CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203045Orig1s000

<u>LABELING</u>

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) Film-Coated Tablets, for oral use
ISENTRESS® (raltegravir) Chewable Tablets, for oral use
Initial U.S. Approval: 2007

----------RECENT MAJOR CHANGES----------

Indications And Usage (1)	12/2011
Dosage And Administration (2)	12/2011
Warnings And Precautions (5.1)	11/2011
Warnings And Precautions (5.3)	12/2011

----------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 (1).

The safety and efficacy of ISENTRESS have not been established in children less than 2 years of age (1.2).

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

ISENTRESS can be administered with or without food (2.1).
ISENTRESS 400 mg film-coated tablets cannot be substituted with ISENTRESS 25 mg and 100 mg chewable tablets (2.1).

Adults

- 400 mg film-coated tablet orally, twice daily (2.2).
- During coadministration with rifampin in adults, 800 mg twice daily (2.1).

Children and Adolescents

- **12 years of age and older:** One 400 mg film-coated tablet orally, twice daily (2.3).
- **6 to less than 12 years of age:**
  - If at least 25 kg in weight:
    One 400 mg film-coated tablet orally, twice daily **OR**
    Chewable tablets: weight based to maximum dose 300 mg twice daily (2.3).
  - If less than 25 kg in weight:
    Chewable tablets: weight based to maximum dose 300 mg twice daily (2.3).
- **2 to less than 6 years of age:**
  - If at least 10 kg in weight:
    Chewable tablets: weight based to maximum dose 300 mg twice daily (2.3).

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

- **Film-Coated Tablets**: 400 mg (3).
- **Chewable Tablets**: 100 mg scored and 25 mg (3).

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

None (4).

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

- Severe, potentially life-threatening and fatal skin reactions have been reported. This includes cases of Stevens-Johnson syndrome, hypersensitivity reaction and toxic epidermal necrolysis. Immediately discontinue treatment with ISENTRESS and other suspect agents if severe hypersensitivity, severe rash, or rash with systemic symptoms or liver aminotransferase elevations develops and monitor clinical status, including liver aminotransferases closely (5.1).
- Monitor for Immune Reconstitution Syndrome (5.2).
- Inform patients with phenylketonuria that the 100 mg and 25 mg chewable tablets contain phenylalanine (5.3).

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

- The most common adverse reactions of moderate to severe intensity (≥2%) which occurred at a higher rate than the comparator are insomnia and headache (6.1 and 6.2).
- Creatine kinase elevations were observed in subjects who received ISENTRESS. Myopathy and rhabdomyolysis have been reported. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions (6.3).

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

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

- Coadministration of ISENTRESS with drugs that are strong inducers of UGT1A1 may result in reduced plasma concentrations of raltegravir (7.2).

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

Pregnancy:

- ISENTRESS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1).
- Pregnancy registry available (8.1).

Nursing Mothers:

- Breastfeeding is not recommended while taking ISENTRESS (8.3).

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

Revised: 12/2011

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Adults

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

This indication is based on analyses of plasma HIV-1 RNA levels through 96 weeks in three double-blind controlled studies of ISENTRESS. Two of these studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, NRTI, PI) treatment-experienced adults and one was conducted in treatment-naïve adults.

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

1.2 Pediatrics

ISENTRESS is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in children and adolescents 2 years of age and older and weighing at least 10 kg *[see Use in Specific Populations (8.4)]*.

This indication is based on the evaluation of safety, tolerability, pharmacokinetic parameters and efficacy of ISENTRESS through at least 24-weeks in a multi-center, open-label, noncomparative study in HIV-1 infected children and adolescents 2 to 18 years of age *[see Clinical Studies (14.3)]*.

The safety and efficacy of ISENTRESS have not been established in children less than 2 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Recommendations

- ISENTRESS Film-Coated Tablets and Chewable Tablets can be administered with or without food *[see Clinical Pharmacology (12.3)]*.
- Maximum dose of chewable tablets is 300 mg twice daily.
- ISENTRESS Chewable Tablets may be chewed or swallowed whole.
- ISENTRESS Film-Coated Tablets must be swallowed whole.
- Because the formulations are not bioequivalent, do not substitute chewable tablets for the 400 mg film-coated tablet.
- During coadministration of ISENTRESS 400 mg film-coated tablets with rifampin, the recommended dosage of ISENTRESS is 800 mg twice daily in adults. There are no data to guide co-administration of ISENTRESS with rifampin in patients below 18 years of age *[see Drug Interactions (7)]*.

2.2 Adults

For the treatment of adult patients with HIV-1 infection, the dosage of ISENTRESS is one 400 mg film-coated tablet administered orally, twice daily.

2.3 Pediatrics

For the treatment of children and adolescents with HIV-1 infection, the dosage of ISENTRESS is as follows:

- **12 years of age and older:** One 400 mg film-coated tablet orally, twice daily
- **6 to less than 12 years of age:**
  If at least 25 kg in weight:
  - One 400 mg film-coated tablet orally, twice daily **OR**
  - Chewable tablets: weight based to maximum dose 300 mg, twice daily as specified in Table 1

  If less than 25 kg in weight:
  - Chewable tablets: weight based to maximum dose 300 mg, twice daily as specified in Table 1
- **2 to less than 6 years of age:**
  If at least 10 kg in weight:
  - Chewable tablets: weight based to maximum dose 300 mg, twice daily as specified in Table 1

Table 1: Recommended Dose* for ISENTRESS Chewable Tablets in Pediatric Patients 2 to Less Than 12 Years of Age

Body Weight (kg)	Dose	Number of Chewable Tablets

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10 to less than 14	75 mg twice daily	3 x 25 mg twice daily
14 to less than 20	100 mg twice daily	1 x 100 mg twice daily
20 to less than 28	150 mg twice daily	1.5 x 100 mg[†] twice daily
28 to less than 40	200 mg twice daily	2 x 100 mg twice daily
at least 40	300 mg twice daily	3 x 100 mg twice daily

[*]The weight-based dosing recommendation for the chewable tablet is based on approximately 6 mg/kg/dose twice daily.
[†]The 100 mg chewable tablet can be divided into equal halves.

