

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

RECENT MAJOR CHANGES

Indications And Usage (1)	01/2009
Dosage And Administration (2)	01/2009
Warnings And Precautions (5)	01/2009

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).
- During coadministration with rifampin, 800 mg twice daily (2).

DOSAGE FORMS AND STRENGTHS

Tablets: 400 mg (3).

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Monitor for Immune Reconstitution Syndrome (5.1).

ADVERSE REACTIONS

- The most common adverse reactions of moderate to severe intensity ($\geq 2\%$) which occurred at a higher exposure adjusted rate compared to placebo are headache, nausea, asthenia and fatigue (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: 01/2009

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ISENTRESS¹ 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 48 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.

2 DOSAGE AND ADMINISTRATION

For the treatment of patients with HIV-1 infection, the dosage of ISENTRESS is 400 mg administered orally, twice daily with or without food. During coadministration with rifampin, the recommended dosage of ISENTRESS is 800 mg 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

Due to rifampin's potent induction of uridine diphosphate glucuronosyltransferase (UGT) 1A1, the recommended dosage of ISENTRESS is 800 mg twice daily during coadministration with rifampin. Caution should be used when coadministering ISENTRESS with other strong inducers of UGT1A1 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 BENCHMRK 2 (Protocols 018 and 019) in antiretroviral treatment-experienced HIV-1 infected adult subjects. A total of 462 subjects received the recommended dose of ISENTRESS 400 mg twice daily in combination with optimized background therapy (OBT) compared to 237 subjects taking placebo in combination with OBT. The median duration of therapy in these trials was 48 weeks for subjects receiving ISENTRESS and 38 weeks for subjects receiving placebo. The total exposure to ISENTRESS was 387

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patient-years versus 156 patient-years on placebo. The rates of discontinuation due to adverse events were 2% in subjects receiving ISENTRESS and 3% in subjects receiving placebo.

Clinical adverse drug reactions (ADRs) were considered by investigators to be causally related to ISENTRESS + OBT or placebo + OBT. Clinical ADRs of moderate to severe intensity occurring in $\geq 2\%$ of subjects treated with ISENTRESS and occurring at a higher exposure adjusted rate compared to placebo are presented in Table 1.

Table 1: Adverse Drug Reactions* of Moderate to Severe Intensity[†] Occurring in $\geq 2\%$ of Treatment-Experienced Adult Subjects Receiving ISENTRESS and at a Higher Exposure Adjusted Rate Compared to Placebo (48 Week Analysis, Exposure Adjusted Incidence Rates)

System Organ Class, Adverse Reactions	Randomized Studies Protocol 018 and 019	
	ISENTRESS 400 mg Twice Daily + OBT (n = 462) [‡]	Placebo + OBT (n = 237) [‡]
	Rate per 100 Patient-Years	Rate per 100 Patient-Years
Nervous System Disorders		
Headache	3	1
Gastrointestinal Disorders		
Nausea	2	1
General Disorders and Administration Site Conditions		
Asthenia	2	1
Fatigue	2	1

*Includes adverse reactions at least possibly, probably, or definitely 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

The following ADRs occurred in $< 2\%$ of subjects receiving ISENTRESS + OBT. These events have been included because of either their seriousness, increased frequency on ISENTRESS compared with placebo or investigator's assessment of potential causal relationship.

Gastrointestinal Disorders: abdominal pain, gastritis

Hepatobiliary Disorders: hepatitis

Immune System Disorders: hypersensitivity

Infections and Infestations: genital herpes, herpes zoster

Nervous System Disorders: dizziness

Renal and Urinary Disorders: renal failure

Adverse Events

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/mm³ 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 2). 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.

Laboratory Abnormalities

The percentages of adult subjects treated with ISENTRESS 400 mg twice daily or placebo in Protocols 018 and 019 with selected Grade 2 to 4 laboratory abnormalities representing a worsening from baseline are presented in Table 2.

