RPV.

RPV at a dose of 25 mg once daily is not likely to have a clinically relevant effect on the exposure of medicinal products metabolized by CYP enzymes.

TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1. TAF is a weak inhibitor of CYP3A in vitro. TAF is not an inhibitor or inducer of CYP3A in vivo.

The drug interaction studies described in Tables 5-8 were conducted with ODEFSEY (FTC/RPV/TAF) or the components of ODEFSEY (FTC, RPV, or TAF) administered individually.

The effects of coadministered drugs on the exposures of RPV and TAF are shown in Tables 5 and 6, respectively. The effects of RPV and TAF on the exposure of coadministered drugs are shown in Tables 7 and 8, respectively. For information regarding clinical recommendations, *see Drug Interactions (7).*

Table 5 Changes in Pharmacokinetic Parameters for RPV in the Presence of Coadministered Drugs in Healthy Subjects

Coadministered Drug	Dose/Schedule		N	Mean Ratio of RPV Pharmacokinetic Parameters With/Without Coadministered Drug (90% CI); No Effect = 1.00		
	Coadministered Drug (mg)	RPV (mg)		C_{max}	AUC	C_{min}
Acetaminophen	500 single dose	150 once daily[a]	16	1.09 (1.01, 1.18)	1.16 (1.10, 1.22)	1.26 (1.16, 1.38)
Atorvastatin	40 once daily	150 once daily[a]	16	0.91 (0.79, 1.06)	0.90 (0.81, 0.99)	0.90 (0.84, 0.96)
Chlorzoxazone	500 single dose taken 2 hours after RPV	150 once daily[a]	16	1.17 (1.08, 1.27)	1.25 (1.16, 1.35)	1.18 (1.09, 1.28)
Ethinylestradiol/ Norethindrone	0.035 once daily /1 mg once daily	25 once daily	15	↔[b]	↔[b]	↔[b]
Famotidine	40 single dose taken 12 hours before RPV	150 single dose[a]	24	0.99 (0.84, 1.16)	0.91 (0.78, 1.07)	NA
Famotidine	40 single dose taken 2 hours before RPV	150 single dose[a]	23	0.15 (0.12, 0.19)	0.24 (0.20, 0.28)	NA
Famotidine	40 single dose taken 4 hours after RPV	150 single dose[a]	24	1.21 (1.06, 1.39)	1.13 (1.01, 1.27)	NA
Ketoconazole	400 once daily	150 once daily[a]	15	1.30 (1.13, 1.48)	1.49 (1.31, 1.70)	1.76 (1.57, 1.97)
Methadone	60-100 once daily, individualized dose	25 once daily	12	↔[b]	↔[b]	↔[b]
Ledipasvir/ Sofosbuvir[c]	90/400 once daily	25 once daily	42	0.97 (0.92, 1.02)	0.95 (0.91, 0.98)	0.93 (0.89, 0.97)

Omeprazole	20 once daily	25 single dose	15	0.30 (0.24, 0.38)	0.35 (0.28, 0.44)	NA
Rifabutin	300 once daily	25 once daily	18	0.69 (0.62, 0.76)	0.58 (0.52, 0.65)	0.52 (0.46, 0.59)
Rifampin	600 once daily	150 once daily[a]	16	0.31 (0.27, 0.36)	0.20 (0.18, 0.23)	0.11 (0.10, 0.13)
Simeprevir	25 once daily	150 once daily	23	1.04 (0.95, 1.30)	1.12 (1.05, 1.19)	1.25 (1.16, 1.35)
Sildenafil	50 single dose	75 once daily[a]	16	0.92 (0.85, 0.99)	0.98 (0.92, 1.05)	1.04 (0.98, 1.09)

CI = Confidence Interval; N = maximum number of subjects with data; NA=Not Available; ↔=no change
a. 25 mg, 75 mg, and 150 mg of RPV is 1, 3, and 6 times the recommended dose of RPV in ODEFSEY, respectively.
b. Comparison based on historic controls.
c. Study conducted with ODEFSEY (FTC/RPV/TAF).

