HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DUTREBIS safely and effectively. See full prescribing information for DUTREBIS.

DUTREBIS™ (lamivudine and raltegravir) tablets, for oral use
Initial U.S. Approval: 2015

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY AND POST-TREATMENT EXACERBATIONS OF HEPATITIS B IN CO-INFECTED PATIENTS

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 reverse transcriptase inhibitors (NRTIs). Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.1)

• Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)

----------INDICATIONS AND USAGE----------

DUTREBIS is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection (1).

---------- DOSAGE AND ADMINISTRATION----------

Adults, adolescents (16 years of age and older), and pediatric patients (6 through 16 years of age and weighing at least 30 kg):

- 150 mg lamivudine/300 mg raltegravir tablet orally, twice daily with or without food (2.1).

---------- DOSAGE FORMS AND STRENGTHS ----------

- Tablets: 150 mg lamivudine and 325.8 mg raltegravir potassium, equivalent to 300 mg raltegravir (3).

----------CONTRAINDICATIONS----------

DUTREBIS is contraindicated in patients with hypersensitivity to lamivudine, raltegravir, or any component of this medicine (4).

---------- WARNINGS AND PRECAUTIONS----------

- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate (5.3).
- Severe, potentially life-threatening and fatal skin reactions have been reported, including Stevens-Johnson syndrome, hypersensitivity reaction and toxic epidermal necrolysis. Discontinue treatment with DUTREBIS if signs and symptoms of severe skin reactions or severe hypersensitivity occur (5.5).
- Monitor for Immune Reconstitution Syndrome (5.6).

---------- ADVERSE REACTIONS ----------

- *Lamivudine:* The most common reported adverse reactions (incidence ≥15%) in adults were headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough. The most common reported adverse reactions (incidence ≥15%) in pediatric patients were fever and cough (6.1).
- *Raltegravir:* The most common adverse reactions of moderate to severe intensity (≥2%) are insomnia, headache, dizziness, nausea and fatigue (6.1).
- Creatine kinase elevations were observed in subjects who received raltegravir. Myopathy and rhabdomyolysis have been reported (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

- Coadministration of DUTREBIS and other drugs may alter the plasma concentration of lamivudine and raltegravir. The potential for drug-drug interactions must be considered prior to and during therapy (7).

----------USE IN SPECIFIC POPULATIONS----------

Patients With Renal Impairment:

- DUTREBIS should not be given in patients with a creatinine clearance of <50 mL/min (8.7).

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

Revised: 2/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY AND POST-TREATMENT EXACERBATIONS OF HEPATITIS B IN CO-INFECTED PATIENTS.

Lactic Acidosis and Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside reverse transcriptase inhibitors (NRTIs) alone or in combination, including lamivudine and other antiretrovirals. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur *[see Warnings and Precautions (5.1)]*.

Exacerbations of Hepatitis B

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, a component of DUTREBIS. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue DUTREBIS and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.2)].*

1 INDICATIONS AND USAGE

DUTREBIS™ is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

DUTREBIS is a fixed-dose combination product containing 150 mg of lamivudine and 300 mg of raltegravir. The recommended dosage of DUTREBIS in adults, adolescents (16 years of age and older), and pediatric patients (6 through 16 years of age and weighing at least 30 kg) is one tablet taken twice daily orally with or without food.

Administer DUTREBIS in conjunction with other antiretroviral agents. The maximum dose of DUTREBIS is one tablet (150 mg lamivudine/300 mg raltegravir) taken twice daily.

2.2 Patients with Renal Impairment

DUTREBIS is not recommended in patients with a creatinine clearance of <50 mL/min. If creatinine clearance decreases to <50 mL/min, DUTREBIS should be switched to the individual components (lamivudine and raltegravir) to allow for lamivudine dose reduction. Please refer to the full prescribing information for lamivudine and raltegravir for dosing instructions.

3 DOSAGE FORMS AND STRENGTHS

- Tablets

  150 mg lamivudine and 325.8 mg raltegravir potassium, equivalent to 300 mg raltegravir, green, oval-shaped, film-coated tablets with "144" on one side.

4 CONTRAINDICATIONS

DUTREBIS is contraindicated in patients with hypersensitivity to lamivudine, raltegravir, or any component of this medicine.

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 NRTIs alone or in combination, including lamivudine and 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 DUTREBIS to any patient with known risk factors for liver disease; however, cases also have been reported in patients with no known risk factors. Treatment with DUTREBIS should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

5.2 Post-treatment Exacerbations of Hepatitis in Patients With HIV-1 and Hepatitis B Virus Co-infection

In clinical trials in non-HIV-1-infected patients treated with lamivudine for chronic hepatitis B, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from postmarketing experience after changes from lamivudine-containing HIV-1 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of post-treatment exacerbations of hepatitis. Safety and efficacy of DUTREBIS have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV.

5.3 Pancreatitis

In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, DUTREBIS should be used with caution. Treatment with DUTREBIS should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur.

5.4 Hepatic Decompensation When Used With Interferon- and Ribavirin-Based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine NRTIs such as lamivudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients *[see Clinical Pharmacology (12.3)]*, hepatic decompensation (some fatal) has occurred in HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and DUTREBIS should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of DUTREBIS should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh >6). See the complete prescribing information for interferon and ribavirin.

5.5 Severe Skin and Hypersensitivity Reactions

Severe, potentially life-threatening, and fatal skin reactions have been reported in patients taking raltegravir. These include cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. Hypersensitivity reactions have also been reported and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure. Discontinue DUTREBIS and other suspect agents immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping DUTREBIS treatment or other suspect agents after the onset of severe rash may result in a life-threatening reaction.

5.6 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including the components of DUTREBIS. During the initial phase of combination antiretroviral

treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia [PCP], 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.

5.7 Fat Redistribution

Redistribution/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.

