

## PRODUCT MONOGRAPH

**Pr ISENTRESS<sup>®</sup>**

raltegravir tablets

400 mg

(as raltegravir potassium)

Human immunodeficiency virus integrase strand transfer inhibitor

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Date of Revision:  
February 10, 2012

**Submission Control No: 149686**

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Pr **ISENTRESS<sup>®</sup>**

**raltegravir potassium**

## **PART I: HEALTH PROFESSIONAL INFORMATION**

### **SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
oral	Film coated tablets 400 mg raltegravir (as raltegravir potassium)	Lactose <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

### **INDICATIONS AND CLINICAL USE**

ISENTRESS<sup>®</sup> (raltegravir) is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients.

This indication is based on the evidence of efficacy of ISENTRESS<sup>®</sup> from the original analysis of 48 week data from 3 ongoing, randomized, double-blind, controlled trials.

Two of these studies, BENCHMRK 1 and BENCHMRK 2, were conducted in antiretroviral treatment-experienced HIV-1 infected adult patients through 96 weeks and one, STARTMRK, was conducted in treatment naïve adults through 156 weeks. These data continue to demonstrate the durable efficacy of ISENTRESS<sup>®</sup>.

### **CONTRAINDICATIONS**

ISENTRESS<sup>®</sup> is contraindicated in patients who are hypersensitive to any component of this medicine. For a complete listing of components, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

## WARNINGS AND PRECAUTIONS

### **Skin**

#### **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<sup>®</sup> 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<sup>®</sup> treatment or other suspect agents after the onset of severe rash may result in a life-threatening reaction.

### **General**

Caution should be used when coadministering ISENTRESS<sup>®</sup> with strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 (e.g., rifampin) due to reduced plasma concentrations of raltegravir (see DRUG INTERACTIONS).

### **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 jirovecii* pneumonia, and tuberculosis, or reactivation of varicella zoster virus), which may necessitate further evaluation and treatment.

### **Musculoskeletal**

Grade 2-4 creatine kinase laboratory abnormalities were observed in patients treated with raltegravir (see ADVERSE REACTIONS). Cases of myopathy and rhabdomyolysis have been reported with raltegravir. A relationship to raltegravir is not clear in a majority of these cases; however there have been isolated post-market reports of myopathy and rhabdomyolysis either with an association to raltegravir or where a relationship to raltegravir could not be ruled out. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions.

### **Special Populations**

**Pregnant Women:** Developmental toxicity studies were performed in rabbits (at doses up to 1000 mg/kg/day) and rats (at doses up to 600 mg/kg/day). The highest doses in these studies produced systemic exposures in these species approximately 3-to 4-fold above the exposure at the recommended human dose. No treatment related external, visceral, or skeletal changes were observed in rabbits. Treatment-related increases over controls in the incidence of supernumerary ribs were seen in rats at 600 mg/kg/day (exposures 4.4-fold above 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 rats, at a maternal dose of 600 mg/kg/day, 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. In rabbits, at a maternal dose of 1000 mg/kg/day, mean drug concentrations in fetal plasma were approximately 2% of the mean maternal concentration at both 1 and 24 hours postdose. Toxicokinetic studies demonstrated placental transfer of drug in both species.

There are no adequate and well-controlled studies in pregnant women; therefore, the safety of ISENTRESS<sup>®</sup> in pregnant women is not known. ISENTRESS<sup>®</sup>, like other antiretroviral agents, is not recommended for use in pregnancy.

### **Antiretroviral Pregnancy Registry**

To monitor maternal-fetal outcomes of pregnant patients exposed to ISENTRESS<sup>®</sup>, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-567-2594.

**Nursing Women:** It is not known whether raltegravir is secreted in human milk. However, raltegravir is secreted in the milk of lactating rats. In rats, at a maternal dose of 600 mg/kg/day, mean drug concentrations in milk were approximately 3-fold greater than in maternal plasma. Breast-feeding is not recommended while taking ISENTRESS<sup>®</sup>. In addition, it is recommended that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV.

**Pediatrics (<16 years of age):** Safety and effectiveness in pediatric patients less than 16 years of age have not been established.

**Geriatrics (≥65 years of age):** Clinical studies of ISENTRESS<sup>®</sup> did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. 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.

## **ADVERSE REACTIONS**

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

### **Treatment-Experienced Adverse Experiences**

The safety assessment of ISENTRESS<sup>®</sup> in treatment-experienced patients is based on the pooled safety data from the randomized clinical studies P018 and P019, reported using the recommended dose of ISENTRESS<sup>®</sup> 400 mg twice daily in combination with optimized background therapy (OBT) in 462 patients, in comparison to 237 patients taking placebo in combination with OBT.

During double-blind treatment, the total follow-up was 1051 patient-years in the group receiving ISENTRESS® 400 mg b.i.d. and 322 patient-years in the group receiving placebo.

For patients in the group receiving ISENTRESS® 400 mg twice daily + OBT (mean follow-up 118.7 weeks) and the comparator group placebo + OBT (mean follow-up 71.0 weeks) in the pooled analysis for studies P018 and P019, the most commonly reported adverse experiences (>10% in either group), of all intensities and regardless of causality were: diarrhea in 26.6% and 24.9%, nausea in 13.6% and 16.0%, headache in 12.1% and 13.5%, nasopharyngitis in 14.3% and 8.9%, fatigue in 12.1% and 5.9%, upper respiratory tract infection in 15.8% and 10.1%, bronchitis in 12.1% and 6.8%, pyrexia in 9.7% and 13.9%, vomiting in 8.9% and 11.0% of patients, respectively.

The following clinical adverse experiences below are regardless of causality and were considered by investigators to be of mild, moderate or severe intensity.

Clinical adverse events of mild, moderate or severe intensity occurring in ≥2% of treatment-experienced adult patients in either treatment group are presented in Table 1.

**Table 1 – Percentage of Patients with Adverse Experience of All Intensities and Regardless of Causality Occurring in ≥2% of Treatment-Experienced Adult Patients in Either Treatment Group**

System Organ Class, Preferred Term, %	Randomized Studies P018 and P019			
	ISENTRESS® 400 mg b.i.d. + OBT (N=462)		Placebo + OBT (N=237)	
	n	(%)	n	(%)
Patients With One Or More Adverse Experiences	433	(93.7)	213	(89.9)
Patients With No Adverse Experience	29	(6.3)	24	(10.1)
<b>Blood And Lymphatic System Disorders</b>	52	(11.3)	23	(9.7)
Anaemia	16	(3.5)	11	(4.6)
Lymphadenopathy	25	(5.4)	7	(3.0)
Neutropenia	6	(1.3)	5	(2.1)
<b>Cardiac Disorders</b>	31	(6.7)	9	(3.8)
<b>Ear And Labyrinth Disorders</b>	28	(6.1)	6	(2.5)
<b>Endocrine Disorders</b>	12	(2.6)	7	(3.0)
<b>Eye Disorders</b>	44	(9.5)	18	(7.6)
Conjunctivitis	16	(3.5)	1	(0.4)
<b>Gastrointestinal Disorders</b>	262	(56.7)	126	(53.2)
Abdominal Discomfort	6	(1.3)	6	(2.5)
Abdominal Distension	17	(3.7)	8	(3.4)
Abdominal Pain	35	(7.6)	13	(5.5)
Abdominal Pain Upper	21	(4.5)	11	(4.6)
Aphthous Stomatitis	6	(1.3)	5	(2.1)
Constipation	22	(4.8)	2	(0.8)
Diarrhea	123	(26.6)	59	(24.9)
Dyspepsia	15	(3.2)	3	(1.3)
Flatulence	19	(4.1)	8	(3.4)
Gastritis	11	(2.4)	8	(3.4)
Gastroesophageal Reflux Disease	10	(2.2)	3	(1.3)
Haemorrhoids	14	(3.0)	6	(2.5)
Nausea	63	(13.6)	38	(16.0)
Vomiting	41	(8.9)	26	(11.0)
<b>General Disorders And Administration Site Conditions</b>	194	(42.0)	94	(39.7)
Asthenia	20	(4.3)	9	(3.8)