Table 6 Changes in Pharmacokinetic Parameters for TAF in the Presence of the Coadministered Drug[a] in Healthy Subjects

Coadministered Drug	Dose of Coadministered Drug (mg)	TAF (mg)	N	Mean Ratio of Tenofovir Alafenamide Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Cobicistat[b]	150 once daily	8 once daily	12	2.83 (2.20, 3.65)	2.65 (2.29, 3.07)	NC
Ledipasvir/ Sofosbuvir[c]	90/400 once daily	25 once daily	42	1.03 (0.94, 1.14)	1.32 (1.25, 1.40)	NC

CI=Confidence Interval; N=maximum number of subjects with data; NC=Not Calculated
a. All interaction studies conducted in healthy volunteers.
b. Increases TAF exposure via inhibition of intestinal P-glycoprotein.
c. Study conducted with ODEFSEY (FTC/RPV/TAF).

Table 7 Changes in Pharmacokinetic Parameters for Coadministered Drugs in the Presence of RPV in Healthy Subjects

Coadministered Drug	Dose/Schedule		N	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters With/Without RPV (90% CI); No Effect = 1.00		
	Coadministered Drug (mg)	RPV (mg)		C_{max}	AUC	C_{min}
Acetaminophen	500 single dose	150 once daily[a]	16	0.97 (0.86, 1.10)	0.92 (0.85, 0.99)	NA
Atorvastatin 2-hydroxy-atorvastatin 4-hydroxy-atorvastatin	40 once daily	150 once daily[a]	16	1.35 (1.08, 1.68) 1.58 (1.33, 1.87) 1.28 (1.15, 1.43)	1.04 (0.97, 1.12) 1.39 (1.29, 1.50) 1.23 (1.13, 1.33)	0.85 (0.69, 1.03) 1.32 (1.10, 1.58) NA
Chlorzoxazone	500 single dose taken 2 hours after RPV	150 once daily[a]	16	0.98 (0.85, 1.13)	1.03 (0.95, 1.13)	NA
Digoxin	0.5 single dose	25 once daily	22	1.06 (0.97, 1.17)	0.98 (0.93, 1.04)[b]	NA
Ethinylestradiol Norethindrone	0.035 once daily 1 mg once daily	25 once daily	17	1.17 (1.06, 1.30) 0.94 (0.83, 1.06)	1.14 (1.10, 1.19) 0.89 (0.84, 0.94)	1.09 (1.03, 1.16) 0.99 (0.90, 1.08)
Ketoconazole	400 once daily	150 once daily[a]	14	0.85 (0.80, 0.90)	0.76 (0.70, 0.82)	0.34 (0.25, 0.46)
R(-) methadone S(+) methadone	60-100 once daily, individualized dose	25 once daily	13	0.86 (0.78, 0.95) 0.87 (0.78, 0.97)	0.84 (0.74, 0.95) 0.84 (0.74, 0.96)	0.78 (0.67, 0.91) 0.79 (0.67, 0.92)

Metformin	850 single dose	25 once daily	20	1.02 (0.95, 1.10)	0.97 (0.90, 1.06)[c]	NA
Rifampin	600 once daily	150 once daily[a]	16	1.02 (0.93, 1.12)	0.99 (0.92, 1.07)	NA
25-desacetylrifampin				1.00 (0.87, 1.15)	0.91 (0.77, 1.07)	NA
Simeprevir	150 once daily	25 once daily	21	1.10 (0.97, 1.26)	1.06 (0.94, 1.19)	0.96 (0.83, 1.11)
Sildenafil	50 single dose	75 once daily[a]	16	0.93 (0.80, 1.08)	0.97 (0.87, 1.08)	NA
N-desmethyl-sildenafil				0.90 (0.80, 1.02)	0.92 (0.85, 0.99)[b]	NA

CI=Confidence Interval; N=maximum number of subjects with data; NA=Not Available
a. 25 mg, 75 mg, and 150 mg of RPV is 1, 3, and 6 times the recommended dose of RPV in ODEFSEY, respectively.
b. $AUC_{(0\text{-last})}$
c. N (maximum number of subjects with data for $AUC_{(0\text{-}\infty)}$=15)

Table 8 Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of TAF in Healthy Subjects