5.8 Antiretrovirals Not Recommended

DUTREBIS is not recommended in combination with products containing the individual components of DUTREBIS (lamivudine and raltegravir) or emtricitabine.

6 ADVERSE REACTIONS

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

- Lactic acidosis and severe hepatomegaly with steatosis *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Severe acute exacerbations of hepatitis B *[see Boxed Warning, Warnings and Precautions (5.2)]*.
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C *[see Warnings and Precautions (5.4)]*.
- Pancreatitis *[see Warnings and Precautions (5.3)]*.

6.1 Clinical Trials Experience

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

Clinical trials in patients have not been specifically performed with DUTREBIS. Common adverse reactions to each individual component (lamivudine and raltegravir) are summarized below.

Adult Subjects

Lamivudine

See the lamivudine full prescribing information for complete clinical trial information.

In four controlled clinical trials with lamivudine coadministered with zidovudine in adults, the most common reported adverse reactions (incidence greater than or equal to 15%, all grades) were headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough.

Raltegravir

See the raltegravir full prescribing information for complete clinical trial information.

In Phase 3 clinical trials with raltegravir in treatment-naïve or treatment-experienced adults, the most common reported adverse reactions (incidence greater than or equal to 2%) of at least moderate intensity (greater than or equal to Grade 2) were insomnia, headache, dizziness, nausea, and fatigue.

Creatine kinase elevations were observed in subjects who received raltegravir. Myopathy and rhabdomyolysis have been reported. Monitor patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions and patients with a history of rhabdomyolysis, myopathy or increased serum creatine kinase.

Pediatric Subjects

Lamivudine

See the lamivudine full prescribing information for complete clinical trial information.

In controlled clinical trials with lamivudine oral solution coadministered with zidovudine in pediatric subjects 3 months to 18 years of age, the most common reported adverse reactions (incidence greater than or equal to 15%, all grades) were fever and cough.

Raltegravir

See the raltegravir full prescribing information for complete clinical trial information.

Raltegravir has been studied in 126 antiretroviral treatment-experienced HIV-1 infected children and adolescents 2 to 18 years of age, in combination with other antiretroviral agents in IMPAACT P1066 *[see Use in Specific Populations (8.4)]*. Of the 126 patients, 96 received the recommended dose of raltegravir.

In these 96 children and adolescents, frequency, type and severity of drug-related adverse reactions through Week 24 were comparable to those observed in adults.

6.2 Postmarketing Experience

See the full prescribing information for lamivudine and raltegravir for postmarketing information.

7 DRUG INTERACTIONS

7.1 Effect of Lamivudine and Raltegravir on the Pharmacokinetics of Concomitant Drugs

DUTREBIS

DUTREBIS is not expected to affect the pharmacokinetics of drugs that are substrates of the cytochrome P450 (CYP) enzymes, UGT1A1 or UGT2B7, or P-glycoprotein (e.g., protease inhibitors, NNRTIs, opioid analgesics, statins, azole antifungals, proton pump inhibitors and anti-erectile dysfunction agents).

Raltegravir

Raltegravir does not inhibit (IC_{50}>100 µM) CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A *in vitro*. Moreover, *in vitro*, raltegravir did not induce CYP1A2, CYP2B6 or CYP3A4. A midazolam drug interaction study confirmed the low propensity of raltegravir to alter the pharmacokinetics of agents metabolized by CYP3A4 *in vivo* by demonstrating a lack of effect of raltegravir on the pharmacokinetics of midazolam, a sensitive CYP3A4 substrate. Similarly, raltegravir is not an inhibitor (IC_{50}>50 µM) of UGT1A1 or UGT2B7, and raltegravir does not inhibit P-glycoprotein-mediated transport.

7.2 Effect of Concomitant Drugs on the Pharmacokinetics of Lamivudine and Raltegravir

Lamivudine

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim). No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

Raltegravir

Raltegravir is not a substrate of CYP enzymes. Based on *in vivo* and *in vitro* studies, raltegravir is eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway. Coadministration of DUTREBIS with drugs that inhibit UGT1A1 may increase plasma levels of raltegravir and coadministration of DUTREBIS with drugs that induce UGT1A1 may reduce plasma levels of raltegravir.

7.3 Established and Other Potentially Significant Interactions

Lamivudine

Interferon- and Ribavirin-Based Regimens

Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin *[see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)].*

Trimethoprim/Sulfamethoxazole (TMP/SMX)

No change in dose of either drug is recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat PCP.

Raltegravir

The impact of inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown.

Selected drug interactions are presented in Table 1 *[see Clinical Pharmacology (12.3)]*.

The results of the drug interaction studies represented in the following table were conducted with raltegravir; however, the recommendations are applicable to DUTREBIS as raltegravir is a component of DUTREBIS.

Table 1: Selected Drug Interactions in Adults Receiving Raltegravir

Concomitant Drug Class: Drug Name	Effect on Concentration of Raltegravir	Clinical Comment
HIV-1-Antiviral Agents		
Metal-Containing Antacids		
aluminum and/or magnesium-containing antacids	↓	Coadministration or staggered administration of aluminum and/or magnesium hydroxide-containing antacids and DUTREBIS is not recommended.
Other Agents		
rifampin	↓	DUTREBIS should not be coadministered with rifampin. If coadministration with rifampin is unavoidable, DUTREBIS may be switched to a regimen of the individual components (lamivudine and raltegravir). Please refer to the full prescribing information for the individual components of DUTREBIS for dosing instructions.

7.4 Drugs without Clinically Significant Interactions with Lamivudine and Raltegravir

DUTREBIS

In a drug interaction study with DUTREBIS and etravirine, there was no clinically meaningful change in raltegravir exposures. No dosage adjustment is necessary when these agents are given together.

Lamivudine

A drug interaction study showed no clinically significant interaction between lamivudine and zidovudine.

