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

ISENTRESS (raltegravir) Tablets
Initial U.S. Approval: 2007

----------INDICATIONS AND USAGE----------
ISENTRESS™ is a human immunodeficiency virus integrase strand transfer inhibitor (HIV-1 INSTI) indicated:

- In combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents (1).

The safety and efficacy of ISENTRESS have not been established in treatment-naïve adult patients or pediatric patients (1).

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

- 400 mg administered orally, twice daily with or without food (2.1).

---------- DOSAGE FORMS AND STRENGTHS ----------
Tablets: 400 mg (3).

----------CONTRAINDICATIONS----------
None

----------WARNINGS AND PRECAUTIONS----------
Monitor for Immune Reconstitution Syndrome (5.1)

Drug Interactions

- Caution should be used when coadministering ISENTRESS with strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 (e.g., rifampin) due to reduced plasma concentrations of raltegravir (5.2).

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

- The most common adverse reactions (>10%) of all intensities, reported in subjects in either the ISENTRESS or the placebo treatment group, regardless of causality were: nausea, headache, diarrhea and pyrexia (6.1).
- Creatine kinase elevations were observed in subjects who received ISENTRESS. Myopathy and rhabdomyolysis have been reported; however, the relationship of ISENTRESS to these events is not known. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions (6.1).

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

---------- USE IN SPECIFIC POPULATIONS ----------
Pregnancy:

- ISENTRESS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Physicians are encouraged to register pregnant women exposed to ISENTRESS by calling 1-800-258-4263 so that Merck can monitor maternal and fetal outcomes (8.1).

Nursing Mothers:

- Breast-feeding is not recommended while taking ISENTRESS (8.3).

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

Revised: 10/2007

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ISENTRESS[1] in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.

This indication is based on analyses of plasma HIV-1 RNA levels up through 24 weeks in two controlled studies of ISENTRESS. These studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, NRTI, PI) treatment-experienced adults.

The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response *[see Clinical Studies (14)].*

The safety and efficacy of ISENTRESS have not been established in treatment-naïve adult patients or pediatric patients.

There are no study results demonstrating the effect of ISENTRESS on clinical progression of HIV-1 infection.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

For the treatment of patients with HIV-1 infection, the dosage of ISENTRESS is 400 mg administered orally, twice daily with or without food.

3 DOSAGE FORMS AND STRENGTHS

400 mg pink, oval-shaped, film-coated tablets with "227" on one side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Immune Reconstitution Syndrome

During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, *Mycobacterium* tuberculosis, or reactivation of varicella zoster virus), which may necessitate further evaluation and treatment.

5.2 Drug Interactions

Caution should be used when coadministering ISENTRESS with strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 (e.g., rifampin) due to reduced plasma concentrations of raltegravir *[see Drug Interactions (7)].*

6 ADVERSE REACTIONS

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.

Treatment-Experienced Studies

The safety assessment of ISENTRESS in treatment-experienced subjects is based on the pooled safety data from the randomized, double-blind, placebo-controlled trials, BENCHMRK 1 and

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BENCHMRK 2 (Protocols 018 and 019), and the randomized, double-blind, placebo-controlled, dose-ranging trial (Protocol 005) in antiretroviral treatment-experienced HIV-1 infected adult subjects reported using the recommended dose of ISENTRESS 400 mg twice daily in combination with optimized background therapy (OBT) in 507 subjects, in comparison to 282 subjects taking placebo in combination with OBT. During double-blind treatment, the total follow-up was 332.2 patient-years in the ISENTRESS 400 mg twice daily group and 150.2 patient-years in the placebo group.

The most commonly (>10%) reported adverse reactions, of all intensities, regardless of causality in subjects treated with ISENTRESS and OBT versus placebo and OBT are presented in Table 1.

Table 1: Percentage of Subjects with the Most Commonly Reported (>10%) Adverse Reactions of All Intensities* and Regardless of Causality Occurring in Treatment-Experienced Adult Subjects

System Organ Class, Adverse Reactions	Randomized Studies P005, P018 and P019	
	ISENTRESS 400 mg twice daily + OBT (n=507)† %	Placebo + OBT (n=282)† %
Gastrointestinal Disorders		
Diarrhea	16.6	19.5
Nausea	9.9	14.2
Nervous System Disorders		
Headache	9.7	11.7
General Disorders and Administration Site Conditions		
Pyrexia	4.9	10.3

*Intensities are defined as follows: Mild (awareness of sign or symptom, but easily tolerated); Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).
†n=total number of subjects per treatment group.

The clinical adverse reactions listed below were considered by investigators to be of moderate to severe intensity and causally related to any drug in the combination regimen (ISENTRESS/placebo alone or in combination with OBT, or OBT alone):

Common Adverse Reactions

Drug-related clinical adverse reactions of moderate to severe intensity occurring in ≥2% of subjects treated with ISENTRESS + OBT are presented in Table 2.