Coadministered Drug	Dose of Coadministered Drug (mg)	TAF (mg)	N	Mean Ratio of Coadministered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Cobicistat	150 once daily	8 once daily	14	1.06 (1.00, 1.12)	1.09 (1.03, 1.15)	1.11 (0.98, 1.25)
Midazolam[a]	2.5 once daily, orally	25 once daily	18	1.02 (0.92, 1.13)	1.12 (1.03, 1.22)	NC
	1 once daily IV			0.99 (0.89, 1.11)	1.08 (1.04, 1.14)	NC
Ledipasvir[b]	90/400 once daily	25 once daily	41	1.01 (0.97, 1.05)	1.02 (0.97, 1.06)	NC
Sofosbuvir[b]				0.96 (0.89, 1.04)	1.05 (1.01, 1.09)	NC
GS-331007[b,c]				0.96 (0.89, 1.04)	1.05 (1.01, 1.09)	NC

CI=Confidence Interval; N=maximum number of subjects with data; NC=Not Calculated
a. A sensitive CYP3A4 substrate.
b. Study conducted with ODEFSEY (FTC/RPV/TAF).
c. The predominant circulating nucleoside metabolite of sofosbuvir.

12.4 Microbiology

Mechanism of Action

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 (RT) 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.

Rilpivirine: RPV is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor of HIV-1 and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 RT. RPV does not inhibit the human cellular DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Tenofovir Alafenamide: TAF is a phosphonoamidate 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 has activity against human immunodeficiency virus (HIV-1). Cell culture studies have shown that both tenofovir and FTC 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 toxicity to mitochondria cell culture.

Antiviral Activity in Cell Culture

Emtricitabine, Rilpivirine, and Tenofovir Alafenamide: The combinations of FTC, RPV, and TAF were not antagonistic with each other in cell culture combination antiviral activity assays. In addition, FTC, RPV, and TAF were not antagonistic with a panel of representatives from the major classes of approved anti-HIV agents (NNRTIs, NRTIs, INSTIs, and PIs).

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 (PBMCs). The EC_{50} values for FTC were in the range of 0.0013–0.64 microM. 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 microM) and showed strain-specific activity against HIV-2 (EC_{50} values ranged from 0.007–1.5 microM).

Rilpivirine: RPV exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median EC_{50} value for HIV-1_{IIIB} of 0.73 nM. RPV demonstrated limited activity in cell culture against HIV-2 with a median EC_{50} value of

5220 nM (range 2510–10,830 nM). RPV demonstrated antiviral activity against a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC_{50} values ranging from 0.07–1.01 nM and was less active against group O primary isolates with EC_{50} values ranging from 2.88–8.45 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 2.0–14.7 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 0.10–12.0 nM) and strain specific activity against HIV-2 (EC_{50} values ranged from 0.91–2.63 nM).

Resistance

In Cell Culture

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.

Rilpivirine: RPV-resistant strains were selected in cell culture starting from wild-type HIV-1 of different origins and subtypes as well as NNRTI-resistant HIV-1. The frequently observed amino acid substitutions that emerged and conferred decreased phenotypic susceptibility to RPV included: L100I, K101E, V106I and A, V108I, E138K and G, Q, R, V179F and I, Y181C and I, V189I, G190E, H221Y, F227C, and M230I and L.

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 HIV-1-Infected Subjects With No Antiretroviral Treatment History

Emtricitabine and Tenofovir Alafenamide: The resistance profile of ODEFSEY for the treatment of HIV-1 infection is based on studies of FTC+TAF with EVG+COBI in the treatment of HIV-1 infection. In a pooled analysis of antiretroviral-naïve subjects, genotyping was performed on plasma HIV-1 isolates from all subjects with HIV-1 RNA greater than 400 copies per mL at confirmed virologic failure, at Week 48, or at time of early study drug discontinuation. Genotypic resistance developed in 7 of 14 evaluable subjects. The resistance–associated substitutions that emerged were M184V/I (N=7) and K65R (N=1). Three subjects had virus with emergent R, H, or E at the polymorphic Q207 residue in reverse transcriptase.