3 DOSAGE FORMS AND STRENGTHS

- Film-coated Tablets
  400 mg pink, oval-shaped, film-coated tablets with "227" on one side.
- Chewable Tablets
  100 mg are pale orange, oval-shaped, orange-banana flavored, chewable tablets scored on both sides and imprinted on one face with the Merck logo and "477" on opposite sides of the score.
  25 mg pale yellow, round, orange-banana flavored, chewable tablets with the Merck logo on one side and "473" on the other side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Severe Skin and Hypersensitivity Reactions

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

5.2 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.

5.3 Phenylketonurics

ISENTRESS Chewable Tablets contain phenylalanine, a component of aspartame. Each 25 mg ISENTRESS Chewable Tablet contains approximately 0.05 mg phenylalanine. Each 100 mg ISENTRESS Chewable Tablet contains approximately 0.10 mg phenylalanine. Phenylalanine can be harmful to patients with phenylketonuria.

6 ADVERSE REACTIONS

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.

6.1 Clinical Trials Experience: Treatment-Naïve Adults

The following safety assessment of ISENTRESS in treatment-naïve subjects is based on the randomized double-blind active controlled study of treatment-naïve subjects, STARTMRK (Protocol 021) with ISENTRESS 400 mg twice daily in combination with a fixed dose of emtricitabine 200 mg (+) tenofovir 300 mg, (N=281) versus efavirenz (EFV) 600 mg at bedtime in combination with emtricitabine

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(+) tenofovir, (N=282). During double-blind treatment, the total follow-up for subjects receiving ISENTRESS 400 mg twice daily + emtricitabine (+) tenofovir was 480 patient-years and 463 patient-years for subjects receiving efavirenz 600 mg at bedtime + emtricitabine (+) tenofovir.

In Protocol 021, the rate of discontinuation of therapy due to adverse reactions was 4% in subjects receiving ISENTRESS + emtricitabine (+) tenofovir and 7% in subjects receiving efavirenz + emtricitabine (+) tenofovir.

The clinical adverse drug reactions (ADRs) listed below were considered by investigators to be causally related to ISENTRESS + emtricitabine (+) tenofovir or efavirenz + emtricitabine (+) tenofovir. Clinical ADRs of moderate to severe intensity occurring in ≥2% of treatment-naïve subjects treated with ISENTRESS and occurring at a higher rate than efavirenz are presented in Table 2.

Table 2: Adverse Reactions* of Moderate to Severe Intensity† Occurring in ≥2% of Treatment-Naïve Adult Subjects Receiving ISENTRESS and at a Higher Rate Compared to Efavirenz (96 Week Analysis)

System Organ Class, Preferred Term	Randomized Study Protocol 021	
	ISENTRESS 400 mg Twice Daily + Emtricitabine (+) Tenofovir (n = 281)‡ %	Efavirenz 600 mg At Bedtime + Emtricitabine (+) Tenofovir (n = 282)‡ %
Psychiatric Disorders		
Insomnia	4	3

*Includes adverse experiences considered by investigators to be 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

Laboratory Abnormalities

The percentages of adult subjects treated with ISENTRESS 400 mg twice daily or efavirenz in Protocol 021 with selected Grades 2 to 4 laboratory abnormalities that represent a worsening Grade from baseline are presented in Table 3.

Table 3: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Naïve Subjects (96 Week Analysis)

Laboratory Parameter Preferred Term (Unit)	Limit	Randomized Study Protocol 021 ISENTRESS 400 mg Twice Daily + Emtricitabine (+) Tenofovir (N = 281)	Efavirenz 600 mg At Bedtime + Emtricitabine (+) Tenofovir (N = 282)
Hematology			
Absolute neutrophil count ($10^3/\mu L$)			
Grade 2	0.75 - 0.999	3%	4%
Grade 3	0.50 - 0.749	2%	1%
Grade 4	<0.50	<1%	<1%
Hemoglobin (gm/dL)			
Grade 2	7.5 - 8.4	1%	1%
Grade 3	6.5 - 7.4	<1%	1%
Grade 4	<6.5	<1%	0%
Platelet count ($10^3/\mu L$)			
Grade 2	50 - 99.999	2%	0%
Grade 3	25 - 49.999	<1%	<1%
Grade 4	<25	0%	0%
Blood chemistry			

Fasting (non-random) serum glucose test (mg/dL)			
Grade 2	126 - 250	3%	4%
Grade 3	251 - 500	1%	0%
Grade 4	>500	0%	0%
Total serum bilirubin			
Grade 2	1.6 - 2.5 x ULN	4%	0%
Grade 3	2.6 - 5.0 x ULN	1%	0%
Grade 4	>5.0 x ULN	0%	0%
Serum aspartate aminotransferase			
Grade 2	2.6 - 5.0 x ULN	4%	5%
Grade 3	5.1 - 10.0 x ULN	2%	2%
Grade 4	>10.0 x ULN	1%	<1%
Serum alanine aminotransferase			
Grade 2	2.6 - 5.0 x ULN	6%	9%
Grade 3	5.1 - 10.0 x ULN	1%	2%
Grade 4	>10.0 x ULN	1%	1%
Serum alkaline phosphatase			
Grade 2	2.6 - 5.0 x ULN	1%	3%
Grade 3	5.1 - 10.0 x ULN	0%	<1%
Grade 4	>10.0 x ULN	0%	<1%

ULN = Upper limit of normal range

Lipids, Change from Baseline

Changes from baseline in fasting lipids are shown in Table 4.

Table 4: Lipid Values, Mean Change from Baseline, Protocol 021

Laboratory Parameter Preferred Term	ISENTRESS 400 mg Twice Daily + Emtricitabine (+) Tenofovir N = 281			Efavirenz 600 mg At Bedtime + Emtricitabine (+) Tenofovir N = 282		
			Change from Baseline at Week 96			Change from Baseline at Week 96
	Baseline Mean (mg/dL)	Week 96 Mean (mg/dL)	Mean Change (mg/dL)	Baseline Mean (mg/dL)	Week 96 Mean (mg/dL)	Mean Change (mg/dL)
LDL-Cholesterol*	96	103	7	93	115	21
HDL-Cholesterol*	39	42	3	38	48	10
Total Cholesterol*	159	169	10	156	194	38
Triglyceride*	125	121	-4	137	177	40

*Fasting (non-random) laboratory tests.

Notes:

N = Number of subjects in the treatment group. The analysis is based on all available data.