Table 2: Percentage of Subjects with Drug-Related* Adverse Reactions of Moderate to Severe Intensity† Occurring in ≥2% of Treatment-Experienced Adult Subjects

System Organ Class, Adverse Reactions	Randomized Studies P005, P018 and P019	
	ISENTRESS 400 mg Twice Daily + OBT (n = 507)‡ %	Placebo + OBT (n = 282)‡ %
Gastrointestinal Disorders		
Diarrhea	3.7	4.6
Nausea	2.2	3.2
Nervous System Disorders		
Headache	2.4	1.4

*Includes adverse reactions at least possibly, probably, or very likely related to the drug.
†Intensities are defined as follows: Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity). ‡n=total number of subjects per treatment group.

Less Common Adverse Reactions

Drug-related adverse reactions occurring in at least 1% but less than 2% of treatment-experienced subjects (n=507) receiving ISENTRESS + OBT and of moderate (discomfort enough to cause interference with usual activity) to severe (incapacitating with inability to work or do usual activity) intensity are listed below by system organ class:

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Gastrointestinal Disorders: abdominal pain, vomiting
General Disorders and Administration Site Conditions: asthenia, fatigue
Nervous System Disorders: dizziness
Skin and Subcutaneous Tissue Disorders: lipodystrophy acquired

Discontinuations

In the pooled analyses for studies P005, P018 and P019, the rates of discontinuation of therapy due to adverse reactions were 2.0% in subjects receiving ISENTRESS + OBT and 1.4% in subjects receiving placebo + OBT.

Serious Events

Drug Related

The following serious drug-related reactions were reported in the clinical studies, P005, P018 and P019: hypersensitivity (hypersensitivity was seen in 2 subjects with ISENTRESS; therapy was interrupted and upon rechallenge the subjects were able to resume drug), anemia, neutropenia, myocardial infarction, gastritis, hepatitis, herpes simplex, toxic nephropathy, renal failure, chronic renal failure and renal tubular necrosis.

Regardless of Drug Relationship

Cancers were reported in treatment-experienced subjects who initiated ISENTRESS with OBT; several were recurrent. The types and rates of specific cancers were those expected in a highly immunodeficient population (many had CD4+ cell counts below 50 cells/mm^3 and most had prior AIDS diagnoses). The cancers included Kaposi's sarcoma, lymphoma, squamous cell carcinoma, hepatocellular carcinoma and anal cancer. Most subjects had other risk factors for cancer including tobacco use, papillomavirus and active hepatitis B virus infection. It is unknown if these cancer diagnoses were related to ISENTRESS use.

Grade 2-4 creatine kinase laboratory abnormalities were observed in subjects treated with ISENTRESS (see Table 3). Myopathy and rhabdomyolysis have been reported; however, the relationship of ISENTRESS to these events is not known. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions.

Patients with Co-existing Conditions

Patients Co-infected with Hepatitis B and/or Hepatitis C Virus

In the clinical studies, P018 and P019, subjects with chronic (but not acute) active hepatitis B and/or hepatitis C virus co-infection (N = 113/699 or 16.2%) were permitted to enroll provided that baseline liver function tests did not exceed 5 times the upper limit of normal (ULN). The rates of AST and ALT abnormalities were somewhat higher in the subgroup of subjects with hepatitis B and/or hepatitis C virus co-infection for both treatment groups. In general the safety profile of ISENTRESS in subjects with hepatitis B and/or hepatitis C virus co-infection was similar to subjects without hepatitis B and/or hepatitis C virus co-infection. Grade 2 or higher laboratory abnormalities that represent a worsening from baseline of AST, ALT or total bilirubin occurred in 26%, 27% and 12%, respectively, of raltegravir-treated coinfected subjects as compared to 9%, 8% and 7% of all other raltegravir-treated subjects.

Laboratory Abnormalities

The percentages of adult subjects treated with ISENTRESS 400 mg twice daily in P005, P018 and P019 with selected Grades 2 to 4 laboratory abnormalities that represent a worsening from baseline are presented in Table 3.

Table 3: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Experienced Subjects

Laboratory Parameter Preferred Term (Unit)	Limit	Randomized Studies P005, P018 and P019	
		ISENTRESS 400 mg Twice Daily + OBT (N = 507)	Placebo + OBT (N = 282)
Hematology			
Absolute neutrophil count ($10^3/\mu L$)			
Grade 2	0.75 - 0.999	3.7%	7.4%
Grade 3	0.50 - 0.749	2.4%	2.5%
Grade 4	<0.50	1.0%	1.1%