Raltegravir

In drug interaction studies, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of the following: hormonal contraceptives, methadone, lamivudine, tenofovir, etravirine, darunavir/ritonavir, telaprevir, or boceprevir. Moreover, atazanavir, atazanavir/ritonavir, boceprevir, calcium carbonate antacids, darunavir/ritonavir, efavirenz, etravirine, omeprazole, or tipranavir/ritonavir did not have a clinically meaningful effect on the pharmacokinetics of raltegravir. No dose adjustment is required when DUTREBIS is coadministered with these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant patients exposed to DUTREBIS, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Risk Summary

There are no adequate and well-controlled studies with DUTREBIS, lamivudine, or raltegravir in pregnant women. Lamivudine caused increased early embryolethality in rabbits at exposure levels similar to those in humans. Raltegravir induced treatment-related increases in the incidence of supernumerary ribs in rats at 3-fold the exposure at the recommended human dose. DUTREBIS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples, while amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels *[see Clinical Pharmacology (12.3)]*. It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared with other HIV-1-infected patients. There have been no pharmacokinetic studies conducted with raltegravir in pregnant patients.

Animal Data

Lamivudine

Lamivudine is not teratogenic at oral doses up to 4000 mg/kg/day (130 times human exposures) in rats and 1000 mg/kg/day (60 times human exposures) in rabbits. Evidence of increased early embryolethality was seen in rabbits at exposure levels similar to those in humans but there was no indication of this effect in rats at exposure levels up to 35 times those in humans. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

Raltegravir

Developmental toxicity studies were performed in rabbits (at oral doses up to 1000 mg/kg/day) and rats (at oral doses up to 600 mg/kg/day). The reproductive toxicity study in rats was performed with pre-, peri-, and postnatal evaluation. The highest doses in these studies produced systemic exposures in these species approximately 3- to 4-fold the exposure at the recommended human dose. In both rabbits and rats, no treatment-related effects on embryonic/fetal survival or fetal weights were observed. In addition, no treatment-related external, visceral, or skeletal changes were observed in rabbits. However, treatment-related increases over controls in the incidence of supernumerary ribs were seen in rats at 600 mg/kg/day (exposures 3-fold the exposure at the recommended human dose).

Placenta transfer of drug was demonstrated in both rats and rabbits. At a maternal dose of 600 mg/kg/day in rats, mean drug concentrations in fetal plasma were approximately 1.5- to 2.5-fold greater than in maternal plasma at 1 hour and 24 hours postdose, respectively. Mean drug concentrations in fetal plasma were approximately 2% of the mean maternal concentration at both 1 and 24 hours postdose at a maternal dose of 1000 mg/kg/day in rabbits.

8.3 Nursing Mothers

DUTREBIS

Breastfeeding is not recommended while taking DUTREBIS. In addition, it is recommended that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1.

Lamivudine

Lamivudine is excreted into human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

Raltegravir

It is not known whether raltegravir is secreted in human milk. However, raltegravir is secreted in the milk of lactating rats. Mean drug concentrations in milk were approximately 3-fold greater than those in maternal plasma at a maternal dose of 600 mg/kg/day in rats. There were no effects in rat offspring attributable to exposure of raltegravir through the milk.

8.4 Pediatric Use

DUTREBIS

DUTREBIS is indicated in pediatric patients 6 through 16 years of age and weighing at least 30 kg *[see Indications and Usage (1) and Dosage and Administration (2.1)]*. DUTREBIS should not be used in children below 6 years of age or in patients weighing less than 30 kg due to weight based dosing requirements in this patient population.

8.5 Geriatric Use

Separate clinical trials of each component of DUTREBIS (lamivudine and raltegravir) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects. Because lamivudine is substantially excreted by the kidney and elderly patients are more likely to have decreased renal function, renal function should be monitored. A reduction in renal function may necessitate switching DUTREBIS to a regimen of lamivudine and raltegravir. Please refer to the full prescribing information for lamivudine and raltegravir for dosing instructions.

8.6 Use in Patients with Hepatic Impairment

No dose adjustment for DUTREBIS is required for patients with mild to moderate hepatic insufficiency.

Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

The effect of severe hepatic impairment on the pharmacokinetics of raltegravir has not been studied.

8.7 Use in Patients with Renal Impairment

DUTREBIS should not be given in patients with a creatinine clearance of <50 mL/min *[see Dosage and Administration (2.2)]*.

10 OVERDOSAGE

DUTREBIS

In the event of an overdose, it is reasonable to employ the standard supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required. The extent to which DUTREBIS may be dialyzable is unknown.

Lamivudine

Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

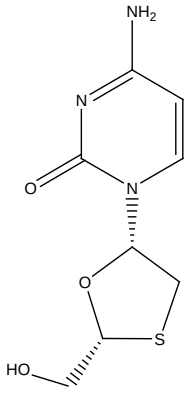
11 DESCRIPTION

DUTREBIS

DUTREBIS is available for oral use as a film-coated tablet containing 150 mg of lamivudine and 325.8 mg of raltegravir potassium, equivalent to 300 mg of raltegravir and the inactive ingredients: croscarmellose sodium, hypromellose (2910), lactose monohydrate, magnesium stearate, microcrystalline cellulose, and silicon dioxide [colloidal]. The film-coating contains: FD&C Blue #2, hypromellose, lactose monohydrate, titanium dioxide, triacetin, and yellow iron oxide.

Lamivudine

Lamivudine is an HIV-1 nucleoside analogue reverse transcriptase inhibitor. The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3. It has the following structural formula:

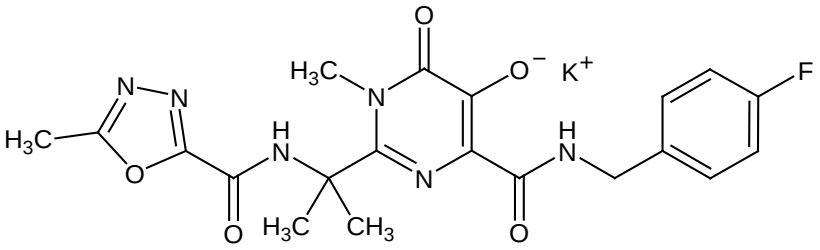


Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.