If subjects initiated or increased serum lipid-reducing agents, the last available lipid values prior to the change in therapy were used in the analysis. If the missing data was due to other reasons, subjects were censored thereafter for the analysis. At baseline, serum lipid-reducing agents were used in 5% of subjects in the group receiving ISENTRESS and 3% in the efavirenz group. Through Week 96, serum lipid-reducing agents were used in 7% of subjects in the group receiving ISENTRESS and 9% in the efavirenz group.

6.2 Clinical Trials Experience: Treatment-Experienced Adults

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 96 weeks for subjects receiving ISENTRESS and 38 weeks for subjects receiving placebo. The total exposure to ISENTRESS was 708 patient-years versus 244 patient-years on placebo. The rates of discontinuation due to adverse events were 4% in subjects receiving ISENTRESS and 5% in subjects receiving placebo.

Clinical ADRs were considered by investigators to be causally related to ISENTRESS + OBT or placebo + OBT. Clinical ADRs of moderate to severe intensity occurring in ≥2% of subjects treated with ISENTRESS and occurring at a higher rate compared to placebo are presented in Table 5.

Table 5: Adverse Drug Reactions* of Moderate to Severe Intensity† Occurring in ≥2% of Treatment-Experienced Adult Subjects Receiving ISENTRESS and at a Higher Rate Compared to Placebo (96 Week Analysis)

System Organ Class, Adverse Reactions	Randomized Studies Protocol 018 and 019	
	ISENTRESS 400 mg Twice Daily + OBT (n = 462)‡	Placebo + OBT (n = 237)‡
Nervous System Disorders		
Headache	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.

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 Grade from baseline are presented in Table 6.

Table 6: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Experienced Subjects (96 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 ($10^3/\mu L$)			
Grade 2	0.75 - 0.999	4%	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 ($10^3/\mu L$)			
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	10%	7%
Grade 3	251 - 500	3%	1%
Grade 4	>500	0%	0%

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Total serum bilirubin			
Grade 2	1.6 - 2.5 x ULN	6%	3%
Grade 3	2.6 - 5.0 x ULN	3%	3%
Grade 4	>5.0 x ULN	1%	0%
Serum aspartate aminotransferase			
Grade 2	2.6 - 5.0 x ULN	9%	7%
Grade 3	5.1 - 10.0 x ULN	4%	3%
Grade 4	>10.0 x ULN	1%	1%
Serum alanine aminotransferase			
Grade 2	2.6 - 5.0 x ULN	9%	9%
Grade 3	5.1 - 10.0 x ULN	4%	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	4%	3%
Grade 4	>5.0 x ULN	<1%	<1%
Serum lipase test			
Grade 2	1.6 - 3.0 x ULN	5%	4%
Grade 3	3.1 - 5.0 x ULN	2%	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	4%	3%
Grade 4	≥20.0 x ULN	3%	1%

ULN = Upper limit of normal range

Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Studies

The following ADRs occurred in <2% of treatment-naïve or treatment-experienced subjects receiving ISENTRESS in a combination regimen. These events have been included because of their seriousness, increased frequency on ISENTRESS compared with efavirenz or placebo, or investigator's assessment of potential causal relationship.

Gastrointestinal Disorders: abdominal pain, gastritis, dyspepsia, vomiting, nausea
General Disorders and Administration Site Conditions: fatigue, asthenia
Hepatobiliary Disorders: hepatitis
Immune System Disorders: hypersensitivity
Infections and Infestations: genital herpes, herpes zoster
Nervous System Disorders: dizziness
Psychiatric Disorders: depression (particularly in subjects with a pre-existing history of psychiatric illness), including suicidal ideation and behaviors
Renal and Urinary Disorders: nephrolithiasis, renal failure

6.3 Selected Adverse Events

Cancers were reported in treatment-experienced subjects who initiated ISENTRESS or placebo, both with OBT, and in treatment-naïve subjects who initiated ISENTRESS or efavirenz, both with emtricitabine (+) tenofovir; several were recurrent. The types and rates of specific cancers were those expected in a highly immunodeficient population (many had CD4+ counts below 50 cells/mm^3 and most had prior AIDS diagnoses). The risk of developing cancer in these studies was similar in the group receiving ISENTRESS and the group receiving the comparator.

Grade 2-4 creatine kinase laboratory abnormalities were observed in subjects treated with ISENTRESS (see Table 6). Myopathy and rhabdomyolysis have been reported. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions.

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Rash occurred more commonly in treatment-experienced subjects receiving regimens containing ISENTRESS + darunavir/ritonavir compared to subjects receiving ISENTRESS without darunavir/ritonavir or darunavir/ritonavir without ISENTRESS. However, rash that was considered drug related occurred at similar rates for all three groups. These rashes were mild to moderate in severity and did not limit therapy; there were no discontinuations due to rash.

6.4 Patients with Co-existing Conditions

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

In the randomized, double-blind, placebo-controlled trials, treatment-experienced subjects (N = 114/699 or 16%) and treatment-naïve subjects (N = 34/563 or 6%) with chronic (but not acute) active hepatitis B and/or hepatitis C virus co-infection were permitted to enroll provided that baseline liver function tests did not exceed 5 times the upper limit of normal (ULN). In general the safety profile of ISENTRESS in subjects with hepatitis B and/or hepatitis C virus co-infection was similar to that in subjects without hepatitis B and/or hepatitis C virus co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or hepatitis C virus co-infection for all treatment groups. In treatment-experienced subjects, Grade 2 or higher laboratory abnormalities that represent a worsening Grade from baseline of AST, ALT or total bilirubin occurred in 29%, 34% and 13%, respectively, of co-infected subjects treated with ISENTRESS as compared to 11%, 10% and 9% of all other subjects treated with ISENTRESS. In treatment-naïve subjects, Grade 2 or higher laboratory abnormalities that represent a worsening Grade from baseline of AST, ALT or total bilirubin occurred in 17%, 28% and 17%, respectively, of co-infected subjects treated with ISENTRESS as compared to 6%, 6% and 3% of all other subjects treated with ISENTRESS.

6.5 Clinical Trials Experience: Pediatrics

ISENTRESS has been studied in 126 antiretroviral treatment-experienced HIV-1 infected children and adolescents 2 through 18 years of age, in combination with other antiretroviral agents in IMPAACT P1066 *[see Use in Specific Populations (8.4) and Clinical Studies (14.3)]*. Of the 126 patients, 96 received the recommended dose of ISENTRESS.