System Organ Class, Preferred Term, %	Randomized Studies P018 and P019			
	ISENTRESS® 400 mg b.i.d. + OBT (N=462)		Placebo + OBT (N=237)	
	n	(%)	n	(%)
Chest Pain	17	(3.7)	4	(1.7)
Fatigue	56	(12.1)	14	(5.9)
Oedema Peripheral	16	(3.5)	7	(3.0)
Pyrexia	45	(9.7)	33	(13.9)
<b>Hepatobiliary Disorders</b>	19	(4.1)	11	(4.6)
<b>Immune System Disorders</b>	15	(3.2)	6	(2.5)
<b>Infections And Infestations</b>	328	(71.0)	153	(64.6)
Anogenital Warts	18	(3.9)	4	(1.7)
Bronchitis	56	(12.1)	16	(6.8)
Cellulitis	14	(3.0)	5	(2.1)
Folliculitis	16	(3.5)	2	(0.8)
Gastroenteritis	26	(5.6)	8	(3.4)
Genital Herpes	10	(2.2)	6	(2.5)
Herpes Simplex	16	(3.5)	5	(2.1)
Herpes Zoster	34	(7.4)	4	(1.7)
Influenza	33	(7.1)	10	(4.2)
Nasopharyngitis	66	(14.3)	21	(8.9)
Oesophageal Candidiasis	4	(0.9)	6	(2.5)
Onychomycosis	9	(1.9)	5	(2.1)
Oral Candidiasis	10	(2.2)	23	(9.7)
Pharyngitis	18	(3.9)	5	(2.1)
Pneumonia	33	(7.1)	12	(5.1)
Respiratory Tract Infection	19	(4.1)	1	(0.4)
Rhinitis	9	(1.9)	6	(2.5)
Sinusitis	32	(6.9)	10	(4.2)
Tooth Infection	4	(0.9)	5	(2.1)
Upper Respiratory Tract Infection	73	(15.8)	24	(10.1)
Urinary Tract Infection	15	(3.2)	12	(5.1)
<b>Injury, Poisoning and Procedural Complications</b>	84	(18.2)	34	(14.3)
<b>Investigations</b>	38	(8.2)	23	(9.7)
Weight Decreased	16	(3.5)	9	(3.8)
<b>Metabolism And Nutrition Disorders</b>	75	(16.2)	30	(12.7)
Anorexia	11	(2.4)	7	(3.0)
Decreased Appetite	12	(2.6)	3	(1.3)
Hyperlipidemia	12	(2.6)	1	(0.4)
<b>Musculoskeletal And Connective Tissue Disorders</b>	151	(32.7)	55	(23.2)
Arthralgia	30	(6.5)	10	(4.2)
Back Pain	33	(7.1)	10	(4.2)
Muscle Spasms	17	(3.7)	8	(3.4)
Musculoskeletal Pain	13	(2.8)	2	(0.8)
Myalgia	17	(3.7)	10	(4.2)
Pain In Extremity	31	(6.7)	10	(4.2)
<b>Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)</b>	70	(15.2)	19	(8.0)
Skin Papilloma	31	(6.7)	9	(3.8)
<b>Nervous System Disorders</b>	156	(33.8)	68	(28.7)
Dizziness	33	(7.1)	6	(2.5)
Headache	56	(12.1)	32	(13.5)
Hypoesthesia	10	(2.2)	4	(1.7)
Neuropathy Peripheral	21	(4.5)	9	(3.8)
Paresthesia	11	(2.4)	5	(2.1)
<b>Psychiatric Disorders</b>	80	(17.3)	42	(17.7)
Anxiety	16	(3.5)	9	(3.8)
Depression	18	(3.9)	12	(5.1)

System Organ Class, Preferred Term, %	Randomized Studies P018 and P019			
	ISENTRESS <sup>®</sup> 400 mg b.i.d. + OBT (N=462)		Placebo + OBT (N=237)	
	n	(%)	n	(%)
Insomnia	32	(6.9)	13	(5.5)
<b>Renal and Urinary Disorders</b>	54	(11.7)	21	(8.9)
<b>Reproductive System And Breast Disorders</b>	52	(11.3)	17	(7.2)
Erectile Dysfunction	11	(2.4)	2	(0.8)
<b>Respiratory, Thoracic And Mediastinal Disorders</b>	99	(21.4)	48	(20.3)
Asthma	8	(1.7)	5	(2.1)
Cough	32	(6.9)	14	(5.9)
Oropharyngeal Pain	15	(3.2)	9	(3.8)
Sinus Congestion	5	(1.1)	5	(2.1)
<b>Skin And Subcutaneous Tissue Disorders</b>	171	(37.0)	70	(29.5)
Eczema	8	(1.7)	8	(3.4)
Erythema	11	(2.4)	4	(1.7)
Lipodystrophy Acquired	16	(3.5)	5	(2.1)
Night Sweats	15	(3.2)	5	(2.1)
Pruritus	18	(3.9)	10	(4.2)
Rash	41	(8.9)	10	(4.2)
Skin Lesion	16	(3.5)	2	(0.8)
<b>Vascular Disorders</b>	54	(11.7)	20	(8.4)
Hypertension	35	(7.6)	9	(3.8)

**Less Common Clinical Trial Adverse Drug Reactions (<2%)**

Drug-related adverse experiences occurring in less than 2% of treatment-experienced patients (n=462) receiving ISENTRESS<sup>®</sup> + OBT and of moderate to severe intensity are listed below by system organ class:

**General Disorders and Administration Site Conditions:**

asthenia, fatigue, pyrexia, chills, face edema, peripheral edema

**Cardiac Disorders:**

ventricular extrasystoles

**Ear and Labyrinth Disorders:**

vertigo

**Eye Disorders:**

visual impairment

**Gastrointestinal Disorders:**

diarrhea, nausea, abdominal pain, abdominal distension, abdominal pain upper, vomiting, constipation, abdominal discomfort, dyspepsia, flatulence, gastritis, gastroesophageal reflux disease, dry mouth, eructation

**Hepatobiliary Disorders:**

hepatitis

**Immune System Disorders:**

drug hypersensitivity

**Infections and Infestations:**

herpes simplex, genital herpes, gastroenteritis

**Investigations:**

weight increased, weight decreased

**Metabolism and Nutrition Disorders:**

diabetes mellitus, dyslipidemia, increased appetite, decrease appetite

**Musculoskeletal and Connective Tissue Disorders:**

arthralgia, myalgia, back pain, musculoskeletal pain, osteoporosis, polyarthritis

**Nervous System Disorders:**

dizziness, neuropathy peripheral, paraesthesia, somnolence, tension headache, tremor

**Psychiatric Disorders:**

depression, insomnia, anxiety

**Renal and Urinary Disorders:**

nephritis, nephrolithiasis, nocturia, renal failure, tubulointerstitial nephritis

**Reproductive System and Breast Disorders:**

gynecomastia

**Respiratory, Thoracic and Mediastinal Disorders:**

epistaxis

**Skin and Subcutaneous Tissue Disorders:**

lipodystrophy acquired, rash, hyperhidrosis, dermatitis acneiform, erythema, lipohypertrophy, night sweats, rash macular, rash maculo-papular, rash pruritic, xeroderma, prurigo, lipatrophy, pruritus

**Discontinuations**

In the pooled analyses for studies P018 and P019, the rates of discontinuation of therapy due to adverse experiences were 4.5% in patients receiving ISENTRESS<sup>®</sup> + OBT and 5.5% in patients receiving placebo + OBT.

**Serious Events**

The following serious drug related adverse reactions were reported in clinical studies: gastritis, hepatitis, renal failure, genital herpes, accidental overdose.

**Laboratory Abnormalities**

The percentages of treatment experienced adult patients receiving either ISENTRESS<sup>®</sup> 400 mg twice daily or placebo (both with OBT) in P018 and P019 with selected Grades 2 to 4 laboratory abnormalities that represent a worsening from baseline are presented in Table 2.

**Table 2 – Selected Laboratory Abnormalities Reported in Treatment-Experienced Patients (≥2%)**

Laboratory Parameter Preferred Term	Limit	Grade	Randomized Studies P018 and P019	
			ISENTRESS® 400 mg b.i.d. (N=462) (%)	Placebo (N=237) (%)
<b>hematology laboratory test</b>				
absolute neutrophil count (10 <sup>9</sup> /L)	0.75–0.999	Grade 2	(4.1)	(5.9)
	0.50–0.749	Grade 3	(3.0)	(3.4)
hemoglobin (mmol/L)	1.16–1.31	Grade 2	(1.3)	(2.5)
platelet count (10 <sup>9</sup> /L)	50–99.999	Grade 2	(3.5)	(5.1)
<b>blood chemistry test</b>				
fasting (non-random) serum LDL-C (mmol/L)	4.13–4.90	Grade 2	(14.5)	(8.2)
	≥4.91	Grade 3	(6.5)	(6.5)
fasting (non-random) serum cholesterol (mmol/L)	6.20–7.77	Grade 2	(20.6)	(16.9)
	>7.77	Grade 3	(11.0)	(6.2)
fasting (non-random) serum triglyceride (mmol/L)	5.65–8.48	Grade 2	(9.6)	(10.3)
	8.49–13.56	Grade 3	(6.3)	(5.8)
	>13.56	Grade 4	(4.5)	(2.2)
fasting (non-random) serum glucose test (mmol/L)	6.95–13.88	Grade 2	(11.3)	(7.5)
	13.89–27.75	Grade 3	(2.9)	(1.3)
total serum bilirubin	1.6–2.5 x ULN	Grade 2	(5.6)	(3.0)
	2.6–5.0 x ULN	Grade 3	(3.0)	(2.5)
serum creatinine	1.4–1.8 x ULN	Grade 2	(3.3)	(3.0)
serum aspartate aminotransferase	2.6–5.0 x ULN	Grade 2	(9.5)	(8.5)
	5.1–10.0 x ULN	Grade 3	(4.3)	(3.0)
serum alanine aminotransferase	2.6–5.0 x ULN	Grade 2	(10.8)	(9.7)
	5.1–10.0 x ULN	Grade 3	(4.8)	(2.5)
serum alkaline phosphatase	2.6–5.0 x ULN	Grade 2	(2.2)	(0.4)
serum pancreatic amylase test	2.1–5.0 x ULN	Grade 3	(4.6)	(3.0)
serum lipase test	1.6–3.0 x ULN	Grade 2	(5.9)	(3.8)
	3.1–5.0 x ULN	Grade 3	(2.0)	(0.8)
serum creatine kinase	6.0–9.9 x ULN	Grade 2	(2.6)	(2.1)
	10.0–19.9 x ULN	Grade 3	(4.1)	(2.5)
	≥20.0 x ULN	Grade 4	(3.0)	(1.3)
ULN = Upper limit of normal range.				

**Treatment-Naïve Adverse Experiences**

The following safety assessment of ISENTRESS® in treatment-naïve patients is based on the randomized double-blind active controlled study of treatment-naïve patients, STARTMRK (Protocol 021) with ISENTRESS® 400 mg twice daily in combination with a fixed dose of emtricitabine 200 mg (+) tenofovir 245 mg, (N=281) versus efavirenz (EFV) 600 mg at bedtime in combination with emtricitabine (+) tenofovir (N=282). During double-blind treatment, the total follow-up for patients receiving ISENTRESS® 400 mg twice daily + emtricitabine (+)

tenofovir was 830 patient-years and 788 patient-years for patients receiving efavirenz 600 mg at bedtime + emtricitabine (+) tenofovir.