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Hemoglobin (gm/dL)			
Grade 2	7.5 - 8.4	1.0%	2.8%
Grade 3	6.5 - 7.4	1.0%	0.4%
Grade 4	<6.5	0.0%	0.0%
Platelet count ($10^3/\mu L$)			
Grade 2	50 - 99.999	3.7%	5.7%
Grade 3	25 - 49.999	0.4%	0.4%
Grade 4	<25	0.8%	0.4%
Blood chemistry			
Fasting (non-random) serum glucose test (mg/dL)			
Grade 2	126 - 250	9.3%	6.8%
Grade 3	251 - 500	1.4%	1.4%
Grade 4	>500	0.0%	0.0%
Total serum bilirubin			
Grade 2	1.6 - 2.5 x ULN	5.3%	6.7%
Grade 3	2.6 - 5.0 x ULN	3.2%	2.5%
Grade 4	>5.0 x ULN	0.8%	0.0%
Serum aspartate aminotransferase			
Grade 2	2.6 - 5.0 x ULN	9.1%	5.7%
Grade 3	5.1 - 10.0 x ULN	2.2%	2.1%
Grade 4	>10.0 x ULN	0.4%	0.7%
Serum alanine aminotransferase			
Grade 2	2.6 - 5.0 x ULN	6.9%	7.8%
Grade 3	5.1 - 10.0 x ULN	3.0%	1.4%
Grade 4	>10.0 x ULN	0.6%	1.1%
Serum alkaline phosphatase			
Grade 2	2.6 - 5.0 x ULN	2.0%	0.4%
Grade 3	5.1 - 10.0 x ULN	0.4%	1.1%
Grade 4	>10.0 x ULN	0.4%	0.4%
Serum pancreatic amylase test			
Grade 2	1.6 - 2.0 x ULN	1.4%	0.7%
Grade 3	2.1 - 5.0 x ULN	3.6%	2.1%
Grade 4	>5.0 x ULN	0.2%	0.0%
Serum lipase test			
Grade 2	1.6 - 3.0 x ULN	3.4%	1.8%
Grade 3	3.1 - 5.0 x ULN	0.6%	0.4%
Grade 4	>5.0 x ULN	0.2%	0.0%
Serum creatine kinase			
Grade 2	6.0 - 9.9 x ULN	2.2%	1.4%
Grade 3	10.0 - 19.9 x ULN	2.4%	1.8%
Grade 4	≥20.0 x ULN	2.2%	0.7%

ULN = Upper limit of normal range-

7 DRUG INTERACTIONS

7.1 Effect of Raltegravir on the Pharmacokinetics of Other Agents

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 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 the UDP-glucuronosyltransferases (UGT) tested (UGT1A1, UGT2B7), and raltegravir does not inhibit P-glycoprotein-mediated transport. Based on these data, ISENTRESS is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or P-glycoprotein (e.g., protease inhibitors, NNRTIs, methadone, opioid analgesics, statins, azole antifungals, proton pump inhibitors, oral contraceptives, and anti-erectile dysfunction agents).

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In drug interaction studies, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of the following: lamivudine, tenofovir.

7.2 Effect of Other Agents on the Pharmacokinetics of Raltegravir

Raltegravir is not a substrate of cytochrome P450 (CYP) enzymes. Based on *in vivo* and *in vitro* studies, raltegravir is eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway.

Rifampin, a strong inducer of UGT1A1, reduces plasma concentrations of ISENTRESS. Therefore, caution should be used when coadministering ISENTRESS with rifampin or other strong inducers of UGT1A1 *[see Warnings and Precautions (5.2)].* The impact of other inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown. Other less strong inducers (e.g., efavirenz, nevirapine, rifabutin, St. John's wort) may be used with the recommended dose of ISENTRESS.

Similar to rifampin, tipranavir/ritonavir reduces plasma concentrations of ISENTRESS. However, approximately 100 subjects received raltegravir in combination with tipranavir/ritonavir in Protocols 018 and 019. Comparable efficacy was observed in this subgroup relative to subjects not receiving tipranavir/ritonavir. Based on these data, tipranavir/ritonavir may be coadministered with ISENTRESS without dose adjustment of ISENTRESS.

Atazanavir, a strong inhibitor of UGT1A1, and atazanavir/ritonavir increase plasma concentrations of raltegravir. However, concomitant use of ISENTRESS and atazanavir/ritonavir did not result in a unique safety signal in Protocol 005 and Protocols 018 and 019. Based on these data, atazanavir/ritonavir may be coadministered with ISENTRESS without dose adjustment of ISENTRESS.

Coadministration of ISENTRESS with other drugs that inhibit UGT1A1 may increase plasma levels of raltegravir.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

ISENTRESS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no adequate and well-controlled studies in pregnant women. In addition, there have been no pharmacokinetic studies conducted in pregnant patients.

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.

Antiretroviral Pregnancy Registry

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

8.3 Nursing Mothers

Breast-feeding is not recommended while taking ISENTRESS. In addition, it is recommended that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV.

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 ISENTRESS through the milk.

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8.4 Pediatric Use

Safety and effectiveness of ISENTRESS in pediatric patients less than 16 years of age have not been established.