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

One patient experienced drug related clinical adverse reactions of Grade 3 psychomotor hyperactivity, abnormal behavior and insomnia; one patient experienced a Grade 2 serious drug related allergic rash.

One patient experienced drug related laboratory abnormalities, Grade 4 AST and Grade 3 ALT, which were considered serious.

6.6 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.

Blood and Lymphatic System Disorders: thrombocytopenia
Gastrointestinal Disorders: diarrhea
Hepatobiliary Disorders: hepatic failure (with and without associated hypersensitivity) in patients with underlying liver disease and/or concomitant medications
Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis
Nervous System Disorders: cerebellar ataxia
Psychiatric Disorders: anxiety, paranoia

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 CYP1A2, CYP2B6 or CYP3A4. A midazolam drug interaction study confirmed the low propensity of raltegravir to alter the pharmacokinetics of agents metabolized by CYP3A4 *in vivo* by demonstrating a lack of effect of raltegravir on the pharmacokinetics of midazolam, a sensitive CYP3A4 substrate. Similarly, raltegravir is not an inhibitor (IC_{50}>50 μM) of 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.,

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protease inhibitors, NNRTIs, 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, methadone, lamivudine, tenofovir, etravirine, darunavir/ritonavir.

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, in adults the dose of ISENTRESS should be increased during coadministration with rifampin. There are no data to guide co-administration of ISENTRESS with rifampin in patients below 18 years of age *[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.

All interaction studies were performed in adults.

Selected drug interactions are presented in Table 7 *[see Clinical Pharmacology (12.3)]*.

Table 7: Selected Drug Interactions in Adults

Concomitant Drug Class: Drug Name	Effect on Concentration of Raltegravir	Clinical Comment
HIV-1-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

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

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

The safety, tolerability, pharmacokinetic profile, and efficacy of ISENTRESS were evaluated in HIV-1 infected children and adolescents 2 to 18 years of age in an open-label, multicenter clinical trial, IMPAACT P1066 *[see Clinical Pharmacology (12.3)* and *Clinical Studies (14.3)]*. The safety profile was comparable to that observed in adults *[see Adverse Reactions (6.5)]*. See Dosage and Administration (2.3) for dosing recommendations for children 2 years of age and older. Safety and effectiveness of ISENTRESS in children under 2 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)].*

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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

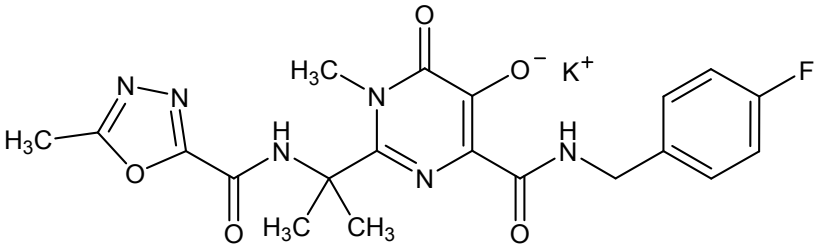
No specific information is available on the treatment of overdosage with ISENTRESS. Doses as high as 1600-mg single dose and 800-mg twice-daily multiple doses were studied in healthy volunteers without evidence of toxicity. Occasional doses of up to 1800 mg per day were taken in the clinical studies 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 $C_{20}H_{20}FKN_6O_5$ 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 400 mg film-coated tablet of ISENTRESS for oral administration contains 434.4 mg of raltegravir (as potassium 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.

Each 100 mg chewable tablet of ISENTRESS for oral administration contains 108.6 mg of raltegravir (as potassium salt), equivalent to 100 mg of raltegravir free phenol and the following inactive ingredients: hydroxypropyl cellulose, sucralose, saccharin sodium, sodium citrate dihydrate, mannitol, red iron oxide, yellow iron oxide, monoammonium glycyrrhizinate, sorbitol, fructose, natural and artificial flavors (orange, banana, and masking that contains aspartame), crospovidone, magnesium stearate, sodium stearyl fumarate, ethylcellulose 20 cP, ammonium hydroxide, medium chain triglycerides, oleic acid, hypromellose 2910/6cP, PEG 400.

Each 25 mg chewable tablet of ISENTRESS for oral administration contains 27.16 mg of raltegravir (as potassium salt), equivalent to 25 mg of raltegravir free phenol and the following inactive ingredients: hydroxypropyl cellulose, sucralose, saccharin sodium, sodium citrate dihydrate, mannitol, yellow iron oxide, monoammonium glycyrrhizinate, sorbitol, fructose, natural and artificial flavors (orange, banana, and masking that contains aspartame), crospovidone, magnesium stearate, sodium stearyl fumarate, ethylcellulose 20 cP, ammonium hydroxide, medium chain triglycerides, oleic acid, hypromellose 2910/6cP, PEG 400.

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12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Raltegravir is an HIV-1 antiviral drug *[see Microbiology (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 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

Adults

Absorption

Raltegravir (film-coated tablet) 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. Based on a formulation comparison study in healthy adult volunteers, the chewable tablet has higher oral bioavailability compared to the 400 mg film-coated tablet.

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 with or without food. Raltegravir was administered without regard to food in the pivotal safety and efficacy studies in HIV-1-infected patients. The effect of consumption of low-, moderate- and high-fat meals on steady-state raltegravir pharmacokinetics was assessed in healthy volunteers administered the 400 mg film-coated tablet. 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.

Administration of the chewable tablet with a high fat meal led to an average 6% decrease in AUC, 62% decrease in C_{max}, and 188% increase in C_{12hr} compared to administration in the fasted state. Administration of the chewable tablet with a high fat meal does not affect raltegravir pharmacokinetics to a clinically meaningful degree and the chewable tablet can be administered without regard to food.

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

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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 doses recommended for HIV-infected children and adolescents 2 to 18 years of age *[see Dosage and Administration (2.3)]* resulted in a pharmacokinetic profile of raltegravir similar to that observed in adults receiving 400 mg twice daily. Table 8 displays steady state pharmacokinetic parameters in the 400 mg film-coated tablet (6 to 18 years of age) and the chewable tablet (2 to less than 12 years of age).