Rilpivirine: In the Week 96 pooled resistance analysis for adult subjects receiving RPV or efavirenz in combination with FTC/TDF, the emergence of resistance was greater among subjects' viruses in the RPV+FTC/TDF arm compared to the efavirenz + FTC/TDF arm and was dependent on baseline viral load. In the Week 96 resistance analysis, 14% (77/550) of the subjects in the RPV+FTC/TDF arm and 8% (43/546) of the subjects in the efavirenz + FTC/TDF arm qualified for resistance analysis; 61% (47/77) of the subjects who qualified for resistance analysis (resistance-analysis subjects) in the RPV+FTC/TDF arm had virus with genotypic and/or phenotypic resistance to RPV compared to 42% (18/43) of the resistance-analysis subjects in the efavirenz + FTC/TDF arm who had genotypic and/or phenotypic resistance to efavirenz. Moreover, genotypic and/or phenotypic resistance to emtricitabine or tenofovir emerged in viruses from 57% (44/77) of the resistance-analysis subjects in the RPV arm compared to 26% (11/43) in the efavirenz arm.

Emerging NNRTI substitutions in the RPV resistance analysis of subjects' viruses included V90I, K101E/P/T, E138K/A/Q/G, V179I/L, Y181C/I, V189I, H221Y, F227C/L, and M230L, which were associated with an RPV phenotypic fold change range of 2.6–621. The E138K substitution emerged most frequently during RPV treatment, commonly in combination with the M184I substitution. The emtricitabine and lamivudine resistance-associated substitutions M184I or V and NRTI resistance-associated substitutions (K65R/N, A62V, D67N/G, K70E, Y115F, K219E/R) emerged more frequently in the RPV resistance-analysis subjects than in efavirenz resistance-analysis subjects.

NNRTI- and NRTI-resistance substitutions emerged less frequently in the resistance analysis of viruses from subjects with baseline viral loads of less than or equal to 100,000 copies/mL compared to viruses from subjects with baseline viral loads of greater than 100,000 copies/mL: 23% (10/44) compared to 77% (34/44) of NNRTI-resistance substitutions and 20% (9/44) compared to 80% (35/44) of NRTI-resistance substitutions. This difference was also observed for the individual emtricitabine/lamivudine and tenofovir resistance substitutions: 22% (9/41) compared to 78% (32/41) for M184I/V and 0% (0/8) compared to 100% (8/8) for K65R/N. Additionally, NNRTI and/or NRTI-resistance substitutions emerged less frequently in the resistance analysis of the viruses from subjects with baseline CD4+ cell counts greater than or equal to 200 cells/mm^3 compared to the viruses from subjects with baseline CD4+ cell counts less than 200 cells/mm^3: 32% (14/44) compared to 68% (30/44) of NNRTI-resistance substitutions and 27% (12/44) compared to 73% (32/44) of NRTI-resistance substitutions.

In Virologically-Suppressed Subjects

Emtricitabine and Tenofovir Alafenamide: One subject was identified with emergent resistance to FTC or TAF (M184M/I) out of 4 virologic failure subjects in a clinical study of virologically-suppressed subjects who switched from a regimen containing FTC+TDF to FTC+TAF with EVG+COBI (N=799).

Rilpivirine: Through Week 48, 4 subjects who switched their protease inhibitor-based regimen to FTC/RPV/TDF (4 of 469 subjects, 0.9%) and 1 subject who maintained their regimen (1 of 159 subjects, 0.6%) developed genotypic and/or phenotypic resistance to a study drug. All 4 of the subjects who had resistance emergence on FTC/RPV/TDF had evidence of FTC resistance and 3 of the subjects had evidence of RPV resistance.

Cross-Resistance

Emtricitabine: FTC-resistant viruses with the M184V/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 (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.

Rilpivirine: Considering all of the available cell culture and clinical data, any of the following amino acid substitutions, when present at baseline, are likely to decrease the antiviral activity of RPV: K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M230I, M230L, and the combination of L100I+K103N.

Cross-resistance in site-directed mutant virus has been observed among NNRTIs. The single NNRTI substitutions K101P, Y181I, and Y181V conferred 52 times, 15 times, and 12 times decreased susceptibility to RPV, respectively. The combination of E138K and M184I showed 6.7 times reduced susceptibility to RPV compared to 2.8 times for E138K alone. The K103N substitution did not show reduced susceptibility to RPV by itself. However, the combination of K103N and L100I resulted in a 7 times reduced susceptibility to RPV. In another study, the Y188L substitution resulted in a reduced susceptibility to RPV of 9 times for clinical isolates and 6 times for site-directed mutants. Combinations of 2 or 3 NNRTI resistance-associated substitutions gave decreased susceptibility to RPV (fold change range of 3.7–554) in 38% and 66% of mutants, respectively.