8.5 Geriatric Use

Clinical studies of ISENTRESS 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. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Use in Patients with Hepatic Impairment

No clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and healthy subjects were observed. 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 *[see Clinical Pharmacology (12.3)].*

8.7 Use in Patients with Renal Impairment

No clinically important pharmacokinetic differences between subjects with severe renal impairment and healthy subjects were observed. No dosage adjustment is necessary *[see Clinical Pharmacology (12.3)].*

10 OVERDOSAGE

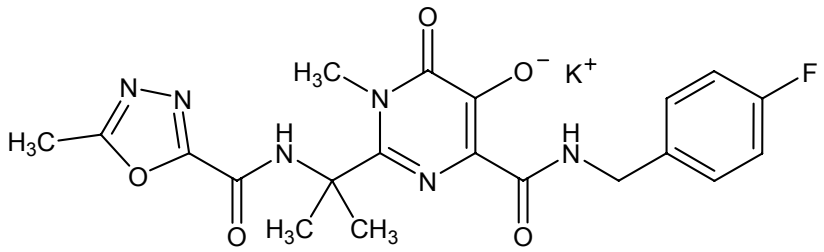
No specific information is available on the treatment of overdosage with ISENTRESS. Doses as high as 1600-mg single dose and 800-mg twice-daily multiple doses were studied in healthy volunteers without evidence of toxicity. Occasional doses of up to 1800 mg per day were taken in the P005/P018 & P019 studies without evidence of toxicity.

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 ISENTRESS may be dialyzable is unknown.

11 DESCRIPTION

ISENTRESS contains raltegravir potassium, 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.

Each film-coated tablet of ISENTRESS for oral administration contains 434.4 mg of raltegravir potassium (as salt), equivalent to 400 mg of raltegravir (free phenol) and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, calcium phosphate dibasic anhydrous, hypromellose 2208, poloxamer 407 (contains 0.01% butylated hydroxytoluene as antioxidant), sodium stearyl fumarate, magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, red iron oxide and black iron oxide.

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12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Raltegravir is an HIV-1 antiviral drug *[see Clinical Pharmacology (12.4)]*.

12.2 Pharmacodynamics

In a monotherapy study raltegravir (400 mg twice daily) demonstrated rapid antiviral activity with mean viral load reduction of 1.66 $\log_{10}$ copies/mL by Day 10.

In Protocol 005 and Protocols 018 and 019, antiviral responses were similar among subjects regardless of dose.

Effects on Electrocardiogram

In a randomized, placebo-controlled, crossover study, 31 healthy subjects were administered a single oral supratherapeutic dose of raltegravir 1600 mg and placebo. Peak raltegravir plasma concentrations were approximately 4-fold higher than the peak concentrations following a 400 mg dose. ISENTRESS did not appear to prolong the QTc interval for 12 hours postdose. After baseline and placebo adjustment, the maximum mean QTc change was -0.4 msec (1-sided 95% upper CI: 3.1 msec).

12.3 Pharmacokinetics

Absorption

Raltegravir is absorbed with a T_{max} of approximately 3 hours postdose in the fasted state. Raltegravir AUC and C_{max} increase dose proportionally over the dose range 100 mg to 1600 mg. Raltegravir C_{12hr} increases dose proportionally over the dose range of 100 to 800 mg and increases slightly less than dose proportionally over the dose range 100 mg to 1600 mg. With twice-daily dosing, pharmacokinetic steady state is achieved within approximately the first 2 days of dosing. There is little to no accumulation in AUC and C_{max}. The average accumulation ratio for C_{12hr} ranged from approximately 1.2 to 1.6.

The absolute bioavailability of raltegravir has not been established.

In subjects who received 400 mg twice daily alone, raltegravir drug exposures were characterized by a geometric mean $AUC_{0\text{-}12hr}$ of 14.3 μM●hr and C_{12hr} of 142 nM.

Considerable variability was observed in the pharmacokinetics of raltegravir. For observed C_{12hr} in Protocols 018 and 019, the coefficient of variation (CV) for inter-subject variability = 212% and the CV for intra-subject variability = 122%.

Effect of Food on Oral Absorption

ISENTRESS may be administered without regard to food. Administration of raltegravir following a high-fat meal increased raltegravir AUC by approximately 19%. A high-fat meal slowed the rate of absorption resulting in an approximately 34% decrease in C_{max}, an 8.5-fold increase in C_{12hr}, and a delay in T_{max} following a single 400 mg dose. The effect of consumption of a range of food types on steady-state pharmacokinetics is not known. Raltegravir was administered without regard to food in the pivotal safety and efficacy studies in HIV-1 positive subjects.

Distribution

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

Metabolism and Excretion

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. Following administration of an oral dose of radiolabeled raltegravir, approximately 51 and 32% of the dose was excreted in feces and urine, respectively. In feces, only raltegravir was present, most of which is likely derived from hydrolysis of raltegravir-glucuronide secreted in bile as observed in preclinical species. Two components, namely raltegravir and raltegravir-glucuronide, were detected in urine and accounted for approximately 9 and 23% of the dose, 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. 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. Thus, the data indicate that the major mechanism of clearance of raltegravir in humans is UGT1A1-mediated glucuronidation.