Table 8: Raltegravir Steady State Pharmacokinetic Parameters Following Administration of Recommended Doses

Age	Formulation	Dose	N[†]	Geometric Mean *(%CV)* $AUC_{0\text{-}12hr}$ (μM•hr)	Geometric Mean *(%CV)* C_{12hr} (nM)
12 to 18 years	Film-coated tablet	400 mg twice daily, regardless of weight[‡]	11	15.7 (*98*%)	333 (*78*%)
6 to less than 12 years	Film-coated tablet	400 mg twice daily, for patients ≥25 kg	11	15.8 (*120*%)	246 (*221*%)
6 to less than 12 years	Chewable tablet	Weight based dosing, see Table 1	10	22.6 (*34*%)	130 (*88*%)
2 to less than 6 years	Chewable tablet	Weight based dosing, see Table 1	12	18.0 (*59*%)	71 (*55*%)

[†]Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose.
[‡]Patients in this age group received approximately 8 mg/kg/dose at time of intensive PK which met PK and safety targets. Based on review of the individual profiles and receipt of a mean dose of 390 mg, 400 mg twice daily was selected as the recommended dose for this age group.

The pharmacokinetics of raltegravir in children under 2 years of age has not been established.

Age

The effect of age (18 years and older) 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 in adults 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 adult 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 adult subjects with severe renal impairment.

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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 adult subjects with *28/*28 genotype (associated with reduced activity of UGT1A1) to 27 adult subjects with wild-type genotype, the geometric mean ratio (90% CI) of AUC was 1.41 (0.96, 2.09).

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

Table 9: Effect of Other Agents on the Pharmacokinetics of Raltegravir in Adults

Coadministered Drug	Coadministered Drug Dose/Schedule	Raltegravir Dose/Schedule	Ratio (90% Confidence Interval) of Raltegravir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00			
			n	C_{max}	AUC	C_{min}
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 (EC_{95}) of viral spread (relative to an untreated virus-infected culture) in human T-lymphoid cell cultures infected with the cell-line adapted HIV-1 variant H9IIIB. In addition, 5 clinical isolates of HIV-1 subtype B had EC_{95} values ranging from 9 to

19 nM in cultures of mitogen-activated human peripheral blood mononuclear cells. In a single-cycle infection assay, raltegravir inhibited infection of 23 HIV-1 isolates representing 5 non-B subtypes (A, C, D, F, and G) and 5 circulating recombinant forms (AE, AG, BF, BG, and cpx) with EC_{50} values ranging from 5 to 12 nM. Raltegravir also inhibited replication of an HIV-2 isolate when tested in CEMx174 cells (EC_{95} value = 6 nM). Additive to synergistic antiretroviral activity was observed when human T-lymphoid cells infected with the H9IIIB variant of HIV-1 were incubated with raltegravir in combination with non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, or nevirapine); nucleoside 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 Y143 (changed to C, H, or R) or Q148 (changed to H, K, or R) or N155 (changed to H) plus one or more additional substitutions (i.e., L74M, E92Q, Q95K/R, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230R, and D232N).

Treatment-Naïve Adult Subjects: By Week 96 in the STARTMRK trial, the primary raltegravir resistance-associated substitutions were observed in 4 (2 with Y143H/R and 2 with Q148H/R) of the 10 virologic failure subjects with evaluable genotypic data from paired baseline and raltegravir treatment-failure isolates.

Treatment-Experienced Adult Subjects: By Week 96 in the BENCHMRK trials, at least one of the primary raltegravir resistance-associated substitutions, Y143C/H/R, Q148H/K/R, and N155H, was observed in 76 of the 112 virologic failure subjects with evaluable genotypic data from paired baseline and raltegravir treatment-failure isolates. The emergence of the primary raltegravir resistance-associated substitutions was observed cumulatively in 70 subjects by Week 48 and 78 subjects by Week 96, 15.2% and 17% of the raltegravir recipients, respectively. Some (n=58) of those HIV-1 isolates harboring one or more of the primary raltegravir resistance-associated substitutions were evaluated for raltegravir susceptibility yielding a median decrease of 26.3-fold (mean 48.9 ± 44.8-fold decrease, ranging from 0.8- to 159-fold) compared to the wild-type reference.

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 96-week data from an ongoing, randomized, double-blind, active-control trial, STARTMRK (Protocol 021) in antiretroviral treatment-naïve HIV-1 infected adult subjects and 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.

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14.1 Treatment-Naïve Adult Subjects

STARTMRK (Protocol 021) is a Phase 3 study to evaluate the safety and antiretroviral activity of ISENTRESS 400 mg twice daily + emtricitabine (+) tenofovir versus efavirenz 600 mg at bedtime plus emtricitabine (+) tenofovir in treatment-naïve HIV-1-infected subjects with HIV-1 RNA >5000 copies/mL. Randomization was stratified by screening HIV-1 RNA level (≤50,000 copies/mL; and >50,000 copies/mL) and by hepatitis status.

Table 10 shows the demographic characteristics of subjects in the group receiving ISENTRESS 400 mg twice daily and subjects in the comparator group.

Table 10: Baseline Characteristics

Randomized Study Protocol 021	ISENTRESS 400 mg Twice Daily (N = 281)	Efavirenz 600 mg At Bedtime (N = 282)
Gender		
Male	81%	82%
Female	19%	18%
Race		
White	41%	44%
Black	12%	8%
Asian	13%	11%
Hispanic	21%	24%
Native American	<1%	<1%
Multiracial	12%	13%
Region		
Latin America	35%	34%
Southeast Asia	12%	10%
North America	29%	32%
EU/Australia	23%	23%
Age (years)		
18-64	99%	99%
≥65	1%	1%
Mean (SD)	38 (9)	37 (10)
Median (min, max)	37 (19 to 67)	36 (19 to 71)
CD4+ Cell Count (cells/microL)		
Mean (SD)	219 (124)	217 (134)
Median (min, max)	212 (1 to 620)	204 (4 to 807)
Plasma HIV-1 RNA (log_{10} copies/mL)		
Mean (SD)	5 (1)	5 (1)
Median (min, max)	5 (3 to 6)	5 (4 to 6)
Plasma HIV-1 RNA (copies/mL)		
Geometric Mean	103205	106215
Median (min, max)	114000 (400 to 750000)	104000 (4410 to 750000)
History of AIDS*		
Yes	19%	21%
Viral Subtype		
Clade B	78%	82%
Non-Clade B†	21%	17%
Baseline Plasma HIV-1 RNA		
≤100,000 copies/mL	45%	49%

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>100,000 copies/mL	55%	51%
Baseline CD4+ Cell Counts		
≤50 cells/mm^3	10%	11%
>50 cells/mm^3 and ≤200 cells/mm^3	37%	37%
>200 cells/mm^3	53%	51%
Hepatitis Status		
Hepatitis B or C Positive[‡]	6%	6%

*Includes additional subjects identified as having a history of AIDS.
[†]Non-Clade B Subtypes (# of subjects): Clade A (4), A/C (1), A/G (2), A1 (1), AE (29), AG (12), BF (6), C (37), D (2), F (2), F1 (5), G (2), Complex (3).
[‡]Evidence of hepatitis B surface antigen or evidence of HCV RNA by polymerase chain reaction (PCR) quantitative test for hepatitis C Virus.
Notes:
ISENTRESS and Efavirenz were administered with emtricitabine (+) tenofovir
N = Number of subjects in each group.