Numbers (%) of patients with clinical adverse experiences and with drug-related adverse experiences in the group receiving ISENTRESS<sup>®</sup>, were less frequent than in the group receiving efavirenz based on the nominal p-values (0.109 and <0.001 respectively).

The most commonly reported clinical adverse experiences (>10% in either group), of all intensities and regardless of causality in patients treated with ISENTRESS<sup>®</sup> + emtricitabine (+) tenofovir versus the patients treated with efavirenz + emtricitabine (+) tenofovir, were: diarrhea in 23.1 and 27.0%, nausea in 16.4% and 13.5%, vomiting in 7.5% and 10.3%, headache in 23.5% and 27.0%, fatigue in 8.2% and 12.8%, influenza in 9.3% and 12.8%, nasopharyngitis in 22.1% and 18.1%, upper respiratory tract infection in 18.9% and 18.4%, arthralgia in 7.8% and 11.0%, dizziness in 8.9% and 37.6%, abnormal dreams in 7.1% and 13.1%, insomnia in 13.9% and 12.4%, cough in 14.9% and 10.3%, pyrexia in 13.5% and 12.1% and rash in 7.5% and 13.1% of patients, respectively.

The following clinical adverse experiences below are regardless of causality and were considered by investigators to be of mild, moderate or severe intensity.

Clinical adverse events of mild, moderate or severe intensity occurring in  $\geq 2\%$  of treatment-naïve adult patients in either treatment group are presented in Table 3.

**Table 3 – Percentage of Patients with Adverse Experience of All Intensities and Regardless of Causality Occurring in ( $\geq 2\%$ ) of Treatment-Naïve Adult Patients in Either Treatment Group**

System Organ Class, Preferred Term, %	Randomized Study Protocol 021			
	ISENTRESS <sup>®</sup> 400 mg b.i.d. (N=281)		Efavirenz 600 mg q.h.s. (N=282)	
	n	(%)	n	(%)
Patients With One Or More Adverse Experiences	268	(95.4)	276	(97.9)
Patients With No Adverse Experience	13	(4.6)	6	(2.1)
<b>Blood And Lymphatic System Disorders</b>	19	(6.8)	9	(3.2)
Lymphadenopathy	11	(3.9)	4	(1.4)
<b>Cardiac Disorders</b>	13	(4.6)	14	(5.0)
<b>Ear And Labyrinth Disorders</b>	25	(8.9)	25	(8.9)
Vertigo	7	(2.5)	13	(4.6)
<b>Eye Disorders</b>	16	(5.7)	33	(11.7)
Conjunctivitis	6	(2.1)	11	(3.9)
<b>Gastrointestinal Disorders</b>	156	(55.5)	167	(59.2)
Abdominal Distension	9	(3.2)	6	(2.1)
Abdominal Pain	20	(7.1)	17	(6.0)
Abdominal Pain Upper	6	(2.1)	12	(4.3)
Constipation	3	(1.1)	6	(2.1)
Diarrhea	65	(23.1)	76	(27.0)
Dyspepsia	21	(7.5)	12	(4.3)
Flatulence	13	(4.6)	19	(6.7)
Gastritis	9	(3.2)	10	(3.5)
Gastroesophageal Reflux Disease	8	(2.8)	7	(2.5)
Hemorrhoids	8	(2.8)	6	(2.1)
Nausea	46	(16.4)	38	(13.5)
Toothache	6	(2.1)	4	(1.4)
Vomiting	21	(7.5)	29	(10.3)

System Organ Class, Preferred Term, %	Randomized Study Protocol 021			
	ISENTRESS® 400 mg b.i.d. (N=281)		Efavirenz 600 mg q.h.s. (N=282)	
	n	(%)	n	(%)
<b>General Disorders And Administration Site Conditions</b>	88	(31.3)	119	(42.2)
Asthenia	16	(5.7)	15	(5.3)
Chest Pain	6	(2.1)	12	(4.3)
Chills	6	(2.1)	7	(2.5)
Fatigue	23	(8.2)	36	(12.8)
Influenza Like Illness	5	(1.8)	10	(3.5)
Malaise	5	(1.8)	6	(2.1)
Oedema Peripheral	4	(1.4)	7	(2.5)
Pain	11	(3.9)	7	(2.5)
Pyrexia	38	(13.5)	34	(12.1)
<b>Hepatobiliary Disorders</b>	9	(3.2)	3	(1.1)
<b>Immune System Disorders</b>	12	(4.3)	10	(3.5)
<b>Infections And Infestations</b>	214	(76.2)	211	(74.8)
Acarodermatitis	7	(2.5)	5	(1.8)
Anogenital Warts	4	(1.4)	10	(3.5)
Body Tinea	3	(1.1)	7	(2.5)
Bronchitis	23	(8.2)	28	(9.9)
Ear Infection	6	(2.1)	5	(1.8)
Folliculitis	8	(2.8)	6	(2.1)
Gastroenteritis	10	(3.6)	15	(5.3)
Genital Herpes	11	(3.9)	12	(4.3)
Herpes Simplex	10	(3.6)	11	(3.9)
Herpes Zoster	14	(5.0)	14	(5.0)
Influenza	26	(9.3)	36	(12.8)
Nasopharyngitis	62	(22.1)	51	(18.1)
Onychomycosis	9	(3.2)	13	(4.6)
Oral Candidiasis	6	(2.1)	4	(1.4)
Oral Herpes	5	(1.8)	9	(3.2)
Otitis Media	5	(1.8)	6	(2.1)
Pharyngitis	23	(8.2)	23	(8.2)
Pneumonia	8	(2.8)	8	(2.8)
Respiratory Tract Infection	3	(1.1)	6	(2.1)
Rhinitis	8	(2.8)	9	(3.2)
Secondary Syphilis	6	(2.1)	3	(1.1)
Sinusitis	21	(7.5)	23	(8.2)
Syphilis	11	(3.9)	12	(4.3)
Tinea Pedis	7	(2.5)	6	(2.1)
Tonsillitis	9	(3.2)	7	(2.5)
Upper Respiratory Tract Infection	53	(18.9)	52	(18.4)
Urinary Tract Infection	5	(1.8)	9	(3.2)
<b>Injury, Poisoning And Procedural Complications</b>	48	(17.1)	53	(18.8)
Contusion	4	(1.4)	8	(2.8)
Muscle Strain	3	(1.1)	7	(2.5)
<b>Investigations</b>	17	(6.0)	24	(8.5)
Weight Decreased	6	(2.1)	10	(3.5)
<b>Metabolism And Nutrition Disorders</b>	30	(10.7)	44	(15.6)
Decreased Appetite	11	(3.9)	19	(6.7)
Hyperlipidemia	1	(0.4)	6	(2.1)
Hypertriglyceridemia	1	(0.4)	6	(2.1)
<b>Musculoskeletal And Connective Tissue Disorders</b>	82	(29.2)	97	(34.4)
Arthralgia	22	(7.8)	31	(11.0)
Back Pain	26	(9.3)	27	(9.6)
Muscle Spasms	2	(0.7)	7	(2.5)
Musculoskeletal Pain	4	(1.4)	6	(2.1)
Myalgia	9	(3.2)	14	(5.0)

System Organ Class, Preferred Term, %	Randomized Study Protocol 021			
	ISENTRESS® 400 mg b.i.d. (N=281)		Efavirenz 600 mg q.h.s. (N=282)	
	n	(%)	n	(%)
Neck Pain	8	(2.8)	2	(0.7)
Pain in Extremity	13	(4.6)	10	(3.5)
<b>Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)</b>	23	(8.2)	28	(9.9)
Kaposi's Sarcoma AIDS Related	1	(0.4)	6	(2.1)
Skin Papilloma	10	(3.6)	8	(2.8)
<b>Nervous System Disorders</b>	112	(39.9)	175	(62.1)
Dizziness	25	(8.9)	106	(37.6)
Headache	66	(23.5)	76	(27.0)
Migraine	7	(2.5)	3	(1.1)
Paraesthesia	7	(2.5)	8	(2.8)
Somnolence	3	(1.1)	22	(7.8)
<b>Psychiatric Disorders</b>	92	(32.7)	120	(42.6)
Abnormal Dreams	20	(7.1)	37	(13.1)
Anxiety	21	(7.5)	23	(8.2)
Depression	25	(8.9)	25	(8.9)
Insomnia	39	(13.9)	35	(12.4)
Nightmare	9	(3.2)	15	(5.3)
Sleep Disorder	1	(0.4)	6	(2.1)
<b>Renal And Urinary Disorders</b>	21	(7.5)	19	(6.7)
Dysuria	8	(2.8)	2	(0.7)
<b>Reproductive System And Breast Disorders</b>	31	(11.0)	34	(12.1)
Erectile Dysfunction	10	(3.6)	4	(1.4)
<b>Respiratory, Thoracic And Mediastinal Disorders</b>	97	(34.5)	80	(28.4)
Asthma	1	(0.4)	6	(2.1)
Cough	42	(14.9)	29	(10.3)
Dyspnea	5	(1.8)	8	(2.8)
Nasal Congestion	13	(4.6)	7	(2.5)
Oropharyngeal Pain	20	(7.1)	13	(4.6)
Productive Cough	8	(2.8)	3	(1.1)
Rhinitis Allergic	12	(4.3)	6	(2.1)
Rhinorrhea	10	(3.6)	10	(3.5)
Sinus Congestion	5	(1.8)	10	(3.5)
<b>Skin And Subcutaneous Tissue Disorders</b>	92	(32.7)	133	(47.2)
Acne	10	(3.6)	5	(1.8)
Dermatitis	8	(2.8)	8	(2.8)
Dermatitis Allergic	1	(0.4)	8	(2.8)
Eczema	7	(2.5)	5	(1.8)
Night Sweats	9	(3.2)	2	(0.7)
Pruritus	12	(4.3)	12	(4.3)
Rash	21	(7.5)	37	(13.1)
Rash Maculo-Papular	2	(0.7)	9	(3.2)
Rash Papular	5	(1.8)	7	(2.5)
Seborrheic Dermatitis	2	(0.7)	9	(3.2)
Skin Lesion	8	(2.8)	6	(2.1)
<b>Vascular Disorders</b>	20	(7.1)	24	(8.5)
Hypertension	15	(5.3)	16	(5.7)