Special Populations

Pediatric

The pharmacokinetics of raltegravir in pediatric patients has not been established.

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Age

The effect of age on the pharmacokinetics of raltegravir was evaluated in the composite analysis. No dosage adjustment is necessary.

Race

The effect of race on the pharmacokinetics of raltegravir was evaluated in the composite analysis. No dosage adjustment is necessary.

Gender

A study of the pharmacokinetics of raltegravir was performed in young healthy males and females. Additionally, the effect of gender was evaluated in a composite analysis of pharmacokinetic data from 103 healthy subjects and 28 HIV-1 infected subjects receiving raltegravir monotherapy with fasted administration. No dosage adjustment is necessary.

Hepatic Impairment

Raltegravir is eliminated primarily by glucuronidation in the liver. A study of the pharmacokinetics of raltegravir was performed in subjects with moderate hepatic impairment. Additionally, hepatic impairment was evaluated in the composite pharmacokinetic analysis. 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

Renal clearance of unchanged drug is a minor pathway of elimination. A study of the pharmacokinetics of raltegravir was performed in subjects with severe renal impairment. Additionally, renal impairment was evaluated in the composite pharmacokinetic analysis. There were no clinically important pharmacokinetic differences between subjects with severe renal impairment and healthy subjects. No dosage adjustment is necessary. Because the extent to which ISENTRESS may be dialyzable is unknown, dosing before a dialysis session should be avoided.

UGT1A1 Polymorphism

Data currently available are not sufficient to determine the impact of UGT1A1 polymorphism on raltegravir pharmacokinetics.

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

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

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}
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)
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)
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)
ritonavir	100 mg twice daily	400 mg single dose	10	0.76 (0.55, 1.04)	0.84 (0.70, 1.01)	0.99 (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)

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12.4 Microbiology

Mechanism of Action

Raltegravir inhibits the catalytic activity of HIV-1 integrase, 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. Raltegravir did not significantly inhibit human phosphoryltransferases including DNA polymerases α, β, and γ.

Antiviral Activity in Cell Culture

Raltegravir at concentrations of 31 ± 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, raltegravir at concentrations of 6 to 50 nM resulted in 95% inhibition of viral spread in cultures of mitogen-activated human peripheral blood mononuclear cells infected with diverse, primary clinical isolates of HIV-1, including isolates resistant to reverse transcriptase inhibitors and protease inhibitors. 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 analog reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, tenofovir, zalcitabine, or zidovudine); protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir); or the entry inhibitor enfuvirtide.

Resistance

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 Q148 (changed to H, K, or R) or N155 (changed to H) plus one or more additional substitutions (i.e., L74M/R, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226D/F/H, S230R and D232N). Amino acid substitution at Y143C/H/R is another pathway to raltegravir resistance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term (2-year) carcinogenicity studies of raltegravir in rodents are ongoing.

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

Description of Clinical Studies

The evidence of efficacy of ISENTRESS is based on the analyses of 24-week data from 2 ongoing, randomized, double-blind, placebo-controlled trials, BENCHMRK 1 and BENCHMRK 2 (Protocols 018 and 019), in antiretroviral treatment-experienced HIV-1 infected adult subjects. These efficacy results were supported by the 48-week analysis of a randomized, double-blind, controlled, dose-ranging trial, Protocol 005, in antiretroviral treatment-experienced HIV-1 infected adult subjects.

Treatment-Experienced Subjects

BENCHMRK 1 and BENCHMRK 2 are Phase III studies to evaluate the safety and antiretroviral activity of ISENTRESS 400 mg twice daily in combination with an optimized background therapy (OBT), versus OBT alone, in HIV-infected subjects, 16 years or older, with documented resistance to at least 1 drug in each of 3 Classes (NNRTIs, NRTIs, PIs) of antiretroviral therapies. Randomization was stratified by degree of resistance to PI (1PI vs. >1PI) and the use of enfuvirtide in the OBT. Prior to randomization, OBT was selected by the investigator based on genotypic/phenotypic resistance testing and prior ART history.

Table 5 shows the demographic characteristics of subjects in the ISENTRESS 400 mg twice daily arm and subjects in the placebo arm.

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Table 5: Baseline Characteristics