Week 96 outcomes from Protocol 021 are shown in Table 11.

Table 11: Virologic Outcomes of Randomized Treatment of Protocol 021 at 96 Weeks

	ISENTRESS 400 mg Twice Daily (N = 281)	**Efavirenz 600 mg At Bedtime (N = 282)**	**Difference (ISENTRESS – Efavirenz) (CI)**
Subjects with HIV-1 RNA less than 50 copies/mL	82%	78%	3.8% (-2.8%, 10.4%)
Virologic Failure*	9%	10%	
No virologic data at Week 96 Window			
Reasons			
Discontinued study due to AE or death[†]	4%	7%	
Discontinued study for other reasons[‡]	5%	4%	
Missing data during window but on study	1%	1%	

*Includes subjects who discontinued prior to Week 96 for lack of efficacy, subjects changed OBT due to lack of efficacy prior to Week 96, or subjects who are ≥50 copies in the 96 week window.
[†]Includes subjects who discontinued due to AE or Death at any time point from Day 1 through the Week 96 window if this resulted in no virologic data on treatment during Week 96 visit window.
[‡]Other includes: withdrew consent, loss to follow-up, moved etc., if the viral load at the time of discontinuation was <50 copies/mL.

The mean changes in CD4 count from baseline were 217 cells/mm^3 in the group receiving ISENTRESS 400 mg twice daily and 199 cells/mm^3 in the group receiving Efavirenz 600 mg at bedtime.

14.2 Treatment-Experienced Adult 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-1-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,

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OBT was selected by the investigator based on genotypic/phenotypic resistance testing and prior ART history.

Table 12 shows the demographic characteristics of subjects in the group receiving ISENTRESS 400 mg twice daily and subjects in the placebo group.

Table 12: 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	36%	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%	84%
Hepatitis B virus only	8%	3%
Hepatitis C virus only	8%	12%
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 13 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 13: 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		

Reference ID: 3061774

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%	18%
1	31%	30%
2	31%	28%
3 or more	18%	20%
Genotypic Sensitivity Score (GSS)†		
0	25%	27%
1	38%	40%
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 96 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 14.

Table 14: Virologic Outcomes of Randomized Treatment of Protocols 018 and 019 at 96 Weeks (Pooled Analysis)

	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	**Placebo + OBT (N = 237)**
Subjects with HIV-1 RNA less than 50 copies/mL	55%	27%
Virologic Failure*	35%	66%
No virologic data at Week 96 Window		
Reasons		
Discontinued study due to AE or death†	3%	3%
Discontinued study for other reasons‡	4%	4%
Missing data during window but on study	4%	<1%

*Includes subjects who switched to open-label raltegravir after Week 16 due to the protocol-defined virologic failure, subjects who discontinued prior to Week 96 for lack of efficacy, subjects changed OBT due to lack of efficacy prior to Week 96, or subjects who were ≥50 copies in the 96 week window.
†Includes subjects who discontinued due to AE or Death at any time point from Day 1 through the Week 96 window if this resulted in no virologic data on treatment during the Week 96 window.
‡Other includes: withdrew consent, loss to follow-up, moved etc., if the viral load at the time of discontinuation was <50 copies/mL.

The mean changes in CD4 count from baseline were 118 cells/mm^3 in the group receiving ISENTRESS 400 mg twice daily and 47 cells/mm^3 for the control group.

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 96 by baseline genotypic and phenotypic sensitivity score are shown in Table 15.

Table 15: Virologic Response at 96 Week Window by Baseline Genotypic/Phenotypic Sensitivity Score

	Percent with HIV-1 RNA <50 copies/mL At Week 96			
	n	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	n	Placebo + OBT (N = 237)
Phenotypic Sensitivity Score (PSS)*				
0	67	43	43	5
1	144	58	71	23
2	142	61	66	32
3 or more	85	48	48	42
Genotypic Sensitivity Score (GSS)*				
0	116	39	65	5
1	177	62	95	26
2	111	61	49	53
3 or more	51	49	23	35

*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.

14.3 Pediatric Subjects

IMPAACT P1066 is a Phase I/II open label multicenter trial to evaluate the pharmacokinetic profile, safety, tolerability, and efficacy of raltegravir in HIV infected children. This study enrolled 126 treatment experienced children and adolescents 2 to 18 years of age. Subjects were stratified by age, enrolling adolescents first and then successively younger children. Subjects received either the 400 mg film-coated tablet formulation (6 to 18 years of age) or the chewable tablet formulation (2 to less than 12 years of age). Raltegravir was administered with an optimized background regimen.

The initial dose finding stage included intensive pharmacokinetic evaluation. Dose selection was based upon achieving similar raltegravir plasma exposure and trough concentration as seen in adults, and acceptable short term safety. After dose selection, additional subjects were enrolled for evaluation of long term safety, tolerability and efficacy. Of the 126 subjects, 96 received the recommended dose of ISENTRESS *[see Dosage and Administration (2.3)]*.

These 96 subjects had a median age of 13 (range 2 to 18) years, were 51% Female, 34% Caucasian, and 59% Black. At baseline, mean plasma HIV-1 RNA was 4.3 $\log_{10}$ copies/mL, median CD4 cell count was 481 cells/mm^3 (range: 0 – 2361) and median CD4% was 23.3% (range: 0 – 44). Overall, 8% had baseline plasma HIV-1 RNA >100,000 copies/mL and 59% had a CDC HIV clinical classification of category B or C. Most subjects had previously used at least one NNRTI (78%) or one PI (83%).