### **Less Common Clinical Trial Adverse Drug Reactions (<2%)**

Drug-related clinical adverse reactions occurring in less than 2% of treatment-naïve patients (n=281) receiving ISENTRESS® + emtricitabine (+) tenofovir and of moderate to severe intensity are listed below by system organ class:

**Blood and Lymphatic System Disorders:**

lymph node pain, neutropenia, anemia, lymphadenopathy

**Ear and Labyrinth Disorders:**

tinnitus, vertigo

**Gastrointestinal Disorders:**

diarrhea, abdominal pain, vomiting, abdominal pain upper, dyspepsia, erosive duodenitis, gastroesophageal reflux disease, abdominal distension

**General Disorders and Administration Site Conditions:**

fatigue, asthenia, submandibular mass

**Hepatic/Biliary:**

Hepatitis alcoholic

**Immune System Disorders:**

immune reconstitution syndrome

**Infections and Infestations:**

herpes zoster, gastroenteritis, folliculitis, lymph node abscess

**Metabolism and Nutrition Disorders:**

decreased appetite, hypercholesterolemia

**Musculoskeletal and Connective Tissue Disorders:**

arthritis, neck pain

**Nervous System Disorders:**

dizziness, hypersomnia, somnolence, memory impairment

**Psychiatric Disorders:**

abnormal dreams, nightmare, anxiety, mental disorder, confusional state, depression, major depression

**Reproductive System and Breast Disorders:**

erectile dysfunction

**Renal and Urinary Disorders:**

nephrolithiasis

## Skin and Subcutaneous Tissue Disorders:

acne, alopecia, skin lesion, lipoatrophy

## Discontinuations

In the study P021, the rate of discontinuation of therapy due to adverse reactions (clinical and laboratory) was 4.6% in patients receiving ISENTRESS<sup>®</sup> + emtricitabine (+) tenofovir and 8.5% in patients receiving efavirenz + emtricitabine (+) tenofovir.

## Serious Events

The following serious drug-related adverse reactions were reported in the clinical study, P021: anemia, immune reconstitution syndrome, mental disorder, suicide attempt.

## CNS Events

In treatment naïve patients (P021) central nervous system (CNS) adverse reactions, as measured by proportion of patients with 1 or more CNS symptoms (described below) were reported significantly less frequently in the group receiving ISENTRESS<sup>®</sup> + emtricitabine (+) tenofovir as compared with the group receiving efavirenz + emtricitabine (+) tenofovir,  $p < 0.001$ ,  $< 0.001$ ,  $< 0.001$  and  $< 0.001$  for cumulative events through Weeks 8, 48, 96 and 156, respectively. In the group receiving ISENTRESS<sup>®</sup>, the percentage of patients with 1 or more CNS symptoms was 20.3% compared to 52.1% in the group receiving efavirenz by Week 8, and 26.3% compared to 58.5% by Week 48, and 28.8% compared to 60.6% by Week 96, and 31.3% compared to 62.4% by Week 156. CNS adverse reactions for this analysis were dizziness, insomnia, concentration impaired, somnolence, depression, nightmare, confusional state, suicidal ideation, nervous system disorder, psychotic disorder, abnormal dreams, suicide attempt, acute psychosis, delirium, depressed level of consciousness, hallucination, auditory hallucination, completed suicide and major depression.

**Table 4 – Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by System Organ Class–Nervous System Disorders and Psychiatric Disorders–Weeks 96 and 156 respectively**

	Randomized Study Protocol 021							
	ISENTRESS <sup>®</sup> 400 mg b.i.d.		Efavirenz 600 mg q.h.s.		ISENTRESS <sup>®</sup> 400 mg b.i.d.		Efavirenz 600 mg q.h.s.	
	(N=281)		(N=282)		(N=281)		(N=282)	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients With One Or More Adverse Experiences	81	(28.8)	171	(60.6)	88	(31.3)	176	(62.4)
Patients With No Adverse Experience	200	(71.2)	111	(39.4)	193	(68.7)	106	(37.6)
<b>Nervous System Disorders</b>	24	(8.5)	120	(42.6)	26	(9.3)	122	(43.3)
Dizziness	23	(8.2)	104	(36.9)	25	(8.9)	106	(37.6)
Nervous System Disorder	0	(0.0)	3	(1.1)	0	(0.0)	3	(1.1)
Somnolence	3	(1.1)	22	(7.8)	3	(1.1)	22	(7.8)
<b>Psychiatric Disorders</b>	66	(23.5)	86	(30.5)	74	(26.3)	92	(32.6)
Abnormal Dreams	21	(7.5)	37	(13.1)	20	(7.1)	37	(13.1)
Confusional State	1	(0.4)	1	(0.4)	1	(0.4)	1	(0.4)
Depressed Mood	2	(0.7)	5	(1.8)	2	(0.7)	5	(1.8)
Depression	17	(6.0)	17	(6.0)	24	(8.5)	23	(8.2)
Depressive Symptom	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.4)

	Randomized Study Protocol 021							
	ISENTRESS <sup>®</sup> 400 mg b.i.d.		Efavirenz 600 mg q.h.s.		ISENTRESS <sup>®</sup> 400 mg b.i.d.		Efavirenz 600 mg q.h.s.	
	(N=281)		(N=282)		(N=281)		(N=282)	
	n	(%)	n	(%)	n	(%)	n	(%)
Hallucination, Auditory	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.4)
Hallucination, Visual	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.4)
Insomnia	34	(12.1)	31	(11.0)	37	(13.2)	35	(12.4)
Major Depression	2	(0.7)	0	(0.0)	2	(0.7)	0	(0.0)
Nightmare	8	(2.8)	14	(5.0)	9	(3.2)	15	(5.3)
Psychotic Disorder	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)
Suicidal Behaviour	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.4)
Suicidal Ideation	0	(0.0)	1	(0.4)	1	(0.4)	1	(0.4)
Suicide Attempt	1	(0.4)	0	(0.0)	3	(1.1)	0	(0.0)

Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

### Laboratory Abnormalities

The percentages of treatment-naïve adult patients receiving either ISENTRESS<sup>®</sup> 400 mg twice daily or efavirenz (both with emtricitabine (+) tenofovir) in P021 with selected Grades 2 to 4 laboratory abnormalities that represent a worsening from baseline are presented in Table 5.

**Table 5 – Selected Laboratory Abnormalities Reported in Treatment-Naïve Patients (≥2%)**

Laboratory Parameter Preferred Term	Limit	Grade	Randomized Study P021	
			ISENTRESS <sup>®</sup> 400 mg b.i.d. (N=281) (%)	Efavirenz 600 mg q.h.s. (N=282) (%)
<b>hematology laboratory test</b>				
absolute neutrophil count (10 <sup>9</sup> /L)	0.75–0.999	Grade 2	( 3.2)	( 4.7)
	0.50–0.749	Grade 3	( 2.1)	( 1.1)
<b>blood chemistry test</b>				
fasting (non-random) serum LDL-C (mmol/L)	4.13–4.90	Grade 2	( 6.6)	(12.2)
	≥4.91	Grade 3	( 1.5)	( 7.3)
fasting (non-random) serum cholesterol (mmol/L)	6.20–7.77	Grade 2	( 8.0)	(17.2)
	>7.77	Grade 3	( 0.0)	( 4.5)
fasting (non-random) serum triglyceride (mmol/L)	5.65–8.48	Grade 2	( 1.1)	(4.5)
fasting (non-random) serum glucose test (mmol/L)	6.95–13.88	Grade 2	( 4.0)	( 5.3)
total serum bilirubin	1.6–2.5 x ULN	Grade 2	( 4.6)	( 0.0)
serum aspartate aminotransferase	2.6–5.0 x ULN	Grade 2	( 4.6)	( 6.8)
	5.1–10.0 x ULN	Grade 3	( 2.8)	( 2.5)
serum alanine aminotransferase	2.6–5.0 x ULN	Grade 2	(9.6)	( 9.3)
serum alkaline phosphatase (IU(alk phos)/L)	2.6–5.0 x ULN	Grade 2	( 1.1)	( 2.9)

ULN = Upper limit of normal range

Through 144 weeks of therapy, ISENTRESS<sup>®</sup> demonstrated minimal effects on serum lipids with small increases in total and LDL cholesterol and a decrease in serum triglycerides. The group treated with efavirenz had a significantly higher mean change from baseline in total cholesterol,

triglycerides, non-HDL-C, and LDL-C. Modest increases in HDL were observed in both groups, significantly higher for efavirenz.

### **Selected Adverse Experiences**

#### **Additional neoplasms, benign, malignant and unspecified**

Cancers were observed in treatment-experienced patients who initiated ISENTRESS<sup>®</sup> or placebo, both with OBT and in treatment-naïve patients who initiated ISENTRESS<sup>®</sup> 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+ cell counts below 50 cells/mm<sup>3</sup> and most had prior AIDS diagnoses). The risk of developing cancer in these studies was similar in the group receiving ISENTRESS<sup>®</sup> and the group receiving the comparator.