BENCHMRK 1 and 2 Pooled	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	Placebo + OBT (N = 237)
Gender n (%)		
Male	405 (87.7)	210 (88.6)
Female	57 (12.3)	27 (11.4)
Race n (%)		
White	301 (65.2)	173 (73.0)
Black	66 (14.3)	26 (11.0)
Asian	16 (3.5)	6 (2.5)
Hispanic	53 (11.5)	19 (8.0)
Others	26 (5.6)	13 (5.5)
Age (years)		
Median (min, max)	45.0 (16 to 74)	45.0 (17 to 70)
CD4+ Cell Count		
Median (min, max), cells/mm^3	119 (1 to 792)	123 (0 to 759)
≤50 cells/mm^3, n (%)	146 (31.6)	78 (32.9)
>50 and ≤200 cells/mm^3, n (%)	173 (37.4)	85 (35.9)
Plasma HIV-1 RNA		
Median (min, max), $\log_{10}$ copies/mL	4.8 (2 to 6)	4.7 (2 to 6)
>100,000 copies/mL, n (%)	164 (35.5)	78 (32.9)
History of AIDS n (%)		
Yes	426 (92.2)	216 (91.1)
Prior Use of ART, Median (1st Quartile, 3rd Quartile)		
Years of ART Use	10.1 (7.4 to 12.1)	10.2 (7.9 to 12.4)
Number of ART	12.0 (9 to 15)	12.0 (9 to 14)
Hepatitis Co-infection* n (%)		
No Hepatitis B or C virus	385 (83.3)	201 (84.8)
Hepatitis B virus only	36 (7.8)	7 (3.0)
Hepatitis C virus only	37 (8.0)	27 (11.4)
Co-infection of Hepatitis B and C virus	4 (0.9)	2 (0.8)
Stratum n (%)		
Enfuvirtide in OBT	175 (37.9)	89 (37.6)
Resistant to ≥2 PI	447 (96.8)	226 (95.4)

*Hepatitis B virus surface antigen positive or hepatitis C virus antibody positive.

Table 6 compares the characteristics of optimized background therapy at baseline in the ISENTRESS 400 mg twice daily arm and subjects in the control arm.

Table 6: Characteristics of Optimized Background Therapy at Baseline

BENCHMRK 1 and 2 Pooled	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	Placebo + OBT (N = 237)
Number of ARTs in OBT		
Median (min, max)	4.0 (1 to 7)	4.0 (2 to 7)
Number of Active PI in OBT by Phenotypic Resistance Test*		
0	166 (35.9)	97 (40.9)
1 or more	278 (60.2)	137 (57.8)

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Phenotypic Sensitivity Score (PSS)†		
0	67 (14.5)	44 (18.6)
1	145 (31.4)	71 (30.0)
2	142 (30.7)	66 (27.8)
3 or more	85 (18.4)	48 (20.3)
Genotypic Sensitivity Score (GSS)†		
0	115 (24.9)	65 (27.4)
1	178 (38.5)	96 (40.5)
2	111 (24.0)	49 (20.7)
3 or more	51 (11.0)	23 (9.7)

*Darunavir use in OBT in darunavir naïve subjects was counted as one active PI.

†The Phenotypic Sensitivity Score (PSS) and the Genotypic Sensitivity Score (GSS) were defined as the total oral ARTs in OBT to which a subject's viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide-naïve subjects was counted as one active drug in OBT in the GSS and PSS. Similarly, darunavir use in OBT in darunavir-naïve subjects was counted as one active drug in OBT.

Week 24 outcomes for subjects on the recommended dose of ISENTRESS 400 mg twice daily from the pooled studies BENCHMRK 1 and 2 are shown in Table 7. The efficacy responses were evaluated based upon the 436 subjects from the pooled studies BENCHMRK 1 and 2 who had completed 24 weeks of treatment or discontinued earlier. All other outcomes were based upon the total 699 subjects who were randomized and treated.

Table 7: Outcomes by Treatment Group through Week 24

BENCHMRK 1 and 2 Pooled n (%)	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	Placebo + OBT (N = 237)
Outcome at Week 24	n (%)	n (%)
Subjects with Week 24 data	286	150
Subjects with HIV-1 RNA less than 400 copies/mL*	216 (75.5)	59 (39.3)
Subjects with HIV-1 RNA less than 50 copies/mL*	179 (62.6)	50 (33.3)
Virologic Failure (confirmed)†,‡	74 (16.0)	121 (51.1)
Non-responder†,‡	13 (2.8)	78 (32.9)
Rebound†,‡	61 (13.2)	43 (18.1)
Death‡,§	6 (1.3)	3 (1.3)
Discontinuation due to adverse experiences‡,§	9 (1.9)	5 (2.1)
Discontinuation due to other reasons‡,§,¶	6 (1.3)	1 (0.4)

*Based upon the 436 subjects with Week 24 data

†Virologic failure: defined as non-responders who did not achieve >1.0 $\log_{10}$ HIV-1 RNA reduction and <400 HIV-1 RNA copies/mL by Week 16, or viral rebound, which was defined as: (a) HIV-1 RNA >400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV-1 RNA <400 copies/mL, or (b) >1.0 $\log_{10}$ increase in HIV-1 RNA above nadir level (on 2 consecutive measurements at least 1 week apart).

‡Based upon the total 699 subjects randomized and treated, not all subjects complete to Week 24

§Includes available data beyond Week 24

¶ Includes loss to follow-up, subjects withdrew consent, noncompliance, protocol violation and other reasons.