Raltegravir

Raltegravir potassium is a human immunodeficiency virus integrase strand transfer inhibitor. The chemical name for raltegravir potassium is *N*-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt.

The empirical formula is $C_{20}H_{20}FKN_6O_5$ and the molecular weight is 482.51. The structural formula is:



Raltegravir potassium is a white to off-white powder. It is soluble in water, slightly soluble in methanol, very slightly soluble in ethanol and acetonitrile and insoluble in isopropanol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

DUTREBIS is a fixed-dose combination of HIV-1 antiviral drugs lamivudine and raltegravir *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

DUTREBIS

No cardiac physiology studies were performed with DUTREBIS.

Raltegravir

The effect of raltegravir 1600 mg (4 times the recommended dose) on QTc interval was evaluated in a randomized, single-dose, placebo-controlled, crossover study in 31 healthy subjects. At a dose 4 times the recommended dose, raltegravir did not prolong the QTc interval to any clinically relevant extent.

Lamivudine

No cardiac physiology studies have been performed with lamivudine.

12.3 Pharmacokinetics

DUTREBIS

In an open-label, single-dose, randomized, two-period, crossover study in healthy subjects (n=108), one DUTREBIS (150 mg lamivudine/300 mg raltegravir) fixed-dose combination tablet was shown to provide comparable lamivudine and raltegravir exposures to one EPIVIR 150 mg tablet plus one ISENTRESS 400 mg tablet.

Due to the higher bioavailability of raltegravir contained in DUTREBIS, the exposures provided by the 300 mg dose of raltegravir are comparable to 400 mg of raltegravir given as the raltegravir poloxamer formulation (ISENTRESS), which accounts for the difference in raltegravir dose.

Please refer to the full prescribing information for raltegravir and lamivudine for additional pharmacokinetic information.

Adults

Absorption

DUTREBIS

When DUTREBIS is administered in the fasted state, raltegravir is absorbed with a T_{max} of approximately 1 hour. The bioavailability of the raltegravir component of DUTREBIS in the fasted state is approximately 60%. Once absorbed, lamivudine and raltegravir distribution, metabolism, and excretion are similar to those of the reference components administered individually as described in the full prescribing information for lamivudine and raltegravir.

Effect of Food on Oral Absorption

An open-label, single-dose, randomized, two-period crossover study assessed the effect of a high fat meal on DUTREBIS administered to 20 healthy male and female subjects. Similar AUC values for fed vs. fasted and somewhat lower C_{max} values (23% for raltegravir and 21% for lamivudine) were observed with DUTREBIS. In addition, higher C_{12h} levels (20% for raltegravir and 53% for lamivudine) were observed.

These changes are not considered clinically meaningful and DUTREBIS can be taken without regard to a meal.

Distribution

Lamivudine

Binding of lamivudine to human plasma proteins is low (<36%). *In vitro* studies showed that over the concentration range of 0.1 to 100 mcg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

Raltegravir

Raltegravir is approximately 83% bound to human plasma protein over the concentration range of 2 to 10 μM.

Metabolism and Excretion

Lamivudine

Metabolism of lamivudine is a minor route of elimination. Within 12 hours after a single oral dose of lamivudine in 6 HIV-1-infected adults, 5.2% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine.

Raltegravir

Studies using isoform-selective chemical inhibitors and cDNA-expressed UDP-glucuronosyltransferases (UGT) show that UGT1A1 is the main enzyme responsible for the formation of raltegravir-glucuronide, the major metabolite of raltegravir.

Elimination

Lamivudine

The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion.

In most single-dose trials in HIV-1-infected subjects, HBV-infected subjects, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{½}$) ranged from 5 to 7 hours.

Raltegravir

Following administration of an oral dose of radiolabeled raltegravir, approximately 51 and 32% of the dose was excreted in feces and urine, respectively. The major circulating entity was raltegravir and represented approximately 70% of the total radioactivity; the remaining radioactivity in plasma was accounted for by raltegravir-glucuronide,

The apparent terminal half-life of raltegravir is approximately 9 hours, with a shorter α-phase half-life (~1 hour) accounting for much of the AUC.

Specific Populations

Pediatric

DUTREBIS

The pharmacokinetics of DUTREBIS in the pediatric patient population has not been studied in clinical trials. DUTREBIS should not be used in children below 6 years of age or in patients weighing less than 30 kg due to weight-based dose adjustments in this patient population *[see Use in Specific Populations (8.4)]*.

Raltegravir

The raltegravir component in DUTREBIS (300 mg raltegravir) fixed-dose combination tablet was shown to provide comparable raltegravir exposures to ISENTRESS (400 mg raltegravir) tablet. Based on modeling and simulation using raltegravir pharmacokinetic data in adults, the pharmacokinetics of raltegravir in DUTREBIS in children was projected to result in exposures that have been previously shown to be safe and efficacious in adults.

Pregnancy

Lamivudine

Lamivudine pharmacokinetics were evaluated in 16 women at 36 weeks gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation using lamivudine 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and

in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, lamivudine amniotic fluid specimens were collected following natural rupture of membranes. Amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg/mL (150 mg twice daily) and 2.1 to 5.2 mcg/mL (300 mg twice daily).

Age, Race, Gender
No studies have been performed to evaluate the effect of age, race, or gender on the pharmacokinetics of DUTREBIS. Recommendations are based on available data from lamivudine and raltegravir. No dosage adjustment for DUTREBIS is required based on age, race, or gender.