Cross-resistance to efavirenz, etravirine, and/or nevirapine is likely after virologic failure and development of RPV resistance.

Tenofovir Alafenamide: 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

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 (23 times the human systemic exposure at the recommended dose of 200 mg per day in ODEFSEY) or in rats at doses up to 600 mg per kg per day (28 times the human systemic exposure at the recommended dose in ODEFSEY).

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 200 mg daily dose in ODEFSEY. 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 200 mg daily dose in ODEFSEY.

Rilpivirine: RPV was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 20, 60, and 160 mg per kg per day were administered to mice and doses of 40, 200, 500, and 1500 mg per kg per day were administered to rats. In rats, there were no drug-related neoplasms. In mice, RPV was positive for hepatocellular neoplasms in both males and females. The observed hepatocellular findings in mice may be rodent-specific. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to RPV were 21 times (mice) and 3 times (rats) relative to those observed in humans at the recommended dose (25 mg once daily) in ODEFSEY.

RPV has tested negative in the absence and presence of a metabolic activation system, in the in vitro Ames reverse mutation assay and in vitro clastogenicity mouse lymphoma assay. RPV did not induce chromosomal damage in the in vivo micronucleus test in mice.

In a study conducted in rats, there were no effects on mating or fertility with RPV up to 400 mg per kg per day, a dose of RPV that showed maternal toxicity. This dose is associated with an exposure that is approximately 40 times higher than the exposure in humans at the recommended dose of 25 mg once daily in ODEFSEY.

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 at the recommended dose of TDF (300 mg) for HIV-1 infection. The tenofovir exposure in these studies was approximately 167 times (mice) and 55 times (rat) those observed in humans after administration of the daily recommended dose of ODEFSEY. At the high dose in female mice, liver adenomas were increased at tenofovir exposures

approximately 10 times (300 mg TDF) and 167 times (ODEFSEY) the exposure observed in humans. 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 62 times the human dose 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 5 (TAF) and 15 (tenofovir) times the exposure seen in humans at the recommended daily TAF dose in ODEFSEY.

14 CLINICAL STUDIES

The efficacy of RPV, FTC, and TAF in the treatment of HIV-1 infection in adults as initial therapy in those with no antiretroviral treatment history and to replace a stable antiretroviral regimen in those who are virologically-suppressed *[see Indications and Usage (1)]* was established in trials of:

- RPV+FTC/TDF in HIV-1 infected adults as initial therapy in those with no antiretroviral treatment history (n=550) and to replace a first or second stable antiretroviral regimen containing a protease inhibitor and ritonavir in those who were virologically-suppressed with no history of virologic failure or for at least 6 months with no known resistance substitutions (n=317). The virologic response rate (i.e., HIV-1 RNA less than 50 copies per mL) in these two populations was 77% at Week 96 and 89% at Week 48, respectively. Among treatment-naïve subjects, the virologic response rate at 96 weeks was 83% in subjects with baseline HIV-1 RNA less than or equal to 100,000 copies per mL and 71% in subjects with baseline HIV-1 RNA greater than 100,000 copies per mL. Further, the virologic response rate at 96 weeks among subjects with baseline CD4+ cell counts less than 200 and greater than or equal to 200 cells/mm^3 were 68% and 82%, respectively.
- FTC+TAF with EVG+COBI in HIV-1 infected adults as initial therapy in those with no antiretroviral treatment history (n=866) and to replace a stable antiretroviral regimen in those who were virologically-suppressed for at least 6 months with no known resistance substitutions (n=799). At Week 48, 92% and 96% of patients in the two populations, respectively, had HIV-1 RNA less than 50 copies per mL.