The mean changes in plasma HIV-1 RNA from baseline were -1.85 $\log_{10}$ copies/mL in the ISENTRESS 400 mg twice daily arm and -0.84 $\log_{10}$ copies/mL for the control arm. The mean increase from baseline in CD4+ cell counts was higher in the arm receiving ISENTRESS 400 mg twice daily (89 cells/mm^3) than in the control arm (35 cells/mm^3).

Virologic responses at Week 24 by baseline genotypic and phenotypic sensitivity score are shown in Table 8.

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Table 8: Virologic Response at Week 24 by Baseline Genotypic/Phenotypic Sensitivity Score

BENCHMRK 1 and 2 Pooled (Noncompleters as failures approach)	Percent with HIV RNA <400 copies/mL at Week 24				Percent with HIV RNA <50 copies/mL at Week 24			
	n	ISENTRESS 400 mg Twice Daily + OBT (N = 286)	n	Placebo + OBT (N = 150)	n	ISENTRESS 400 mg Twice Daily + OBT (N = 286)	n	Placebo + OBT (N = 150)
Phenotypic Sensitivity Score (PSS)*								
0	44	50	26	4	44	41	26	4
1	89	75	50	34	89	66	50	30
2	95	86	36	42	95	70	36	36
3 or more	48	73	33	67	48	56	33	55
Genotypic Sensitivity Score (GSS)*								
0	69	54	40	8	69	41	40	5
1	115	82	64	36	115	70	64	33
2	67	88	27	78	67	75	27	63
3 or more	30	70	18	61	30	53	18	50

*The Phenotypic Sensitivity Score (PSS) and the Genotypic Sensitivity Score (GSS) were defined as the total oral ARTs in OBT to which a subject's viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide-naïve subjects was counted as one active drug in OBT in the GSS and PSS. Similarly, darunavir use in OBT in darunavir-naïve subjects was counted as one active drug in OBT.

16 HOW SUPPLIED/STORAGE AND HANDLING

ISENTRESS tablets 400 mg are pink, oval-shaped, film-coated tablets with “227” on one side. They are supplied as follows:

NDC 0006-0227-61 unit-of-use bottles of 60.

No. 3894

Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling].

Patients should be informed that ISENTRESS is not a cure for HIV infection or AIDS. They should also be told that people taking ISENTRESS may still get infections or other conditions common in people with HIV (opportunistic infections). In addition, patients should be told that the long-term effects of ISENTRESS are not known at this time. Patients should also be told that it is very important that they stay under a physician's care during treatment with ISENTRESS.

Patients should be informed that ISENTRESS does not reduce the chance of passing HIV to others through sexual contact, sharing needles, or being exposed to blood. Patients should be advised to continue to practice safer sex and to use latex or polyurethane condoms or other barrier methods to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Patients should also be advised to never re-use or share needles.

Physicians should instruct their patients that if they miss a dose, they should take it as soon as they remember. If they do not remember until it is time for the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not take two tablets of ISENTRESS at the same time.

Physicians should instruct their patients to read the Patient Package Insert before starting ISENTRESS therapy and to reread each time the prescription is renewed. Patients should be instructed

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to inform their physician or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

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Patient Information
ISENTRESS™ (eye **sen** tris**)**
(raltegravir)
Tablets

Read the patient information that comes with ISENTRESS[1] before you start taking it and each time you get a refill. There may be new information. This leaflet is a summary of the information for patients. Your doctor or pharmacist can give you additional information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is ISENTRESS?

- ISENTRESS is an anti-HIV (antiretroviral) medicine that helps to control HIV infection. The term HIV stands for Human Immunodeficiency Virus. It is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). ISENTRESS is used along with other anti-HIV medicines in patients who are already taking or have taken anti-HIV medicines and the medicines are not controlling their HIV infection. ISENTRESS will NOT cure HIV infection.
- People taking ISENTRESS may still develop infections, including opportunistic infections or other conditions that happen with HIV infection.
- Stay under the care of your doctor during treatment with ISENTRESS.
- The long-term effects of ISENTRESS are not known at this time.
- The safety and effectiveness of ISENTRESS in children less than 16 years of age has not been studied.

ISENTRESS <u>must</u> be used with other anti-HIV medicines.

How does ISENTRESS work?

- ISENTRESS blocks an enzyme which the virus (HIV) needs in order to make more virus. The enzyme that ISENTRESS blocks is called HIV integrase.
- When used with other anti-HIV medicines, ISENTRESS may do two things:
  1. It may reduce the amount of HIV in your blood. This is called your "viral load".
  2. It may also increase the number of white blood cells called CD4 (T) cells that help fight off other infections.
- ISENTRESS may not have these effects in all patients.

Does ISENTRESS lower the chance of passing HIV to other people?
No. ISENTRESS does not reduce the chance of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood.

- Continue to practice safer sex.
- Use latex or polyurethane condoms or other barrier methods to lower the chance of sexual contact with any body fluids. This includes semen from a man, vaginal secretions from a woman, or blood.
- Never re-use or share needles.

Ask your doctor if you have any questions about safer sex or how to prevent passing HIV to other people.