#### **Additional musculoskeletal and connective tissue disorders**

Grade 2-4 creatine kinase laboratory abnormalities were observed in patients treated with ISENTRESS<sup>®</sup> (see Table 2). 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.

#### **Rash**

Rash occurred more commonly in treatment-experienced patients receiving regimens containing ISENTRESS<sup>®</sup> + darunavir compared to patients receiving ISENTRESS<sup>®</sup> without darunavir or darunavir without ISENTRESS<sup>®</sup>. 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.

### **Patients with Co-existing Conditions**

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

In Phase III studies, treatment-experienced patients (N=114/699 or 16%) and treatment-naïve patients (N=34/563 or 6%) with chronic (but not acute) active hepatitis B and/or hepatitis C 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<sup>®</sup> in patients with hepatitis B and/or hepatitis C virus co-infection was similar to that in patients without hepatitis B and/or hepatitis C virus co-infection, although the rates of AST and ALT abnormalities were somewhat higher in the subgroup with hepatitis B and/or hepatitis C virus co-infection for both treatment groups. In treatment-experienced patients, Grade 2 or higher laboratory abnormalities that represent a worsening Grade from baseline of AST, ALT or total bilirubin occurred in 30%, 38% and 14%, respectively, of co-infected patients treated with ISENTRESS<sup>®</sup> as compared to 11%, 13% and 9% of all other patients treated with ISENTRESS<sup>®</sup>. In treatment-naïve patients (P021), Grade 2 or higher laboratory abnormalities that represent a worsening Grade from baseline of AST, ALT or total bilirubin occurred in 17%, 33% and 17%, respectively, of co-infected patients treated with ISENTRESS<sup>®</sup> as compared to 8%, 10% and 5% of all other patients treated with ISENTRESS<sup>®</sup>.

### **Post-Market Adverse Drug Reactions**

The following additional adverse experiences have been reported in postmarketed experience without regard to causality:

**Blood and Lymphatic System Disorders:**

thrombocytopenia

**Musculoskeletal and Connective Tissue Disorders:**

Rhabdomyolysis

**Nervous System Disorders:**

cerebellar ataxia

**Psychiatric Disorders:**

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

**Skin and Subcutaneous Tissue Disorders:**

Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS)

**DRUG INTERACTIONS****Overview**

Raltegravir is not a substrate of cytochrome P450 (CYP) enzymes and 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 meaningful 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<sup>®</sup> 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).

Based on *in vivo* and *in vitro* studies, raltegravir is eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway.

Coadministration of ISENTRESS<sup>®</sup> with drugs that are potent inducers of UGT1A1, such as rifampin (an inducer of numerous drug metabolizing enzymes), reduces plasma concentrations of ISENTRESS<sup>®</sup>. Caution should be used when coadministering ISENTRESS<sup>®</sup> with rifampin or other strong inducers of UGT1A1. (See WARNINGS AND PRECAUTIONS). The impact of other potent inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown. Other less potent inducers (e.g., efavirenz, nevirapine, rifabutin, glucocorticoids, St. John's Wort, pioglitazone) may be used with the recommended dose of ISENTRESS<sup>®</sup>.

Coadministration of ISENTRESS<sup>®</sup> with drugs that are known to be potent UGT1A1 inhibitors (e.g., atazanavir; see table 6) increases plasma levels of ISENTRESS<sup>®</sup>. However, the degree of increase is modest and combination therapy with these inhibitors was well tolerated in the clinical studies such that no dose adjustment is required.

**Drug-Drug Interactions**

**Effect of Raltegravir on the Pharmacokinetics of Other Agents**

In drug interaction studies, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of the following: hormonal contraceptives, methadone, tenofovir, midazolam, lamivudine, etravirine, and darunavir/ritonavir. In a multiple-dose drug interaction study, ethinyl estradiol and norelgestromin AUC values were 98% and 114%, respectively, when coadministered with raltegravir as compared to when administered without raltegravir. In a multiple-dose drug interaction study, tenofovir AUC and trough concentrations when coadministered with raltegravir were 90% and 87% of values obtained with tenofovir monotherapy. In another drug interaction study, midazolam AUC from coadministration was 92% of the value obtained with midazolam alone. In a Phase II study, lamivudine pharmacokinetics were similar in patients receiving combinations with raltegravir versus with efavirenz.

**Effect of Other Agents on the Pharmacokinetics of Raltegravir**

In drug interaction studies, atazanavir, efavirenz, ritonavir, tenofovir, and tipranavir/ritonavir did not have a clinically meaningful effect on the pharmacokinetics of raltegravir. Rifampin, which is a strong inducer of drug metabolizing enzymes, caused a decrease in trough levels of raltegravir. Drug interactions are further described below in Table 6.

**Table 6 – Effect of Other Agents on the Pharmacokinetics of Raltegravir**

Coadministered Drug	Coadministered Drug Dose/Schedule	Raltegravir Dose/Schedule	Clinical Comment	Ratio (90% Confidence Interval) of Raltegravir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00			
				n	C <sub>max</sub>	AUC	C <sub>min</sub>
Protease Inhibitors:							
atazanavir	400 mg daily	100 mg single dose	No dosage adjustment required	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	No dosage adjustment required	10	1.24 (0.87, 1.77)	1.41 (1.12, 1.78)	1.77 (1.39, 2.25)
ritonavir	100 mg twice daily	400 mg single dose	No dosage adjustment required	10	0.76 (0.55, 1.04)	0.84 (0.70, 1.01)	0.99 (0.70, 1.40)
tipranavir/ritonavir	500 mg/200 mg twice daily	400 mg twice daily	No dosage adjustment required	15 (14 for C <sub>min</sub> )	0.82 (0.46, 1.46)	0.76 (0.49, 1.19)	0.45 (0.31, 0.66)
Non-Nucleoside Reverse Transcriptase Inhibitor:							

Coadministered Drug	Coadministered Drug Dose/Schedule	Raltegravir Dose/Schedule	Clinical Comment	Ratio (90% Confidence Interval) of Raltegravir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00			
				n	C <sub>max</sub>	AUC	C <sub>min</sub>
efavirenz	600 mg daily	400 mg single dose	No dosage adjustment required	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	No dosage adjustment required	19	0.89 (0.68, 1.15)	0.90 (0.68, 1.18)	0.66 (0.34, 1.26)
Nucleotide Analog Reverse Transcriptase Inhibitor:							
tenofovir	300 mg daily	400 mg twice daily	No dosage adjustment required	9	1.64 (1.16, 2.32)	1.49 (1.15, 1.94)	1.03 (0.73, 1.45)
Antibacterial: rifampin	600 mg daily	400 mg single dose	Use with caution (see Warnings and Precautions)	9	0.62 (0.37, 1.04)	0.60 (0.39, 0.91)	0.39 (0.30, 0.51)
rifampin	600 mg daily	800 mg twice daily		14	1.62* (1.12, 2.33)	1.27* (0.94, 1.71)	0.47* (0.36, 0.61)

\* Compared to 400 mg twice daily administered alone.

Rash occurred frequently in healthy subjects in a drug-interaction study when darunavir/ritonavir was co-administered with ISENTRESS<sup>®</sup>. Darunavir/ritonavir should be co-administered with ISENTRESS<sup>®</sup> only if the benefits outweigh the risks.

## DOSAGE AND ADMINISTRATION

### Recommended Dose and Dosage Adjustment

For the treatment of adult patients with HIV-1 infection the dosage of ISENTRESS<sup>®</sup> is 400 mg administered orally, twice daily with or without food. ISENTRESS<sup>®</sup> is to be given in a combination regimen with other antiretroviral agents.

### Hepatic/biliary/Pancreatic

There were no clinically important pharmacokinetic differences between patients with moderate hepatic insufficiency and healthy subjects. No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency. The effect of severe hepatic insufficiency on the pharmacokinetics of raltegravir has not been studied.

### Renal

There were no clinically important pharmacokinetic differences between patients with severe renal insufficiency and healthy subjects. No dosage adjustment is necessary.

## OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Activated charcoal may be administered to aid in the removal of unabsorbed drug. The extent to which ISENTRESS<sup>®</sup> may be dialyzable is unknown.

No specific information is available on the treatment of overdose with ISENTRESS<sup>®</sup>. Doses as high as 1600 mg single dose and 800 mg b.i.d. multiple doses were studied in Phase I without evidence of toxicity. Occasional doses of 1800 mg per day were taken in Phase II/III studies without evidence of toxicity. Based upon available data, raltegravir appears to be well tolerated at doses up to 800 mg b.i.d. and when administered with drugs that increase exposure by 50-70% (such as tenofovir and atazanavir).

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

ISENTRESS<sup>®</sup> contains raltegravir, a human immunodeficiency virus integrase strand transfer inhibitor. Raltegravir inhibits the catalytic activity of HIV integrase, an HIV-encoded enzyme that is required for viral replication. Inhibition of integrase prevents the covalent insertion, or integration, of the HIV genome into the host cell genome during the early phase of infection. HIV genomes that fail to integrate cannot direct the production of new infectious viral particles, so inhibiting integration prevents propagation of the viral infection. Raltegravir did not significantly inhibit human phosphoryltransferases including DNA polymerases  $\alpha$ ,  $\beta$ , and  $\gamma$ .

### Pharmacodynamics

#### **Microbiology**

Raltegravir at concentrations of  $31 \pm 20$  nM resulted in 95% inhibition (IC<sub>95</sub>) 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 from 5 non-B subtypes, and isolates resistant to reverse transcriptase inhibitors and protease inhibitors. In a single-cycle infection assay, raltegravir inhibited infection of 23 HIV isolates representing 5 non-B subtypes and 5 circulating recombinant forms with IC<sub>50</sub> values ranging from 5 to 12 nM. Raltegravir also inhibited replication of an HIV-2 isolate when tested in CEMx174 cells (IC<sub>95</sub> = 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 nucleoside analog reverse transcriptase inhibitors (zidovudine, zalcitabine, stavudine, abacavir, tenofovir, didanosine, or lamivudine); non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine, or delavirdine); protease inhibitors (indinavir, saquinavir, ritonavir, amprenavir, lopinavir, nelfinavir, or atazanavir); or the entry inhibitor enfuvirtide.