The efficacy of RPV, FTC, and TAF in the treatment of HIV-1 infection in pediatric patients aged 12 to less than 18 years old and greater than 32-35 kg as initial therapy in those with no antiretroviral treatment history and to replace a stable antiretroviral regimen in those who are virologically-suppressed *[see Indications and Usage (1)]* was established in trials of antiretroviral treatment-naïve HIV-1 infected pediatric subjects 12 to less than 18 years old with:

- RPV in combination with other antiretroviral agents in 36 treatment-naïve HIV-1 infected adolescents weighing at least 32 kg. The majority of subjects (24/36) received RPV in combination with FTC and TDF. Of these 24 subjects, 20 had a baseline HIV-1 RNA less than or equal to 100,000 copies per mL. The virologic response rate in these 20 subjects (i.e., HIV-1 RNA less than 50 copies per mL) was 80% (16/20) at 48 weeks.
- FTC+TAF with EVG+COBI in 23 adolescents weighing at least 35 kg. The virologic response rate (i.e., HIV-1 RNA less than 50 copies per mL) was 91% at 24 weeks.

In the clinical trial of 248 HIV-1 infected adult patients with estimated creatinine clearance greater than 30 mL per minute but less than 70 mL per minute, 95% (235/248) of the combined populations of treatment-naïve (N=6) begun on FTC+TAF with EVG +COBI and those previously virologically suppressed on other regimens (N=242) and switched to FTC+TAF with EVG +COBI had HIV-RNA levels less than 50 copies per mL at Week 24.

16 HOW SUPPLIED/STORAGE AND HANDLING

ODEFSEY tablets are gray, capsule-shaped, and film coated with “GSI” debossed on one side and “255” on the other side. Each bottle contains 30 tablets (NDC 61958-2101-1), a silica gel desiccant, and a polyester coil, and is closed with a child-resistant closure.

Store below 30 °C (86 °F).

- Keep container tightly closed.
- Dispense only in original container.

17 PATIENT COUNSELING INFORMATION

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

Lactic Acidosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to ODEFSEY. Advise patients to stop taking ODEFSEY if they develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.1)]*.

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 ODEFSEY *[see Warnings and Precautions (5.2)]*. Advise the patient to not discontinue ODEFSEY without first informing their healthcare provider.

Severe Skin Reactions and Hypersensitivity

Inform patients that skin reactions ranging from mild to severe, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), have been reported with RPV-containing products. Instruct patients to immediately stop taking ODEFSEY and seek medical attention if they develop a rash associated with any of the following symptoms: fever, blisters, mucosal involvement, eye inflammation (conjunctivitis), severe allergic reaction causing swelling of the face, eyes, lips, mouth, tongue or throat which may lead to difficulty swallowing or breathing, and any signs and symptoms of liver problems, as they may be a sign of a more serious reaction. Patients should understand that if severe rash occurs, they will be closely monitored, laboratory tests will be performed and appropriate therapy will be initiated *[see Warnings and Precautions (5.3)].*

Drug Interactions

ODEFSEY may interact with many drugs and is not recommended to be coadministered with numerous drugs. Advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort *[see Contraindications (4), Warnings and Precautions (5.4) and Drug Interactions (7)]*.

Depressive Disorders

Inform patients that depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) have been reported with RPV. Inform patients to seek immediate medical evaluation if they experience depressive symptoms *[see Warnings and Precautions (5.6)].*

Hepatotoxicity

Inform patients that hepatotoxicity has been reported with RPV, therefore, it is important to inform the healthcare professional if patients have underlying hepatitis B or C or elevations in liver-associated tests prior to treatment *[see Dosage and Administration (2.1) and Warnings and Precautions (5.7)]*.

Fat Redistribution

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known *[see Warnings and Precautions (5.8)].*

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 (5.9)].*

New Onset or Worsening Renal Impairment

Advise patients to avoid taking ODEFSEY with concurrent or recent use of nephrotoxic agents. Renal impairment, including cases of acute renal failure, has been reported in association with the use of tenofovir prodrugs *[see Warnings and Precautions (5.10)].*

Decrease in Bone Mineral Density

Advise patients that decreases in bone mineral density have been observed with the use of drugs similar to ODEFSEY. Consider assessment of bone mineral density (BMD) in patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss *[see Warnings and Precautions (5.11)].*

Missed Dosage

Inform patients that it is important to take ODEFSEY on a regular dosing schedule with a meal and to avoid missing doses, as it can result in development of resistance [*see Dosage and Administration (2.2)]*.