Table 2: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Experienced Subjects (48 Week Analysis)

Laboratory Parameter Preferred Term (Unit)	Limit	Randomized Studies Protocol 018 and 019	
		ISENTRESS 400 mg Twice Daily + OBT (N = 462)	Placebo + OBT (N = 237)
Hematology			
Absolute neutrophil count (10 ³ /μL)			
Grade 2	0.75 - 0.999	3%	5%
Grade 3	0.50 - 0.749	3%	3%
Grade 4	<0.50	1%	<1%
Hemoglobin (gm/dL)			
Grade 2	7.5 - 8.4	1%	3%
Grade 3	6.5 - 7.4	1%	<1%
Grade 4	<6.5	<1%	0%
Platelet count (10 ³ /μL)			
Grade 2	50 - 99.999	3%	5%
Grade 3	25 - 49.999	1%	<1%
Grade 4	<25	1%	<1%
Blood chemistry			
Fasting (non-random) serum glucose test (mg/dL)			
Grade 2	126 - 250	8%	5%
Grade 3	251 - 500	2%	1%
Grade 4	>500	0%	0%
Total serum bilirubin			
Grade 2	1.6 - 2.5 x ULN	5%	3%
Grade 3	2.6 - 5.0 x ULN	2%	2%
Grade 4	>5.0 x ULN	1%	0%
Serum aspartate aminotransferase			
Grade 2	2.6 - 5.0 x ULN	8%	6%
Grade 3	5.1 - 10.0 x ULN	3%	3%
Grade 4	>10.0 x ULN	<1%	1%
Serum alanine aminotransferase			
Grade 2	2.6 - 5.0 x ULN	7%	8%
Grade 3	5.1 - 10.0 x ULN	3%	2%
Grade 4	>10.0 x ULN	1%	2%
Serum alkaline phosphatase			
Grade 2	2.6 - 5.0 x ULN	2%	<1%
Grade 3	5.1 - 10.0 x ULN	<1%	1%
Grade 4	>10.0 x ULN	1%	<1%
Serum pancreatic amylase test			
Grade 2	1.6 - 2.0 x ULN	2%	1%
Grade 3	2.1 - 5.0 x ULN	3%	3%
Grade 4	>5.0 x ULN	<1%	0%
Serum lipase test			
Grade 2	1.6 - 3.0 x ULN	4%	3%
Grade 3	3.1 - 5.0 x ULN	1%	<1%
Grade 4	>5.0 x ULN	0%	0%
Serum creatine kinase			
Grade 2	6.0 - 9.9 x ULN	2%	2%
Grade 3	10.0 - 19.9 x ULN	3%	3%
Grade 4	≥20.0 x ULN	2%	1%

ULN = Upper limit of normal range

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 = 114/699 or 16%) 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 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 Grade from baseline of AST, ALT or total bilirubin occurred in 25%, 31% and 12%, respectively, of co-infected subjects treated with ISENTRESS as compared to 8%, 7% and 8% of all other subjects treated with ISENTRESS.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ISENTRESS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Psychiatric Disorders: depression (particularly in patients with a pre-existing history of psychiatric illness), including suicidal ideation and behaviors

Skin and Subcutaneous Tissue Disorders: rash, Stevens-Johnson syndrome

7 DRUG INTERACTIONS

7.1 Effect of Raltegravir on the Pharmacokinetics of Other Agents

Raltegravir does not inhibit ($IC_{50} > 100 \mu M$) 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 ($IC_{50} > 50 \mu M$) 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 and anti-erectile dysfunction agents).

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

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, the dose of ISENTRESS should be increased during coadministration with rifampin [see *Dosage and Administration (2)*]. The impact of other inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown.

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

Selected drug interactions are presented in Table 3 [see *Clinical Pharmacology (12.3)*].

Table 3: Selected Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Raltegravir	Clinical Comment
HIV-Antiviral Agents		
atazanavir	↑	Atazanavir, a strong inhibitor of UGT1A1, increases plasma concentrations of raltegravir. However, since concomitant use of ISENTRESS with atazanavir/ritonavir did not result in a

		unique safety signal in Phase 3 studies, no dose adjustment is recommended.
atazanavir/ritonavir	↑	Atazanavir/ritonavir increases plasma concentrations of raltegravir. However, since concomitant use of ISENTRESS with atazanavir/ritonavir did not result in a unique safety signal in Phase 3 studies, no dose adjustment is recommended.
efavirenz	↓	Efavirenz reduces plasma concentrations of raltegravir. The clinical significance of this interaction has not been directly assessed.
etravirine	↓	Etravirine reduces plasma concentrations of raltegravir. The clinical significance of this interaction has not been directly assessed.
tipranavir/ritonavir	↓	Tipranavir/ritonavir reduces plasma concentrations of raltegravir. However, since comparable efficacy was observed for this combination relative to other ISENTRESS-containing regimens in Phase 3 studies 018 and 019, no dose adjustment is recommended.
Other Agents		
omeprazole	↑	Coadministration of medicinal products that increase gastric pH (e.g., omeprazole) may increase raltegravir levels based on increased raltegravir solubility at higher pH. However, since concomitant use of ISENTRESS with proton pump inhibitors and H2 blockers did not result in a unique safety signal in Phase 3 studies, no dose adjustment is recommended.
rifampin	↓	Rifampin, a strong inducer of UGT1A1, reduces plasma concentrations of raltegravir. The recommended dosage of ISENTRESS is 800 mg twice daily during coadministration with rifampin.