## **Drug Resistance**

The mutations observed in HIV-1 integrase that contributed to raltegravir resistance (evolved either *in vitro* or in patients treated with raltegravir) generally included a 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 mutations (e.g., L74I/M, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230R, and D232N).

Recombinant viruses containing a single primary mutation (Q148H, K or R, or N155H) displayed decreased replication capacity and reduced susceptibility to raltegravir *in vitro*. Secondary mutations further decreased susceptibility to raltegravir and sometimes acted as compensatory mutations for viral replication capacity.

### Treatment-Naïve 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 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.

## **Cardiac Electrophysiology**

In a randomized, placebo-controlled, crossover study, 31 healthy subjects were administered a single oral supratherapeutic dose of raltegravir 1600 mg and placebo. There was no effect on the QTc interval. Peak raltegravir plasma concentrations were approximately 4-fold higher than the peak concentrations following a 400-mg dose.

## Pharmacokinetics

**Table 7 – Comparison of Raltegravir Plasma Pharmacokinetics in Healthy Adult Male and Female Subjects Administered Multiple Oral Doses of 400 mg Twice Daily Raltegravir in the Fasted State and After a Specified Meal**

	AUC <sub>0-12hr</sub> ( $\mu\text{M}\cdot\text{hr}$ ) <sup>a</sup>	C <sub>max</sub> ( $\mu\text{M}$ ) <sup>a</sup>	C <sub>12hr</sub> (nM) <sup>a</sup>	T <sub>max</sub> (hr) <sup>b</sup>
<b>Fasted</b>	10.0	2.71	110	3.0
<b>Low-Fat Meal</b>	5.38	1.31	94	3.0
<b>Moderate-Fat Meal</b>	11.3	2.85	182	4.0
<b>High-Fat Meal</b>	21.2	5.32	453	4.0

<sup>a</sup>Geometric Mean

<sup>b</sup>Median

**Absorption:** Raltegravir is rapidly absorbed with a T<sub>max</sub> of approximately 3 hours postdose in the fasted state. Raltegravir AUC and C<sub>max</sub> increase dose proportionally over the dose range 100 mg to 1600 mg. Raltegravir C<sub>12hr</sub> increases dose proportionally over the dose range of 100 mg 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 rapidly, within approximately the first 2 days of dosing. There is little to no accumulation in AUC and C<sub>max</sub> and evidence of slight accumulation in C<sub>12hr</sub>. The absolute bioavailability of raltegravir has not been established.

In patients on 400 mg twice daily monotherapy, raltegravir drug exposures were characterized by a geometric mean AUC<sub>0-12hr</sub> of 14.3  $\mu\text{M}\cdot\text{hr}$  and C<sub>12hr</sub> of 142 nM.

### **Effect of Food on Oral Absorption**

ISENTRESS<sup>®</sup> 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 did not affect raltegravir AUC to a clinically meaningful degree with an increase of 13% relative to fasting. Raltegravir C<sub>12 hr</sub> was 66% higher and C<sub>max</sub> was 5% higher following a moderate-fat meal compared to fasting. Administration of raltegravir following a high-fat meal increased AUC and C<sub>max</sub> by approximately 2-fold and increased C<sub>12 hr</sub> by 4.1-fold. Administration of raltegravir following a low-fat meal decreased AUC and C<sub>max</sub> by 46% and 52%, respectively; C<sub>12 hr</sub> 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  $\mu\text{M}$ .

**Metabolism and Excretion:** The apparent terminal half-life of raltegravir is approximately 9 hours, with a shorter  $\alpha$ -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 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 and Conditions**

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

**Geriatrics:** The effect of age on the pharmacokinetics of raltegravir was evaluated in the composite analysis and the population pharmacokinetic (PK) analysis. There was no clinically meaningful effect of age on raltegravir pharmacokinetics. No dosage adjustment is necessary.

**Gender:** A study of the pharmacokinetics of raltegravir was performed in young healthy males and females. Additionally, the effect of gender was evaluated in a composite analysis of pharmacokinetic data from 103 healthy subjects and 28 HIV patients receiving raltegravir monotherapy with fasted administration. The effect of gender was also evaluated in a population PK analysis of concentration data from 80 healthy subjects and HIV patients receiving raltegravir alone or in combination with other drugs and in fasted and fed conditions. There were no clinically important pharmacokinetic differences due to gender. No dosage adjustment is necessary.

**Race:** The effect of race on the pharmacokinetics of raltegravir was evaluated in the composite analysis. There was no clinically meaningful effect of race on raltegravir pharmacokinetics. No dosage adjustment is necessary.

**Body Mass Index (BMI):** The composite analysis assessed the effect of BMI on the pharmacokinetics of raltegravir. There was no clinically meaningful effect of BMI on raltegravir pharmacokinetics. Additionally, no clinically meaningful effect of body weight on raltegravir pharmacokinetics was identified in the population PK analysis. No dosage adjustment is necessary.

**Hepatic Insufficiency:** Raltegravir is eliminated primarily by glucuronidation in the liver. A study of the pharmacokinetics of raltegravir was performed in patients with moderate hepatic insufficiency. Additionally, hepatic insufficiency was evaluated in the composite pharmacokinetic analysis. There were no clinically important pharmacokinetic differences between patients with moderate hepatic insufficiency and healthy subjects. No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency. The effect of severe hepatic insufficiency on the pharmacokinetics of raltegravir has not been studied.

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

**Genetic 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).

## **STORAGE AND STABILITY**

Store at room temperature (15°C–30°C).

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

### **Dosage Forms**

ISENTRESS<sup>®</sup> film-coated 400-mg tablets are pink, oval-shaped, with 227 on one side. They are supplied as unit-of-use bottles of 60.

### **Composition**

Each film-coated tablet of ISENTRESS<sup>®</sup> 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: calcium phosphate dibasic anhydrous, hypromellose 2208, lactose monohydrate, magnesium stearate, microcrystalline cellulose, poloxamer 407 (contains 0.01% butylated hydroxytoluene as antioxidant), sodium stearyl fumarate. In addition, the film coating contains the following inactive ingredients: black iron oxide and red iron oxide, polyethylene glycol 3350, polyvinyl alcohol, talc and titanium dioxide.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

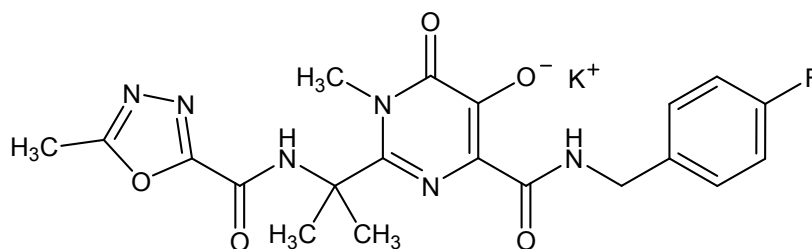
Proper name: raltegravir potassium

Chemical name: *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

Molecular formula: C<sub>20</sub>H<sub>20</sub>FKN<sub>6</sub>O<sub>5</sub>

Molecular mass: 482.51

Structural formula:



Physicochemical properties:

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.

**Table 8 – Solubility of Raltegravir (potassium salt) in Aqueous Solutions**

pH	Raltegravir Conc (mg/mL)	Final pH
2 (0.01N HCl)	0.01	2.4
4 (50mM Na citrate)	0.01	4.4
5 (50mM Na citrate)	0.03	5.4
6 (50mM Na phosphate)	0.02	6.1
7 (50mM Na phosphate)	0.48	6.8
8 (50mM Na phosphate)	>30	-
10 (0.01N NaOH)	>30	-
Water	70.79	-

## CLINICAL TRIALS

### Description of Clinical Trials

This indication is based on the evidence of durable efficacy of ISENTRESS<sup>®</sup> from the original analysis of 48 week data from 3 ongoing, randomized, double-blind, controlled trials.

Two of these studies, BENCHMRK 1 and BENCHMRK 2, were conducted in antiretroviral treatment-experienced HIV-1 infected adult patients through 96 weeks and one, STARTMRK, was conducted in treatment naïve adults through 156 weeks. These data continue to demonstrate the durable efficacy of ISENTRESS<sup>®</sup>.

### Treatment-Experienced Patients

BENCHMRK 1 and BENCHMRK 2 are Phase III studies to evaluate the safety and antiretroviral activity of ISENTRESS<sup>®</sup> 400 mg b.i.d. in combination with an optimized background therapy (OBT), versus OBT alone, in HIV-infected patients, 16 years or older, with documented resistance to at least 1 drug in each of 3 classes (NRTIs, NNRTIs, 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 9 shows the demographic characteristics between patients in the group receiving ISENTRESS<sup>®</sup> 400 mg b.i.d. and patients in the group receiving placebo.