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to ODEFSEY *[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
ODEFSEY® (oh-DEF-see)
(emtricitabine, rilpivirine and tenofovir alafenamide) tablets

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

Read this Patient Information before you start taking ODEFSEY and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

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

ODEFSEY can cause serious side effects, including:

- **Build-up of lactic acid in your blood (lactic acidosis).** Lactic acidosis may happen in some people who take ODEFSEY or similar medicines (nucleoside analogs). Lactic acidosis is a serious medical emergency that can lead to death.

  Lactic acidosis can be hard to identify early, because the symptoms could seem like symptoms of other health problems. **Call your healthcare provider right away if you get any of the following symptoms which could be signs of lactic acidosis:**

  - feel very weak or tired
  - have unusual (not normal) muscle pain
  - have trouble breathing
  - have stomach pain with nausea or vomiting
  - feel cold, especially in your arms and legs
  - feel dizzy or lightheaded
  - have a fast or irregular heartbeat

- **Severe liver problems**. Severe liver problems may happen in people who take ODEFSEY. In some cases, these liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis).

  Call your healthcare provider right away if you get any of the following symptoms of liver problems:

  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark "tea-colored" urine
  - loss of appetite
  - light-colored bowel movements (stools)
  - nausea
  - pain, aching, or tenderness on the right side of your stomach area

  You may be more likely to get lactic acidosis or severe liver problems if you are female, very overweight (obese), or have been taking ODEFESY or a similar medicine containing nucleoside analog for a long time.

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

For more information about side effects, see the section **"What are the possible side effects of ODEFSEY?"**

What is ODEFSEY?

ODEFSEY is a prescription medicine that is used to treat Human Immunodeficiency Virus-1 (HIV-1) in people 12 years of age and older:

- who have not received anti-HIV-1 medicines in the past and who have an amount of HIV-1 in their blood (this is called "viral load") that is no more than 100,000 copies/mL, **or**
- to replace their current anti-HIV-1 medicines:
  - in people who have been on the same anti-HIV-1 medicine regimen for at least 6 months, **and**
  - who have an amount of HIV-1 in their blood that is less than 50 copies/mL, **and**
  - have never failed past HIV-1 treatment.

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

ODEFSEY contains the prescription medicines emtricitabine, rilpivirine and tenofovir alafenamide.

It is not known if ODEFSEY is safe and effective in children under 12 years of age or who weigh less than 77 lb (35 kg).

ODEFSEY may help:

- Reduce the amount of HIV-1 in your blood. This is called "viral load".
- Increase the number of CD4+ (T) cells in your blood that help fight off other infections.

Reducing the amount of HIV-1 and increasing the CD4+ (T) cells in your blood may help improve your immune system. This may reduce your risk of death or getting infections that can happen when your immune system is weak (opportunistic infections).

ODEFSEY does not cure HIV-1 infections or AIDS. You must keep taking HIV-1 medicines to control HIV-1 infection and decrease HIV-related illnesses.

Avoid doing things that can spread HIV-1 infection to others.

- Do not share or re-use needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
- Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Ask your healthcare provider if you have any questions about how to prevent passing HIV-1 to other people.

Who should not take ODEFSEY?

- **Do not take ODEFSEY if you also take a medicine that contains:**
- carbamazepine (CARBATROL®, EPITOL®, EQUETRO®, TEGRETOL®, TEGRETOL-XR®, TERIL®)
- dexamethasone (OZURDEX®, MAXIDEX®, DECADRON®, BAYCADRON™)
- dexlansoprazole (DEXILANT®)
- esomeprazole (NEXIUM®, VIMOVO®)
- lansoprazole (PREVACID®)
- omeprazole (PRILOSEC®, ZEGERID®)
- oxcarbazepine (TRILEPTAL®)
- pantoprazole sodium (PROTONIX®)
- phenobarbital (LUMINAL®)
- phenytoin (DILANTIN®, DILANTIN-125®, PHENYTEK®)
- rabeprazole (ACIPHEX®)
- rifampin (RIFADIN®, RIFAMATE®, RIFATER®, RIMACTANE®)
- rifapentine (PRIFTIN®)
- St. John's wort (*Hypericum perforatum*) or a product that contains St. John's wort

What should I tell my healthcare provider before taking ODEFSEY?