Hepatic Impairment
DUTREBIS
No study has been performed with DUTREBIS in subjects with hepatic insufficiency. Recommendations are based on available data from lamivudine and raltegravir. No dosage adjustment for DUTREBIS is required for patients with mild to moderate hepatic insufficiency.
Lamivudine
Lamivudine pharmacokinetic parameters were not altered by diminishing hepatic function; therefore, no dose adjustment for lamivudine is required for patients with impaired hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.
Raltegravir
Raltegravir is eliminated primarily by glucuronidation in the liver. A study of the pharmacokinetics of raltegravir was performed in adult subjects with moderate hepatic impairment. Additionally, hepatic impairment was evaluated in the composite pharmacokinetic analysis in clinical studies of raltegravir. There were no clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and healthy subjects. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of raltegravir has not been studied.

Renal Impairment
DUTREBIS
No study has been performed with DUTREBIS in subjects with renal insufficiency. Recommendations are based on available data from the individual components. DUTREBIS should not be given in patients with a creatinine clearance of <50 mL/min. Renal function should be monitored in patients more likely to have decreased renal function. If creatinine clearance decreases to <50 mL/min, DUTREBIS should be switched to a regimen of lamivudine and raltegravir. Please refer to the full prescribing information for lamivudine and raltegravir for dosing instructions.
Lamivudine
The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-1-infected adults with impaired renal function.

Exposure (AUC_∞), C_{max}, and half-life increased with diminishing renal function (as expressed by creatinine clearance). Apparent total oral clearance (Cl/F) of lamivudine decreased as creatinine clearance decreased. T_{max} was not significantly affected by renal function. When administered as an individual component, the lamivudine dose should be adjusted for patients with creatinine clearance <50 mL/min. If creatinine clearance decreases to <50 mL/min, DUTREBIS should be switched to a regimen of lamivudine and raltegravir. Please refer to the full prescribing information for lamivudine and raltegravir for dosing instructions. *[See Dosage and Administration (2.2).]*
Raltegravir
Renal clearance of unchanged drug is a minor pathway of elimination. A study of the pharmacokinetics of raltegravir was performed in adult subjects with severe renal impairment. Additionally, renal impairment was evaluated in the composite pharmacokinetic analysis in clinical studies of raltegravir. There were no clinically important pharmacokinetic differences between subjects with severe renal impairment and healthy subjects. No dosage adjustment is necessary.

UGT1A1 Polymorphism
Raltegravir

There is no evidence that common UGT1A1 polymorphisms alter raltegravir pharmacokinetics to a clinically meaningful extent. In a comparison of 30 adult subjects with *28/*28 genotype (associated with reduced activity of UGT1A1) to 27 adult subjects with wild-type genotype, the geometric mean ratio (90% CI) of AUC was 1.41 (0.96, 2.09).

Drug Interactions *[see Drug Interactions (7)]*

DUTREBIS

One drug interaction study was conducted for DUTREBIS and etravirine. In addition, drug interaction studies were conducted with lamivudine or raltegravir coadministered with other commonly used drugs. The results of the drug interaction studies are summarized in Tables 2, 3 and 4. For information regarding clinical recommendations, see *Drug Interactions (7)*.

Table 2: Effect of Etravirine on the Pharmacokinetics of Lamivudine/Raltegravir in Adults

Coadministered Drug	**Coadministered Drug Dose/Schedule**	**Lamivudine/Raltegravir Dose/Schedule**	**Ratio (90% Confidence Interval) of Raltegravir Pharmacokinetic Parameters with/without Coadministered Drug; Prespecified bounds: 0.5, 2.0**	
			N	$C12_{hr}$
Etravirine	200 mg etravirine twice daily for 15 days (Period 2)	Lamivudine/raltegravir tablet (150 mg/300 mg) as a single dose on Day 1, Period 1, and on Day 14, Period 2	18	0.86 (0.63, 1.17) No dosage adjustment necessary

Lamivudine

Interferon Alfa

There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a trial of 19 healthy male subjects *[see Warnings and Precautions (5.4)]*.

Ribavirin

In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n=18), stavudine (n=10), or zidovudine (n=6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects *[see Warnings and Precautions (5.4)]*.

Trimethoprim/Sulfamethoxazole

Table 3: Effect of Trimethoprim/Sulfamethoxazole on the Pharmacokinetics of Lamivudine

Coadministered Drug and Dose	Drug and Dose	N	Concentrations of Lamivudine (% Change)			Concentration of coadministered drug
			AUC Mean (SD)	Oral CL Mean (SD)	Renal CL Mean (SD)	
Trimethoprim 160 mg/Sulfamethoxazole 800 mg daily x 5 days	Lamivudine Single 300 mg	14	Increase 43% (23%)	Decrease 29% (13%)	Decrease 30% (36%)	Not altered

Zidovudine

No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg q 12 hr) *[see Drug Interactions (7.4)]*.

Raltegravir

The results of the drug interaction studies represented in the following table were conducted with raltegravir.