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.

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

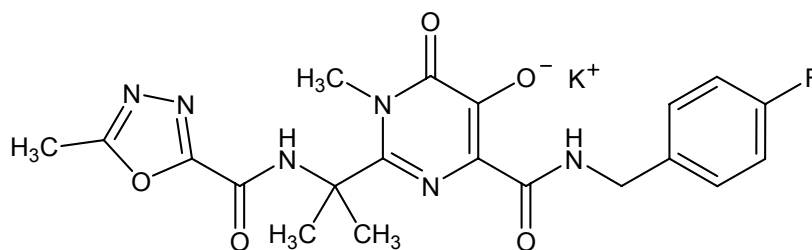
No specific information is available on the treatment of overdosage with ISENTRESS. Doses as high as 1600-mg single dose and 800-mg twice-daily multiple doses were studied in healthy volunteers without evidence of toxicity. Occasional doses of up to 1800 mg per day were taken in the clinical studies of HIV-1 infected subjects 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 C₂₀H₂₀FN₆O₅ 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.

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 log₁₀ copies/mL by Day 10.

In the randomized, double-blind, placebo-controlled, dose-ranging trial, 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_{0-12hr} 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 with or without food. Raltegravir was administered without regard to food in the pivotal safety and efficacy studies in HIV-infected patients. The effect of consumption of low-, moderate- and high-fat meals on steady-state raltegravir pharmacokinetics was assessed in healthy volunteers. Administration of multiple doses of raltegravir following a moderate-fat meal (600 Kcal, 21 g fat) did not affect raltegravir AUC to a clinically meaningful degree with an increase of 13% relative to fasting. Raltegravir C_{12hr} was 66% higher and C_{max} was 5% higher following a moderate-fat meal compared to fasting. Administration of raltegravir following a high-fat meal (825 Kcal, 52 g fat) increased

AUC and C_{max} by approximately 2-fold and increased C_{12hr} by 4.1-fold. Administration of raltegravir following a low-fat meal (300 Kcal, 2.5 g fat) decreased AUC and C_{max} by 46% and 52%, respectively; C_{12hr} was essentially unchanged. Food appears to increase pharmacokinetic variability relative to fasting.

Distribution

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

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.

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 healthy adult 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

There is no evidence that common UGT1A1 polymorphisms alter raltegravir pharmacokinetics to a clinically meaningful extent. In a comparison of 30 subjects with *28/*28 genotype (associated with reduced activity of UGT1A1) to 27 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)]

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)
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 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)

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 (EC₉₅) 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 (EC₉₅ 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, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230R and D232N). Amino acid substitution at Y143C/H/R is another pathway to raltegravir resistance. By Week 48 in the BENCHMRK trials, at least one of the 3 primary raltegravir resistance-associated substitutions, Y143C/H/R, Q148H/K/R, and N155H, was observed in 63 (64.3%) of the 98 virologic failure subjects with evaluable genotypic data from paired baseline and raltegravir treatment-failure isolates. Some (n=18) of those HIV isolates harboring one or more of the 3 primary raltegravir resistance-associated substitutions were evaluated for raltegravir susceptibility yielding a median decrease of 47.3-fold (mean 73.1 ± 60.8-fold decrease, ranging from 0.9- to 200-fold) compared to baseline isolates.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Description of Clinical Studies

The evidence of durable efficacy of ISENTRESS is based on the analyses of 48-week data from 2 ongoing, randomized, double-blind, placebo-controlled studies, 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 study, Protocol 005, in antiretroviral treatment-experienced HIV-1 infected adult subjects.

Treatment-Experienced Subjects

BENCHMRK 1 and BENCHMRK 2 are Phase 3 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 group receiving ISENTRESS 400 mg twice daily and subjects in the placebo group.