Before taking ODEFSEY, tell your healthcare provider if you:

- have liver problems, including hepatitis B or C virus infection
- have kidney problems
- have a history of depression or suicidal thoughts
- have bone problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if ODEFSEY can harm your unborn baby. Tell your healthcare provider if you become pregnant while taking ODEFSEY.

  Pregnancy Registry: There is a pregnancy registry for women who take antiviral medicines 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 ODEFSEY.
  - 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 ODEFSEY can pass to your baby in your breast milk. It is not known if the other medicines in ODEFSEY 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, vitamins, and herbal supplements.

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

How should I take ODEFSEY?

- Take ODEFSEY exactly as your healthcare provider tells you to take it. ODEFSEY is taken by itself (not with other HIV-1 medicines) to treat HIV-1 infection.
- Take ODEFSEY 1 time each day with a meal.
- Do not change your dose or stop taking ODEFSEY without first talking with your healthcare provider. Stay under a healthcare provider's care when taking ODEFSEY.
- Do not miss a dose of ODEFSEY.
- If you take too much ODEFSEY, call your healthcare provider or go to the nearest hospital emergency room right away.
- When your ODEFSEY 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 ODEFSEY and become harder to treat.

What are the possible side effects of ODEFSEY?

ODEFSEY may cause serious side effects, including:

- **See "What is the most important information I should know about ODEFSEY?"**
- **Severe skin rash and allergic reactions.** Skin rash is a common side effect of ODEFSEY. Rash can be serious. Call your healthcare provider right away if you get a rash. In some cases, rash and allergic reaction may need to be treated in a hospital.

  If you get a rash with any of the following symptoms, stop taking ODEFSEY and call your healthcare provider or get medical help right away:
  - fever
  - skin blisters
  - mouth sores
  - swelling of the face, lips, mouth, or throat
  - trouble breathing or swallowing
  - pain on the right side of the stomach

(abdominal) area
- redness or swelling of the eyes (conjunctivitis)
- dark “tea colored” urine

- **Depression or mood changes. Tell your healthcare provider right away if you have any of the following symptoms:**
  - feel sad or hopeless
  - feel anxious or restless
  - have thoughts of hurting yourself (suicide) or have tried to hurt yourself
- **Change in liver enzymes.** People with a history of hepatitis B or C virus infection or who have certain liver enzyme changes may have an increased risk of developing new or worsening liver problems during treatment with ODEFSEY. Liver problems can also happen during treatment with ODEFSEY in people without a history of liver disease. Your healthcare provider may need to do tests to check your liver enzymes before and during treatment with ODEFSEY.
- **Changes in body fat** can happen in people who take HIV-1 medicine. These changes may include increased amount of fat in the upper back and neck (“buffalo hump”), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms and face may also happen. The exact cause and long-term health effects of these conditions are not known.
- **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 before you start and while you are taking ODEFSEY. Your healthcare provider may tell you to stop taking ODEFSEY if you develop new or worse kidney problems.
- **Bone problems** can happen in some people who take ODEFSEY. Bone problems may include bone pain, softening or thinning (which may lead to fractures). Your healthcare provider may need to do tests to check your bones.

The most common side effects of **rilpivirine**, one of the medicines in ODEFSEY, include depression, trouble sleeping (insomnia), and headache.

The most common side effect of **emtricitabine and tenofovir alafenamide**, two of the medicines in ODEFSEY, is nausea.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ODEFSEY. For more information, ask your healthcare provider or pharmacist.

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 ODEFSEY?

- Store ODEFSEY below 86 °F (30 °C).
- Keep ODEFSEY in its original container.
- Keep the container tightly closed.

Keep ODEFSEY and all medicines out of reach of children.

General information about the safe and effective use of ODEFSEY.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ODEFSEY for a condition for which it was not prescribed. Do not give ODEFSEY 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 ODEFSEY that is written for health professionals.

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

What are the ingredients in ODEFSEY?

Active ingredients: emtricitabine, rilpivirine, and tenofovir alafenamide.

Inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate 20, and povidone. The tablet film coating contains iron oxide black, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

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

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This Patient Information has been approved by the U.S. Food and Drug Administration
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