Table 4: Effect of Other Agents on the Pharmacokinetics of Raltegravir in Adults

Coadministered Drug	Coadministered Drug Dose/Schedule	Raltegravir Dose/Schedule	Ratio (90% Confidence Interval) of Raltegravir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00			
			n	C_{max}	AUC	C_{min}
aluminum and magnesium hydroxide antacid	20 mL single dose given with raltegravir	400 mg twice daily	25	0.56 (0.42, 0.73)	0.51 (0.40, 0.65)	0.37 (0.29, 0.48)
	20 mL single dose given 2 hours before raltegravir		23	0.49 (0.33, 0.71)	0.49 (0.35, 0.67)	0.44 (0.34, 0.55)
	20 mL single dose given 2 hours after raltegravir		23	0.78 (0.53, 1.13)	0.70 (0.50, 0.96)	0.43 (0.34, 0.55)
atazanavir	400 mg daily	100 mg single dose	10	1.53 (1.11, 2.12)	1.72 (1.47, 2.02)	1.95 (1.30, 2.92)
atazanavir/ritonavir	300 mg/100 mg daily	400 mg twice daily	10	1.24 (0.87, 1.77)	1.41 (1.12, 1.78)	1.77 (1.39, 2.25)
boceprevir	800 mg three times daily	400 mg single dose	22	1.11 (0.91-1.36)	1.04 (0.88-1.22)	0.75 (0.45-1.23)
calcium carbonate antacid	3000 mg single dose given with raltegravir	400 mg twice daily	24	0.48 (0.36, 0.63)	0.45 (0.35, 0.57)	0.68 (0.53, 0.87)
efavirenz	600 mg daily	400 mg single dose	9	0.64 (0.41, 0.98)	0.64 (0.52, 0.80)	0.79 (0.49, 1.28)
etravirine	200 mg twice daily	400 mg twice daily	19	0.89 (0.68, 1.15)	0.90 (0.68, 1.18)	0.66 (0.34, 1.26)
omeprazole	20 mg daily	400 mg single dose	14 (10 for AUC)	4.15 (2.82, 6.10)	3.12 (2.13, 4.56)	1.46 (1.10, 1.93)
rifampin	600 mg daily	400 mg single dose	9	0.62 (0.37, 1.04)	0.60 (0.39, 0.91)	0.39 (0.30, 0.51)
rifampin	600 mg daily	400 mg twice daily when administered alone; 800 mg twice daily when administered with rifampin	14	1.62 (1.12, 2.33)	1.27 (0.94, 1.71)	0.47 (0.36, 0.61)
ritonavir	100 mg twice	400 mg single	10	0.76	0.84	0.99

Coadministered Drug	Coadministered Drug Dose/Schedule	Raltegravir Dose/Schedule	Ratio (90% Confidence Interval) of Raltegravir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00			
			n	C_{max}	AUC	C_{min}
	daily	dose		(0.55, 1.04)	(0.70, 1.01)	(0.70, 1.40)
tenofovir	300 mg daily	400 mg twice daily	9	1.64 (1.16, 2.32)	1.49 (1.15, 1.94)	1.03 (0.73, 1.45)
tipranavir/ritonavir	500 mg/200 mg twice daily	400 mg twice daily	15 (14 for C_{min})	0.82 (0.46, 1.46)	0.76 (0.49, 1.19)	0.45 (0.31, 0.66)

12.4 Microbiology

Mechanism of Action

Lamivudine

Lamivudine is an HIV-1 nucleoside analogue reverse transcriptase inhibitor (NRTI). Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is the inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue into viral DNA.

Raltegravir

Raltegravir inhibits the strand transfer activity of HIV-1 integrase (integrase strand transfer inhibitor; INSTI), an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the covalent insertion, or integration, of unintegrated linear HIV-1 DNA into the host cell genome preventing the formation of the HIV-1 provirus. The provirus is required to direct the production of progeny virus, so inhibiting integration prevents propagation of the viral infection.

Antiviral Activity in Cell Culture

Lamivudine

The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC_{50} values (50% effective concentrations) were in the range of 0.003 to 15 µM (1 µM=0.23 mcg/mL). HIV-1 from therapy-naïve subjects with no amino acid substitutions associated with resistance gave median EC_{50} values of 0.429 µM (range: 0.200 to 2.007 µM) from Virco (n=92 baseline samples from COLA40263) and 2.35 µM (1.37 to 3.68 µM) from Monogram Biosciences (n=135 baseline samples from ESS30009). The EC_{50} values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 µM, and against HIV-2 isolates from 0.003 to 0.120 µM in peripheral blood mononuclear cells. Ribavirin (50 µM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells. In HIV-1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity.

Raltegravir

Raltegravir at concentrations of 31 $\pm$ 20 nM resulted in 95% inhibition (EC_{95}) of viral spread (relative to an untreated virus-infected culture) in human T-lymphoid cell cultures infected with the cell-line adapted HIV-1 variant H9IIIB. In addition, 5 clinical isolates of HIV-1 subtype B had EC_{95} values ranging from 9 to 19 nM in cultures of mitogen-activated human peripheral blood mononuclear cells. In a single-cycle infection assay, raltegravir inhibited infection of 23 HIV-1 isolates representing 5 non-B subtypes (A, C, D, F, and G) and 5 circulating recombinant forms (AE, AG, BF, BG, and cpx) with EC_{50} values ranging from 5 to 12 nM. Raltegravir also inhibited replication of an HIV-2 isolate when tested in CEMx174 cells (EC_{95} value=6 nM). Additive to synergistic antiretroviral activity was observed when human T-lymphoid cells infected with the H9IIIB variant of HIV-1 were incubated with raltegravir in combination with non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, or nevirapine); nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, tenofovir, or zidovudine); protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir); or the entry inhibitor enfuvirtide.

Resistance

Lamivudine

Lamivudine-resistant variants of HIV-1 have been selected in cell culture and in subjects treated with lamivudine. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in

the HIV-1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine (M184V/I).

Raltegravir

The mutations observed in the HIV-1 integrase coding sequence that contributed to raltegravir resistance (evolved either in cell culture or in subjects treated with raltegravir) generally included an amino acid substitution at either Y143 (changed to C, H, or R) or Q148 (changed to H, K, or R) or N155 (changed to H) plus one or more additional substitutions (i.e., L74M, E92Q, Q95K/R, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230R, and D232N). E92Q and F121C are occasionally seen in the absence of substitutions at Y143, Q148, or N155 in raltegravir-treatment failure subjects.

Cross Resistance

Lamivudine

Cross-resistance has been observed among NRTIs. The M184I/V lamivudine resistance substitution confers resistance to emtricitabine. Lamivudine-resistant HIV-1 mutants were also cross-resistant to didanosine (ddI). In some subjects treated with zidovudine plus didanosine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Raltegravir

Cross-resistance has been observed among INSTIs. Amino acid substitutions in HIV-1 integrase conferring resistance to raltegravir generally also confer resistance to elvitegravir. Substitutions at amino acid Y143 confer greater reductions in susceptibility to raltegravir than to elvitegravir, and the E92Q substitution confers greater reductions in susceptibility to elvitegravir than to raltegravir. Viruses harboring a substitution at amino acid Q148, along with one or more other raltegravir resistance substitutions, may also have clinically significant resistance to dolutegravir.