Ninety-three (97%) subjects 2 to 18 years of age completed 24 weeks of treatment (3 discontinued due to non-compliance). At Week 24, 54% achieved HIV RNA <50 copies/mL; 72% achieved HIV RNA <400 copies/mL or ≥1 $\log_{10}$ HIV RNA drop from baseline. The mean CD4 count (percent) increase from baseline to Week 24 was 119 cells/mm^3 (3.8%).

Reference ID: 3061774

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

ISENTRESS tablets 100 mg are pale orange, oval-shaped, orange-banana flavored, chewable tablets scored on both sides and imprinted on one face with the Merck logo and "477" on opposite sides of the score. They are supplied as follows:

NDC 0006-0477-61 unit-of-use bottles of 60.

No. 3965

ISENTRESS tablets 25 mg are pale yellow, round, orange-banana flavored, chewable tablets with the Merck logo on one side and "473" on the other side. They are supplied as follows:

NDC 0006-0473-61 unit-of-use bottles of 60.

No. 3972

Storage and Handling

400 mg Film-coated Tablets and Chewable Tablets

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

Chewable Tablets

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

17 PATIENT COUNSELING INFORMATION

[See FDA-approved patient labeling (Patient Information).]

Patients should be informed that severe and potentially life-threatening rash has been reported. Patients should be advised to immediately contact their healthcare provider if they develop rash. Instruct patients to immediately stop taking ISENTRESS and other suspect agents, and seek medical attention if they develop a rash associated with any of the following symptoms as it may be a sign of a more serious reaction such as Stevens-Johnson syndrome, toxic epidermal necrolysis or severe hypersensitivity: fever, generally ill feeling, extreme tiredness, muscle or joint aches, blisters, oral lesions, eye inflammation, facial swelling, swelling of the eyes, lips, mouth, breathing difficulty, and/or signs and symptoms of liver problems (e.g., yellowing of the skin or whites of the eyes, dark or tea colored urine, pale colored stools/bowel movements, nausea, vomiting, loss of appetite, or pain, aching or sensitivity on the right side below the ribs). Patients should understand that if severe rash occurs, they will be closely monitored, laboratory tests will be ordered and appropriate therapy will be initiated. Patients should also be told that it is very important that they remain under a physician's care during treatment with ISENTRESS.

Patients should be informed that ISENTRESS is not a cure for HIV infection or AIDS. Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain on continuous HIV therapy to control HIV infection and decrease HIV-related illnesses. 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 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 or other injection equipment, or share personal items that can have blood or body fluids on them, such as toothbrushes and razor blades.

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 double their next dose or take more than the prescribed dose.

Patients should be informed that the chewable tablet forms can be chewed or swallowed whole, but the film-coated tablets should only be swallowed whole.

Reference ID: 3061774

Physicians should alert patients with phenylketonuria that ISENTRESS Chewable Tablets contain phenylalanine *[see Warnings and Precautions (5.3)].*

Physicians should instruct their patients to read the Patient Information 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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U.S. Patent Nos. US 7,169,780

Patient Information

ISENTRESS® (eye **sen** tris**)**
(raltegravir)
Film-Coated Tablets
ISENTRESS® (eye **sen** tris**)**
(raltegravir)
Chewable Tablets

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

What is ISENTRESS?

ISENTRESS is a prescription HIV medicine used with other HIV medicines to treat adults and children 2 years of age and older with human immunodeficiency virus (HIV-1) infection. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

When used with other HIV medicines, ISENTRESS may reduce the amount of HIV in your blood (called "viral load"). ISENTRESS may also help to increase the number of CD4 (T) cells in your blood which help fight off other infections. Reducing the amount of HIV and increasing the CD4 (T) cell count may improve your immune system. This may reduce your risk of death or infections that can happen when your immune system is weak (opportunistic infections).
It is not known if ISENTRESS is safe and effective in children under 2 years of age.

ISENTRESS does not cure HIV infection or AIDS. People taking ISENTRESS may still develop infections or other conditions associated with HIV infection. Some of these conditions are pneumonia, herpes virus infections, and Mycobacterium avium complex (MAC) infections.

Patients must stay on continuous HIV therapy to control infection and decrease HIV-related illnesses.

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

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

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

What should I tell my doctor before taking ISENTRESS?
Before taking ISENTRESS, tell your doctor if you:

- have liver problems.
- have phenylketonuria (PKU). ISENTRESS Chewable Tablets contain phenylalanine as part of the artificial sweetener, aspartame. The artificial sweetener may be harmful to people with PKU.
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if ISENTRESS can harm your unborn baby.

  Pregnancy Registry: You and your doctor will need to decide if taking ISENTRESS is right for you. If you take ISENTRESS while you are pregnant, talk to your doctor about how you can be

included in the Antiretroviral Pregnancy Registry. The purpose of the registry is to follow the health of you and your baby.

- are breastfeeding or plan to breastfeed.
  - Do not breastfeed if you are taking ISENTRESS. You should not breastfeed if you have HIV because of the risk of passing HIV to your baby.
  - Talk with your doctor about the best way to feed your baby.

Tell your doctor about all the medicines you take, including: prescription and non-prescription medicines, vitamins, and herbal supplements. Taking ISENTRESS and certain other medicines may affect each other causing serious side effects. ISENTRESS may affect the way other medicines work and other medicines may affect how ISENTRESS works.

Especially tell your doctor if you take:

- rifampin (Rifadin, Rifamate, Rifater, Rimactane), a medicine commonly used to treat tuberculosis.

Ask your doctor or pharmacist if you are not sure whether any of your medicines are included in the list above.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine. Do not start any new medicines while you are taking ISENTRESS without first talking with your doctor.

How should I take ISENTRESS?

- **Take ISENTRESS exactly as prescribed by your doctor.**
- You should stay under the care of your doctor while taking ISENTRESS.
- Do not change your dose of ISENTRESS, switch between the film-coated tablet and the chewable tablet or stop your treatment without talking with your doctor first.
- Take ISENTRESS by mouth, with or without food.
- If your child is taking ISENTRESS, your child's doctor will decide the right dose based on your child's age and weight.
- ISENTRESS Chewable Tablets may be chewed or swallowed whole.
- ISENTRESS Film-Coated Tablets must be swallowed whole.
- 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 double your next dose or take more than your prescribed dose.
- If you take too much ISENTRESS, call your doctor or go to the nearest emergency room right away.
- Do not run out of ISENTRESS. Get your ISENTRESS refilled from your doctor or pharmacy before you run out.