What should I tell my doctor before and during treatment with ISENTRESS?
Tell your doctor about all of your medical conditions. Include any of the following that applies to you:

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- You have any allergies.
- You are pregnant or plan to become pregnant.
  - ISENTRESS is not recommended for use during pregnancy. ISENTRESS has not been studied in pregnant women. If you take ISENTRESS while you are pregnant, talk to your doctor about how you can be included in the Antiretroviral Pregnancy Registry.
- You are breast-feeding or plan to breast-feed.
  - It is recommended that HIV-infected women should not breast-feed their infants. This is because their babies could be infected with HIV through their breast milk.
  - Talk with your doctor about the best way to feed your baby.

Tell your doctor about all the medicines you take. Include the following:

- prescription medicines
- non-prescription medicines
- vitamins
- herbal supplements

Know the medicines you take.

- Keep a list of your medicines. Show the list to your doctor and pharmacist when you get a new medicine.

How should I take ISENTRESS?

Take ISENTRESS <u>exactly</u> as your doctor has prescribed. The recommended dose is as follows:

- Take only one 400 mg tablet at a time.
- Take it twice a day.
- Take it by mouth.
- Take it with or without food.

Do not change your dose or stop taking ISENTRESS or your other anti-HIV medicines without first talking with your doctor.

IMPORTANT: Take ISENTRESS exactly as your doctor prescribed and at the right times of day because if you don't:

- The amount of virus (HIV) in your blood may increase if the medicine is stopped for even a short period of time.
- The virus may develop resistance to ISENTRESS and become harder to treat.
- Your medicines may stop working to fight HIV.
- The activity of ISENTRESS may be reduced (due to resistance).

If you fail to take ISENTRESS the way you should, here's what to do:

- 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 and go back to your regular schedule. Do NOT take two tablets of ISENTRESS at the same time. In other words, do NOT take a double dose.
- If you take too much ISENTRESS, call your doctor or local Poison Control Center.

Be sure to keep a supply of your anti-HIV medicines.

- When your ISENTRESS supply starts to run low, get more from your doctor or pharmacy.
- Do not wait until your medicine runs out to get more.

What are the possible side effects of ISENTRESS?

When ISENTRESS has been given with other anti-HIV drugs, the most common side effects included:

- diarrhea

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- nausea
- headache

A condition called Immune Reconstitution Syndrome can happen in some patients with advanced HIV infection (AIDS) when combination antiretroviral treatment is started. Signs and symptoms of inflammation from opportunistic infections that a person has or had may occur as the medicines work to control the HIV infection and strengthen the immune system. Call your doctor right away if you notice any signs or symptoms of an infection after starting ISENTRESS with other anti-HIV medicines.

Contact your doctor promptly if you experience unexplained muscle pain, tenderness, or weakness while taking ISENTRESS.

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

These are not all the side effects of ISENTRESS. For more information, ask your doctor or pharmacist.

How should I store ISENTRESS?

- Store ISENTRESS at room temperature (68 to 77°F).
- **Keep ISENTRESS and all medicines out of the reach of children.**

General information about the use of ISENTRESS

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets.

- Do not use ISENTRESS for a condition for which it was not prescribed.
- Do not give ISENTRESS to other people, even if they have the same symptoms you have. It may harm them.

This leaflet gives you the most important information about ISENTRESS.

- If you would like to know more, talk with your doctor.
- You can ask your doctor or pharmacist for additional information about ISENTRESS that is written for health professionals.
- For more information go to www.ISENTRESS.com or call 1-800-622-4477.

What are the ingredients in ISENTRESS?
Active ingredient: Each film-coated tablet contains 400 mg of raltegravir.

Inactive ingredients: Microcrystalline cellulose, lactose monohydrate, calcium phosphate dibasic anhydrous, hypromellose 2208, poloxamer 407 (contains 0.01% butylated hydroxytoluene as antioxidant), sodium stearyl fumarate, magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, red iron oxide and black iron oxide.

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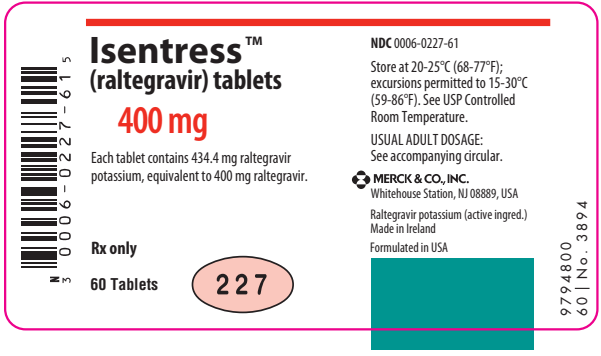
Isentress™
(raltegravir) tablets
400 mg
Each tablet contains 434.4 mg raltegravir potassium, equivalent to 400 mg raltegravir.
Rx only
60 Tablets
227
NDC 0006-0227-61
Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). See USP Controlled Room Temperature.
USUAL ADULT DOSAGE:
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