13 NONCLINICAL TOXICOLOGY

No animal studies have been conducted with DUTREBIS. The following data are based on findings in separate studies with the individual components of DUTREBIS (lamivudine and raltegravir).

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lamivudine

Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV-1 infection. Lamivudine was not active in a microbial mutagenicity screen or an *in vitro* cell transformation assay, but showed weak *in vitro* mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2,000 mg/kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection. In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

Raltegravir

Carcinogenicity studies of raltegravir in mice did not show any carcinogenic potential. At the highest dose levels, 400 mg/kg/day in females and 250 mg/kg/day in males, systemic exposure was 1.8-fold (females) or 1.2-fold (males) greater than the AUC (54 μM●hr) at the 400-mg twice daily human dose. Treatment-related squamous cell carcinoma of nose/nasopharynx was observed in female rats dosed with 600 mg/kg/day raltegravir for 104 weeks. These tumors were possibly the result of local irritation and inflammation due to local deposition and/or aspiration of drug in the mucosa of the nose/nasopharynx during dosing. No tumors of the nose/nasopharynx were observed in rats dosed with 150 mg/kg/day (males) and 50 mg/kg/day (females) and the systemic exposure in rats was 1.7-fold (males) to 1.4-fold (females) greater than the AUC (54 μM●hr) at the 400-mg twice daily human dose.

No evidence of mutagenicity or genotoxicity was observed in *in vitro* microbial mutagenesis (Ames) tests, *in vitro* alkaline elution assays for DNA breakage, and *in vitro* and *in vivo* chromosomal aberration studies.

No effect on fertility was seen in male and female rats at doses up to 600 mg/kg/day which resulted in a 3-fold exposure above the exposure at the recommended human dose.

14 CLINICAL STUDIES

Clinical trials have not been specifically performed with DUTREBIS. The indication of DUTREBIS is based on efficacy and safety data demonstrated in clinical trials with lamivudine *[see lamivudine full prescribing information]* and with raltegravir *[see raltegravir full prescribing information].*

16 HOW SUPPLIED/STORAGE AND HANDLING

DUTREBIS tablets (150 mg lamivudine/300 mg raltegravir) are green, oval-shaped, film-coated tablets with "144" on one side. They are supplied as follows:

NDC 0006-3054-60 unit-of-use bottles of 60.

No. 3054

Storage and Handling

150 mg lamivudine/300 mg raltegravir tablets

Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). See USP Controlled Room Temperature.

Store in the original package with the bottle tightly closed. Keep the desiccant in the bottle to protect from moisture.

17 PATIENT COUNSELING INFORMATION

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

General Information

Instruct patients to reread patient labeling each time the prescription is renewed.

Inform patients they should remain under the care of a physician when using DUTREBIS. Instruct patients to inform their physician or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

Inform patients that DUTREBIS is not a cure for HIV-1 infection and they may continue to experience illnesses associated with HIV-1 infection such as opportunistic infections. Inform patients that sustained decreases in plasma HIV RNA are associated with a reduced risk of progression to AIDS and death. Instruct patients to remain on continuous HIV therapy to control HIV infection and decrease HIV-related illnesses.

Advise patients to avoid doing things that can spread HIV-1 infection to others.

- Do not share 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 safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- Do not breastfeed. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk. Lamivudine is excreted in human breast milk; however it is unknown if raltegravir can be passed to the baby through breast milk and whether it could harm the baby.

General Dosing Instructions

Advise patients not to miss a dose of DUTREBIS. Instruct patients that if they miss a dose of DUTREBIS, they should take it as soon as they remember. If they do not remember until it is time for the next dose, instruct them to skip the missed dose and go back to the regular schedule. Instruct patients not to double the next dose or take more than the prescribed dose.

Severe and Potentially Life-threatening Rash

Inform patients that severe and potentially life-threatening rash has been reported. Advise patients to immediately contact their healthcare provider if they develop rash. Instruct patients to immediately stop taking DUTREBIS and other suspect agents, and seek medical attention if they develop a rash associated with any of the following symptoms as it may be a sign of a more serious reaction such as Stevens-Johnson syndrome, toxic epidermal necrolysis or severe hypersensitivity: fever, generally ill feeling, extreme tiredness, muscle or joint aches, blisters, oral lesions, eye inflammation, facial swelling, swelling

of the eyes, lips, mouth, breathing difficulty, and/or signs and symptoms of liver problems. Tell patients that if severe rash occurs, they will be closely monitored, laboratory tests will be ordered and appropriate therapy will be initiated.

Lactic Acidosis/Hepatomegaly

Inform patients that some HIV medicines, including DUTREBIS, can cause a rare, but serious condition called lactic acidosis with liver enlargement and inform patients of the signs and symptoms of lactic acidosis *[see Warnings and Precautions (5.1)]*.

Rhabdomyolysis

Instruct patients to immediately report to their healthcare provider any unexplained muscle pain, tenderness, or weakness while taking DUTREBIS.

Drug Interactions

Instruct patients not to take DUTREBIS with aluminum and/or magnesium containing antacids *[see Drug Interactions (7.3)]*.

HIV-1/HBV Co-infection

Inform patients co-infected with HIV-1 and HBV that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Advise patients to discuss any changes in regimen with their physician *[see Warnings and Precautions (5.2)]*.

Risk of Pancreatitis

Advise parents or guardians to monitor pediatric patients for signs and symptoms of pancreatitis *[see Warnings and Precautions (5.3)]*.