**Table 9 – Baseline Population Characteristics**

<b>BENCHMRK 1 and 2 Pooled</b>	<b>ISENTRRESS® 400 mg b.i.d. + OBT (N=462)</b>	<b>Placebo + OBT (N=237)</b>
<b>Gender n (%)</b>		
Male	405 (87.7)	210 (88.6)
Female	57 (12.3)	27 (11.4)
<b>Race n (%)</b>		
White	301 (65.2)	173 (73.0)
Black	65 (14.1)	26 (11.0)
Asian	16 ( 3.5)	6 ( 2.5)
Hispanic	53 (11.5)	19 ( 8.0)
Others	27 ( 5.8)	13 ( 5.5)
<b>Age (years)</b>		
Median (min, max)	45.0 (16 to 74)	45.0 (17 to 70)
<b>CD4 Cell Count</b>		
Median (min, max), cells/mm <sup>3</sup>	119 (1 to 792)	123 (0 to 759)
≤50 cells/mm <sup>3</sup> , n (%)	146 (31.6)	78 (32.9)
>50 and ≤200 cells/mm <sup>3</sup> , n (%)	173 (37.4)	85 (35.9)
<b>Plasma HIV RNA</b>		
Median (min, max), log <sub>10</sub> copies/mL	4.8 (2.3 to 5.9)	4.7 (2.3 to 5.9)
≥100,000 copies/mL, n (%)	165 (35.7)	78 (32.9)
<b>History of AIDS n (%)</b>		
Yes	427 (92.4)	215 (90.7)
<b>Prior Use of ART, Median (1<sup>st</sup> Quartile, 3<sup>rd</sup> Quartile)</b>		
Years of ART Use	10.1 (7.3 to 12.1)	10.2 (7.9 to 12.4)
Number of ART	12.0 (9 to 15)	12.0 (9 to 14)
<b>Hepatitis Co-infection* n (%)</b>		
No Hepatitis B or C	385 (83.3)	200 (84.4)
Hepatitis B only	36 ( 7.8)	7 ( 3.0)
Hepatitis C only	37 ( 8.0)	28 (11.8)
Co-infection of Hepatitis B and C	4 ( 0.9)	2 ( 0.8)
<b>Stratum n (%)</b>		
Enfuvirtide in OBT	175 (37.9)	89 (37.6)
Resistant to ≥2 PI	447 (96.8)	226 (95.4)
*Hepatitis B surface antigen positive or hepatitis C antibody positive.		

Table 10 compares the characteristics of optimized background therapy at baseline in the group receiving ISENTRESS® 400 mg b.i.d. and patients in the control group.

**Table 10 – Characteristics of Optimized Background Therapy at Baseline**

<b>BENCHMRK 1 and 2 Pooled</b>	<b>ISENTRESS<sup>®</sup> 400 mg b.i.d. + OBT (N=462)</b>	<b>Placebo + OBT (N=237)</b>
<b>Number of ARTs in OBT</b>		
Median (min, max)	4 (1 to 7)	4 (2 to 7)
<b>Number of Active PI in OBT by Phenotypic Resistance Test<sup>*</sup></b>		
0	165 (35.7)	96 (40.5)
1 or more	278 (60.2)	137 (57.8)
<b>Phenotypic Sensitivity Score (PSS)<sup>†</sup></b>		
0	67 (14.5)	43 (18.1)
1	144 (31.2)	71 (30.0)
2	142 (30.7)	66 (27.8)
3 or more	85 (18.4)	48 (20.3)
<b>Genotypic Sensitivity Score (GSS)<sup>†</sup></b>		
0	116 (25.1)	65 (27.4)
1	177 (38.3)	95 (40.1)
2	111 (24.0)	49 (20.7)
3 or more	51 (11.0)	23 (9.7)
<p><sup>*</sup> Darunavir use in OBT in darunavir naïve patients was counted as one active PI.</p> <p><sup>†</sup> The Phenotypic Sensitivity Score (PSS) and the Genotypic Sensitivity Score (GSS) were defined as the total oral ARTs in OBT to which a patient's viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide-naïve patients was counted as one active drug in OBT in the GSS and PSS. Similarly, darunavir use in OBT in darunavir-naïve patients was counted as one active drug in OBT.</p>		

Week 96 outcomes for the 699 patients randomized and treated with the recommended dose of ISENTRESS<sup>®</sup> 400 mg b.i.d. or comparator in the pooled BENCHMRK 1 and 2 studies are shown in Table 11.

**Table 11 – Virologic Outcomes of Randomized Treatment of Protocols 018 and 019 at 96 Weeks (Pooled Analysis)**

	<b>ISENTRESS® 400 mg Twice Daily +OBT (N=462)</b>	<b>Placebo + OBT (N=237)</b>
<b>Subjects with HIV-1 RNA less than 50 copies/mL</b>	55%	27%
<b>Virologic Failure*</b>	35%	66%
<b>No virologic data at Week 96 Window</b>		
<b><u>Reasons</u></b>		
<b>Discontinued study due to AE or death†</b>	3%	3%
<b>Discontinued study for other reasons‡</b>	4%	4%
<b>Missing data during window but on study</b>	4%	<1%
<p>* 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 <math>\geq 50</math> copies in the 96 week window.</p> <p>† 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.</p> <p>‡ Other includes: withdrew consent, loss to follow-up, moved etc., if the viral load at the time of discontinuation was <math>&lt; 50</math> copies/mL.</p>		

The mean changes in plasma HIV-1 RNA from baseline were  $-1.81 \log_{10}$  copies/mL in the group receiving ISENTRESS® 400 mg b.i.d. and  $-0.75 \log_{10}$  copies/mL for the control group. The mean increase from baseline in CD4+ cell counts was higher in the group receiving ISENTRESS® 400 mg b.i.d. (118 cells/mm<sup>3</sup>) than in the control group (47 cells/mm<sup>3</sup>).

**Table 12 – Proportion of Patients With HIV RNA <50 Copies/mL Over Time—Protocols 018 and 019 Combined (Non-Completer = Failure Approach<sup>†</sup>)**

Endpoint	Visit	Response				Difference in Percent Response [Group A Minus Group B] <sup>‡</sup> (95% CI)
		ISENTRESS <sup>®</sup> 400 mg b.i.d. (Group A)		Placebo (Group B)		
		n/N	% (95% CI)	n/N	% (95% CI)	
Proportions with HIV RNA <50 copies/mL	Week 2	102/462	22.1 (18.4, 26.1)	24/237	10.1 ( 6.6, 14.7)	12.0 ( 6.3, 17.2)
	Week 4	195/459	42.5 (37.9, 47.2)	43/237	18.1 (13.5, 23.7)	24.3 (17.4, 30.8)
	Week 8	247/458	53.9 (49.2, 58.6)	66/236	28.0 (22.3, 34.2)	26.0 (18.4, 33.1)
	Week 12	275/460	59.8 (55.1, 64.3)	74/237	31.2 (25.4, 37.5)	28.6 (21.0, 35.7)
	Week 16	283/457	61.9 (57.3, 66.4)	82/236	34.7 (28.7, 41.2)	27.2 (19.5, 34.5)
	Week 24	289/461	62.7 (58.1, 67.1)	80/237	33.8 (27.8, 40.2)	28.9 (21.3, 36.2)
	Week 32	282/453	62.3 (57.6, 66.7)	78/237	32.9 (27.0, 39.3)	29.3 (21.7, 36.6)
	Week 40	290/458	63.3 (58.7, 67.7)	78/237	32.9 (27.0, 39.3)	30.4 (22.8, 37.6)
	Week 48	285/459	62.1 (57.5, 66.5)	78/237	32.9 (27.0, 39.3)	29.2 (21.5, 36.4)
	Week 60	281/456	61.6 (57.0, 66.1)	72/236	30.5 (24.7, 36.8)	31.1 (23.5, 38.2)
	Week 72	269/460	58.5 (53.8, 63.0)	70/237	29.5 (23.8, 35.8)	28.9 (21.4, 36.1)
	Week 84	265/460	57.6 (52.9, 62.2)	66/237	27.8 (22.2, 34.0)	29.8 (22.3, 36.8)
	Week 96	262/460	57.0 (52.3, 61.5)	62/237	26.2 (20.7, 32.2)	30.8 (23.4, 37.7)

<sup>†</sup> Approach to handling missing values: Non-Completer = Failure (NC=F) Approach.  
<sup>‡</sup> A positive value means ISENTRESS<sup>®</sup> is better than Placebo.  
 Note: ISENTRESS<sup>®</sup> and Placebo were administered with Optimized Background Therapy (OBT).  
 N = Number of patients in each treatment group.  
 n = Number of patients in each subcategory.

Virologic responses at Week 96 by baseline genotypic and phenotypic sensitivity score are shown in Table 13.

**Table 13– 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)
<b>Phenotypic Sensitivity Score (PSS)*</b>				
0	67	43	43	5
1	144	58	71	23
2	142	61	66	32
3 or more	85	48	48	42
<b>Genotypic Sensitivity Score (GSS)*</b>				
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 patient’s viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide-naïve patients was counted as one active drug in OBT in the GSS and PSS. Similarly, darunavir use in OBT in darunavir-naïve patients was counted as one active drug in OBT.

### **Switch of Suppressed Patients from Lopinavir (+) Ritonavir to Raltegravir**

The SWITCHMRK 1 & 2 studies evaluated HIV-infected patients receiving suppressive (screening HIV RNA <50 copies/mL; stable regimen >3 months) therapy with lopinavir 200 mg (+) ritonavir 50 mg 2 tablets twice daily plus at least 2 nucleoside reverse transcriptase inhibitors and randomized them 1:1 to continue lopinavir (+) ritonavir 2 tablets twice daily (n=174 and n=178, respectively) or replace lopinavir (+) ritonavir with raltegravir 400 mg twice daily (n=174 and n=176, respectively). Patients with a prior history of virological failure were not excluded and the number of previous antiretroviral therapies was not limited.

These studies were terminated after the primary efficacy analysis at Week 24 because they failed to demonstrate non-inferiority of raltegravir versus lopinavir (+) ritonavir. In both studies at Week 24, suppression of HIV RNA to less than 50 copies/ml was maintained in 84.4 % of the raltegravir group versus 90.6 % of the lopinavir (+) ritonavir group, (Non-completer = Failure). In patients who had never experienced virological failure before study entry, similar virologic response rates were seen in the raltegravir and the lopinavir (+) ritonavir groups.