Table 5: Baseline Characteristics

Randomized Studies Protocol 018 and 019	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	Placebo + OBT (N = 237)
Gender		
Male	88%	89%
Female	12%	11%
Race		

White	65%	73%
Black	14%	11%
Asian	3%	3%
Hispanic	11%	8%
Others	6%	5%
Age (years)		
Median (min, max)	45 (16 to 74)	45 (17 to 70)
CD4+ Cell Count		
Median (min, max), cells/mm ³	119 (1 to 792)	123 (0 to 759)
≤50 cells/mm ³	32%	33%
>50 and ≤200 cells/mm ³	37%	36%
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	35%	33%
History of AIDS		
Yes	92%	91%
Prior Use of ART, Median (1st Quartile, 3rd Quartile)		
Years of ART Use	10 (7 to 12)	10 (8 to 12)
Number of ART	12 (9 to 15)	12 (9 to 14)
Hepatitis Co-infection*		
No Hepatitis B or C virus	83%	85%
Hepatitis B virus only	8%	3%
Hepatitis C virus only	8%	11%
Co-infection of Hepatitis B and C virus	1%	1%
Stratum		
Enfuvirtide in OBT	38%	38%
Resistant to ≥2 PI	97%	95%

*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 group receiving ISENTRESS 400 mg twice daily and subjects in the control group.

Table 6: Characteristics of Optimized Background Therapy at Baseline

Randomized Studies Protocol 018 and 019	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	Placebo + OBT (N = 237)
Number of ARTs in OBT		
Median (min, max)	4 (1 to 7)	4 (2 to 7)
Number of Active PI in OBT by Phenotypic Resistance Test*		
0	36%	41%
1 or more	60%	58%
Phenotypic Sensitivity Score (PSS)[†]		
0	15%	19%
1	31%	30%
2	31%	28%
3 or more	18%	20%
Genotypic Sensitivity Score (GSS)[†]		
0	25%	28%
1	39%	41%
2	24%	21%
3 or more	11%	10%

*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 48 outcomes for the 699 subjects randomized and treated with the recommended dose of ISENTRESS 400 mg twice daily or placebo in the pooled BENCHMRK 1 and 2 studies are shown in Table 7.

Table 7: Outcomes by Treatment Group through Week 48

Randomized Studies Protocol 018 and 019	ISENTRESS 400 mg Twice Daily + OBT	Placebo + OBT
	(N = 462)	(N = 237)
Outcome at Week 48		
Subjects with HIV-1 RNA less than 400 copies/mL	72%	37%
Subjects with HIV-1 RNA less than 50 copies/mL	62%	33%
Virologic Failure (confirmed) [†]	23%	57%
Non-responder [†]	3%	30%
Rebound [†]	20%	26%
Death [‡]	2%	3%
Discontinuation due to adverse experiences	2%	3%
Discontinuation due to other reasons [§]	2%	2%

[†]Virologic failure: defined as non-responders who did not achieve >1.0 log₁₀ 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 log₁₀ increase in HIV-1 RNA above nadir level (on 2 consecutive measurements at least 1 week apart).

[‡] Two additional subjects died while receiving open-label raltegravir therapy: one subject subsequent to discontinuing double-blind placebo and one subject subsequent to discontinuing double-blind raltegravir.

[§]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 -1.71 log₁₀ copies/mL in the group receiving ISENTRESS 400 mg twice daily and -0.78 log₁₀ copies/mL for the control group. The mean increase from baseline in CD4+ cell counts was higher in the group receiving ISENTRESS 400 mg twice daily (109 cells/mm³) than in the control group (45 cells/mm³).

Treatment-emergent CDC Category C events occurred in 4% of the group receiving ISENTRESS 400 mg twice daily and 5% of the control group.

Virologic responses at Week 48 by baseline genotypic and phenotypic sensitivity score are shown in Table 8.

Table 8: Virologic Response at Week 48 by Baseline Genotypic/Phenotypic Sensitivity Score

Randomized Studies Protocol 018 and 019 (Noncompleters as failures approach)	Percent with HIV RNA <400 copies/mL at Week 48				Percent with HIV RNA <50 copies/mL at Week 48			
	n	ISENTRESS 400 mg Twice Daily + OBT (N = 459) [†]	n	Placebo + OBT (N = 237)	n	ISENTRESS 400 mg Twice Daily + OBT (N = 459)	n	Placebo + OBT (N = 237)
Phenotypic Sensitivity Score (PSS)*								
0	69	54	44	5	69	48	44	2
1	143	71	72	33	143	58	72	28
2	141	82	66	41	141	70	66	36

3 or more	85	74	48	63	85	68	48	58
Genotypic Sensitivity Score (GSS)*								
0	115	50	66	8	115	43	66	3
1	175	77	96	39	175	63	96	35
2	111	86	49	65	111	76	49	59
3 or more	51	73	23	52	51	69	23	48

*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.

†Three patients were excluded from the week 48 analysis because of missing data immediately flanked by 2 successes.

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

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