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Patient Information
DUTREBIS™ (DOO-tre-bis)
(lamivudine and raltegravir)
tablets

Read this Patient Information before you start taking DUTREBIS 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 DUTREBIS?

• **Build-up of acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take DUTREBIS or similar medicines (nucleoside analogues). 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 the following symptoms that 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 and 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 can happen in people who take DUTREBIS. In some cases, these severe 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 have any of the following signs or symptoms of liver problems**:

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

You may be more likely to get lactic acidosis or serious liver problems if you are female, very overweight (obese), or have been taking nucleoside analogue medicines for a long time.

• **Worsening of hepatitis B infection.** If you have both HIV-1 and hepatitis B (HBV) virus infections, your HBV may get worse (flare-up) if you stop taking DUTREBIS. A “flare-up” is when your HBV infection suddenly returns in a worse way than before.

• Do not run out of DUTREBIS. Refill your prescription or talk to your healthcare provider before your DUTREBIS is all gone.
• Do not stop DUTREBIS without first talking to your healthcare provider.
• If you stop taking DUTREBIS, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your HBV infection.

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

What is DUTREBIS?
DUTREBIS is a prescription HIV-1 (Human Immunodeficiency Virus) medicine used with other antiretroviral medicines to treat people with HIV-1 infection. HIV-1 is the virus that causes AIDS (Acquired Immunodeficiency Syndrome).
DUTREBIS contains the prescription medicines EPIVIR (lamivudine) and ISENTRESS (raltegravir).

DUTREBIS should not be used in children under 6 years of age or in people who weigh less than 66 lbs (30 kg).

When used with other antiretroviral medicines to treat HIV-1 infection, DUTREBIS 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).

DUTREBIS does not cure HIV-1 infection 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 any body fluids such as semen, vaginal secretions, or blood.

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

Who should not take DUTREBIS?

Do not take DUTREBIS if you are allergic to lamivudine, raltegravir, or any of the ingredients in DUTREBIS. See the end of this leaflet for a complete list of ingredients in DUTREBIS.

What should I tell my healthcare provider before taking DUTREBIS?
Before you take DUTREBIS, tell your healthcare provider if you:

- have liver problems, including hepatitis B or C
- have pancreas problems
- have a history of a muscle disorder called rhabdomyolysis or myopathy
- have increased levels of creatine kinase in your blood
- are seriously overweight (especially if you are a woman) as you are more likely to develop a very serious condition called lactic acidosis (build-up of lactic acid in the body), which can be life-threatening
- have kidney problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if DUTREBIS can harm your unborn baby.

  Pregnancy Registry: There is a pregnancy registry for women who take antiretroviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take DUTREBIS.**
    - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
    - 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 interact with DUTREBIS. **Keep a list of your medicines to show your healthcare provider and pharmacist.**

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

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

How should I take DUTREBIS?

- **Take DUTREBIS exactly as your healthcare provider tells you.**
- **Take one tablet of DUTREBIS two times each day.**
- **You can take DUTREBIS with or without food.**
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose. Then go back to your regular schedule. Do not double your next dose or take more DUTREBIS than prescribed.
- If you take too much DUTREBIS, call your healthcare provider or go to the

nearest hospital emergency room right away.

What are the possible side effects of DUTREBIS?

DUTREBIS can cause serious side effects including:

- **Serious skin reactions and allergic reactions.** Some people who take DUTREBIS develop serious skin reactions and allergic reactions that can be severe, and may become life-threatening or lead to death. If you develop a rash with any of the following symptoms, stop using DUTREBIS and call your healthcare provider right away:

  - fever
  - generally not feeling well
  - extreme tiredness
  - muscle or joint aches
  - blisters or sores in mouth
  - blisters or peeling of the skin
  - redness or swelling of the eyes
  - swelling of the face, lips, mouth, or tongue
  - problems breathing

Sometimes allergic reactions can affect body organs, such as your liver. Call your healthcare provider right away if you have any signs or symptoms of liver problems. See "What is the most important information I should know about DUTREBIS?"

- **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 new symptoms after starting your HIV-1 medicine.

- **Risk of inflammation of the pancreas (pancreatitis).** Children may be at risk for developing pancreatitis during treatment with DUTREBIS if they:
  - have taken nucleoside analogue medicines in the past
  - have a history of pancreatitis, or
  - have other risk factors for pancreatitis.

Call your healthcare provider right away if your child develops signs and symptoms of pancreatitis including severe upper stomach-area pain, with or without nausea and vomiting. Your healthcare provider may tell you to stop giving DUTREBIS to your child if their symptoms and blood test results show that your child may have pancreatitis.

The most common side effects of lamivudine in adults include:

- headache
- nausea
- generally not feeling well
- tiredness
- nasal signs and symptoms
- diarrhea
- cough

The most common side effects of lamivudine in children include:

- fever
- cough

The most common side effects of raltegravir include:

- trouble sleeping
- headache
- dizziness
- nausea
- tiredness

Tell your healthcare provider right away if you get muscle pain, tenderness, or weakness that is not normal while taking DUTREBIS. These may be signs of a rare serious muscle problem that can lead to kidney problems.

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 DUTREBIS. 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 DUTREBIS?

- Store DUTREBIS tablets at room temperature between 68-77°F (20-25°C).
- Store tablets in the original package with the bottle tightly closed.
- Keep the drying agent (desiccant) packet in the bottle to protect from moisture.

Keep DUTREBIS and all medicines out of the reach of children.

General information about DUTREBIS

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

For more information go to www.DUTREBIS.com or call 1-800-622-4477.

What are the ingredients in DUTREBIS?
Active ingredients: lamivudine and raltegravir
Inactive ingredients: croscarmellose sodium, hypromellose (2910), lactose monohydrate, magnesium stearate, microcrystalline cellulose, and silicon dioxide [colloidal]. The film coating contains FD&C Blue #2, hypromellose, lactose monohydrate, titanium dioxide, triacetin, and yellow iron oxide.

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

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