What are the possible side effects of ISENTRESS?

ISENTRESS can cause serious side effects including:

- **Serious skin reactions and allergic reactions.** Severe and life-threatening skin reactions and allergic reactions have been reported in some patients taking ISENTRESS. If you develop a rash with any of the following symptoms, stop using ISENTRESS and contact your doctor right away:
  - fever
  - generally ill feeling
  - extreme tiredness
  - muscle or joint aches

- blisters or sores in mouth
- blisters or peeling of the skin
- redness or swelling of the eyes
- swelling of the mouth or face
- problems breathing

Liver problems may be caused by an allergic reaction. Contact your doctor right away if you have any of the following signs or symptoms of liver problems:

- yellowing of the skin or whites of the eyes
- dark or tea colored urine
- pale colored stools/bowel movements
- nausea/vomiting
- loss of appetite
- pain, aching or tenderness on the right side below the ribs

- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your doctor right away if you start having new symptoms after starting your HIV medicine.
- **Phenylketonuria (PKU). ISENTRESS Chewable Tablets** contain phenylalanine as part of the artificial sweetener, aspartame. The artificial sweetener may be harmful to people with PKU.

The most common side effects of ISENTRESS include:

- headache
- trouble sleeping

Less common side effects include:

- nausea
- tiredness
- weakness
- stomach pain
- dizziness
- depression
- suicidal thoughts and actions

Tell your doctor right away if you get unexplained muscle pain, tenderness, or weakness while taking ISENTRESS. This may be a sign of a rare but serious muscle problem that can lead to kidney problems.

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

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

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ISENTRESS?

Film-Coated Tablets:

- Store ISENTRESS Film-Coated Tablets at room temperature between 68°F to 77°F (20°C to 25°C).

Chewable Tablets:

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

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

General information about 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 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?

ISENTRESS Film-Coated Tablets:

Active ingredient: 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.
The film coating contains: polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, red iron oxide and black iron oxide.

ISENTRESS Chewable Tablets:

Active ingredient: raltegravir
Inactive ingredients: hydroxypropyl cellulose, sucralose, saccharin sodium, sodium citrate dihydrate, mannitol, red iron oxide (100 mg tablet only), yellow iron oxide, monoammonium glycyrrhizinate, sorbitol, fructose, natural and artificial flavors (orange, banana, and masking that contains aspartame), crospovidone, magnesium stearate, sodium stearyl fumarate, ethylcellulose 20 cP, ammonium hydroxide, medium chain triglycerides, oleic acid, hypromellose 2910/6cP, PEG 400.

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

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Revised December 2011

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U.S. Patent Nos. US 7,169,780

Reference ID: 3061774

Isentress®
(raltegravir)
CHEWABLE Tablets

25 mg

NDC 0006-0473-61

Isentress®
(raltegravir)
CHEWABLE Tablets

25 mg

For Pediatric Patients 2 to less than 12 Years of Age

Phenylketonurics: *contains phenylalanine (a component of aspartame) 0.05 mg per 25 mg chewable tablet.*

Each tablet contains 27.16 mg raltegravir potassium, equivalent to 25 mg raltegravir.

Rx only

60 Tablets

Lot
Exp.

Isentress®
(raltegravir)
CHEWABLE Tablets

25 mg

Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Store in the original package with bottle cap tightly closed. Keep the desiccant in the bottle to protect product from moisture.

USUAL DOSAGE: See Package Insert.

Keep this and all drugs out of the reach of children.

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Manuf. by:
Patheon Pharmaceuticals, Inc.
Cincinnati, OH 45237, USA

6036403

Isentress®
(raltegravir)
CHEWABLE Tablets

25 mg

For Pediatric Patients 2 to less than 12 Years of Age

Each tablet contains 27.16 mg raltegravir potassium, equivalent to 25 mg raltegravir.

60 Tablets

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3965

NDC 0006-0473-61

Isentress®

(raltegravir) CHEWABLE Tablets

25 mg

For Pediatric Patients 2 to less than 12 Years of Age

Phenylketonurics: *contains phenylalanine (a component of aspartame) 0.05 mg per 25 mg chewable tablet.*

Rx only

60 Tablets

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Manuf. by:
Patheon Pharmaceuticals, Inc.
Cincinnati, OH 45237, USA

6036303

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N 3 0006-0473-61 6

Each tablet contains 27.16 mg raltegravir potassium, equivalent to 25 mg raltegravir.

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

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

USUAL DOSAGE: See Package Insert.

Keep this and all drugs out of the reach of children.

Lot

Exp.

Isentress®
(raltegravir)
CHEWABLE Tablets

100 mg

NDC 0006-0477-61

Isentress®
(raltegravir)
CHEWABLE Tablets

100 mg

For Pediatric Patients 2 to less than 12 Years of Age

Phenylketonurics: *contains phenylalanine (a component of aspartame) 0.10 mg per 100 mg chewable tablet.*

Each tablet contains 108.6 mg raltegravir potassium, equivalent to 100 mg raltegravir.

Rx only

60 Tablets

Lot
Exp.

Isentress®
(raltegravir)
CHEWABLE Tablets

100 mg

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Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Store in the original package with bottle cap tightly closed. Keep the desiccant in the bottle to protect product from moisture.

USUAL DOSAGE: See Package Insert.

Keep this and all drugs out of the reach of children.

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Manuf. by:
Patheon Pharmaceuticals, Inc.
Cincinnati, OH 45237, USA

N 3 0006-0477-61 4

6036503

Isentress®
(raltegravir)
CHEWABLE Tablets

100 mg

For Pediatric Patients 2 to less than 12 Years of Age

Each tablet contains 108.6 mg raltegravir potassium, equivalent to 100 mg raltegravir.

60 Tablets

NDC 0006-0477-61

Isentress®

(raltegravir) CHEWABLE Tablets

100 mg

For Pediatric Patients 2 to less than 12 Years of Age

Phenylketonurics: *contains phenylalanine (a component of aspartame) 0.10 mg per 100 mg chewable tablet.*

Rx only

60 Tablets

Each tablet contains 108.6 mg raltegravir potassium, equivalent to 100 mg raltegravir.

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

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

USUAL DOSAGE: See Package Insert.

Keep this and all drugs out of the reach of children.

N 3 0006-0477-61 4

Lot

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/s/

JEFFREY S MURRAY
12/21/2011