### **Treatment-Naïve Patients**

STARTMRK is a Phase III 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-infected patients with HIV RNA >5000 copies/mL. Randomization was stratified by screening HIV RNA level (≤50,000 copies/mL; and >50,000 copies/mL) and by hepatitis status.

Table 14 shows the demographic characteristics between patients in the group receiving ISENTRESS<sup>®</sup> 400 mg twice daily and patients in the group receiving efavirenz.

**Table 14 – Patient Baseline Characteristics**

	<b>ISENTRESS<sup>®</sup> 400 mg Twice Daily (N=281)</b>	<b>Efavirenz 600 mg At Bedtime (N=282)</b>	<b>Total  (N=563)</b>
<b>Gender n (%)</b>			
Male	227 (80.8)	231 (81.9)	458 (81.3)
Female	54 (19.2)	51 (18.1)	105 (18.7)
<b>Race n (%)</b>			
White	116 (41.3)	123 (43.6)	239 (42.5)
Black	33 (11.7)	23 ( 8.2)	56 ( 9.9)
Asian	36 (12.8)	32 (11.3)	68 (12.1)
Hispanic	60 (21.4)	67 (23.8)	127 (22.6)
Native American	1 ( 0.4)	1 ( 0.4)	2 ( 0.4)
Multiracial	35 (12.5)	36 (12.8)	71 (12.6)
<b>Region n (%)</b>			
Latin America	99 (35.2)	97 (34.4)	196 (34.8)
Southeast Asia	34 (12.1)	29 (10.3)	63 (11.2)
North America	82 (29.2)	90 (31.9)	172 (30.6)
EU/Australia	66 (23.5)	66 (23.4)	132 (23.4)
<b>Age (years)</b>			
18-64 n (%)	279 (99.3)	278 (98.6)	557 (98.9)
≥65 n (%)	2 (0.7)	4 (1.4)	6 (1.1)
Mean (SD)	37.6 (9.0)	36.9 (10.0)	37.2 (9.5)
Median (min, max)	37.0 (19 to 67)	36.0 (19 to 71)	37.0 (19 to 71)
<b>CD4 Cell Count (cells/microL)</b>			
N <sup>†</sup>	281	281	562
Mean (SD)	218.9 (124.2)	217.4 (133.6)	218.1 (128.8)
Median (min, max)	212.0 (1 to 620)	204.0 (4 to 807)	207.5 (1 to 807)
<b>Plasma HIV RNA (log<sub>10</sub> copies/mL)</b>			
N <sup>†</sup>	281	282	563
Mean (SD)	5.0 (0.6)	5.0 (0.6)	5.0 (0.6)
Median (min, max)	5.1 (2.6 to 5.9)	5.0 (3.6 to 5.9)	5.0 (2.6 to 5.9)
<b>Plasma HIV RNA (copies/mL)</b>			
N <sup>†</sup>	281	282	563
Geometric Mean	103 205	10 6215	104 702
Median (min, max)	114 000 (400 to 750 000)	104 000 (4 410 to 750 000)	110 000 (400 to 750 000)
<b>History of AIDS n (%)</b>			
Yes	52 (18.5)	59 (20.9)	111 (19.7)

	<b>ISENTRESS<sup>®</sup> 400 mg Twice Daily (N=281)</b>	<b>Efavirenz 600 mg At Bedtime (N=282)</b>	<b>Total (N=563)</b>
<b>Stratum n (%)</b>			
Screening HIV RNA $\leq$ 50,000 Hepatitis B or C Positive <sup>‡</sup>	75 (26.7) 18 (6.4)	80 (28.4) 16 (5.7)	155 (27.5) 34 (6.0)
<b>Viral Subtype n (%)</b>			
Clade B	219 (77.9)	230 (81.6)	449 (79.8)
Non-Clade B <sup>§</sup>	59 (21.0)	47 (16.7)	106 (18.8)
Missing	3 (1.1)	5 (1.8)	8 (1.4)
<b>Baseline Plasma HIV RNA<sup>†</sup> n (%)</b>			
$\leq$ 50,000 copies/mL	79 (28.1)	84 (29.8)	163 (29.0)
$>$ 50,000 copies/mL	202 (71.9)	198 (70.2)	400 (71.0)
$\leq$ 100,000 copies/mL	127 (45.2)	139 (49.3)	266 (47.2)
$>$ 100,000 copies/mL	154 (54.8)	143 (50.7)	297 (52.8)
<b>Baseline CD4 Cell Counts n (%)</b>			
$\leq$ 50 cells/mm <sup>3</sup>	27 (9.6)	31 (11.0)	58 (10.3)
$>$ 50 cells/mm <sup>3</sup> and $\leq$ 200 cells/mm <sup>3</sup>	104 (37.0)	105 (37.2)	209 (37.1)
$>$ 200 cells/mm <sup>3</sup>	150 (53.4)	145 (51.4)	295 (52.4)
missing	0 (0.0)	1 (0.4)	1 (0.2)
<sup>†</sup> Patients with missing results excluded. <sup>‡</sup> Evidence of hepatitis B surface antigen or evidence of HCV RNA by polymerase chain reaction (PCR) quantitative test for hepatitis C Virus. <sup>§</sup> Non-Clade B Subtypes (# of patients): 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) Notes: ISENTRESS <sup>®</sup> and efavirenz were administered with emtricitabine (+) tenofovir N = Number of patients in each group. n (%) = Number (percent) of patients in each sub-category.			

Patients receiving ISENTRESS<sup>®</sup> achieved viral suppression (HIV RNA  $<$ 50 copies/mL) earlier than those receiving efavirenz, both in combination with emtricitabine (+) tenofovir.

Week 156 outcomes are shown in Table 15.

**Table 15 – Virologic Outcomes of Randomized Treatment of protocol 021 at 156 Weeks**

	<b>ISENTRRESS<sup>®</sup> 400 mg Twice Daily (N=281)</b>	<b>Efavirenz 600mg At bedtime (N=282)</b>	<b>Difference (ISENTRRESS<sup>®</sup> – Efavirenz) (CI)</b>
<b>Subjects with HIV-1 RNA less than 50 copies/mL</b>	76%	68%	7.4% (-0.1%, 14.7%)
<b>Virologic Failure*</b>	9%	13%	
<b>No virologic data at Week 156 Window</b> <b>Reasons</b>			
<b>Discontinued study due to AE or death<sup>†</sup></b>	4%	7%	
<b>Discontinued study for other reasons<sup>‡</sup></b>	10%	10%	
<b>Missing data during window but on study</b>	1%	1%	
<p>* Includes subjects who discontinued prior to Week 156 for lack of efficacy or subjects who are <math>\geq 50</math> copies in the 156 week window.  <sup>†</sup> Includes subjects who discontinued due to AE or Death at any time point from Day 1 through the Week 156 window if this resulted in no virologic data on treatment during Week 156 visit window.  <sup>‡</sup> Other includes: withdrew consent, loss to follow-up, moved etc., if the viral load at the time of discontinuation was <math>&lt; 50</math> copies/mL.</p>			

The mean changes in CD4 count from baseline were 281 cells/mm<sup>3</sup> in the group receiving ISENTRESS<sup>®</sup> 400 mg twice daily and 241 cells/mm<sup>3</sup> in the group receiving efavirenz 600 mg at bedtime.

In the STARTMRK trial of combination antiretroviral therapy in treatment-naïve patients, ISENTRESS<sup>®</sup> with emtricitabine (+) tenofovir demonstrated through 156 weeks consistent virologic and immunologic efficacy relative to efavirenz with emtricitabine (+) tenofovir across demographic and baseline prognostic factors, including: baseline plasma vRNA level  $> 100,000$  copies/mL, baseline CD4 cells  $\leq 50$  cells/mm<sup>3</sup>, demographic groups (including age, gender, region, and race), viral subtypes (comparing non-clade B as a group to clade B), and viral hepatitis co-infection status (hepatitis B and/or C).

## Long-Term Treatment-Naïve Results

**Table 16 – Proportion of Patients With HIV RNA <50 Copies/mL Over Time–Protocol 021 (Non-Completer = Failure Approach)<sup>†</sup>**

Endpoint	Visit	Response				Difference in Percent Response [Group A Minus Group B] <sup>‡</sup> (95% CI)
		ISENTRRESS <sup>®</sup> 400 mg b.i.d. (Group A)		Efavirenz 600 mg q.h.s. (Group B)		
		n/N	% (95% CI)	n/N	% (95% CI)	
Proportions with HIV RNA <50 copies/mL	Week 2	62/281	22.1 (17.4, 27.4)	6/282	2.1 (0.8, 4.6)	20.3 (15.1, 26.0)
	Week 4	144/279	51.6 (45.6, 57.6)	33/282	11.7 (8.2, 16.0)	40.6 (34.0, 47.1)
	Week 8	209/281	74.4 (68.9, 79.4)	107/282	37.9 (32.3, 43.9)	37.0 (29.6, 44.1)
	Week 12	227/278	81.7 (76.6, 86.0)	169/282	59.9 (54.0, 65.7)	22.1 (15.1, 29.2)
	Week 16	242/281	86.1 (81.5, 89.9)	219/281	77.9 (72.6, 82.6)	8.4 (2.2, 14.8)
	Week 24	244/279	87.5 (83.0, 91.1)	239/282	84.8 (80.0, 88.7)	2.7 (-3.1, 8.5)
	Week 32	241/278	86.7 (82.1, 90.5)	239/280	85.4 (80.7, 89.3)	1.3 (-4.5, 7.2)
	Week 40	239/280	85.4 (80.7, 89.3)	234/281	83.3 (78.4, 87.4)	2.1 (-4.0, 8.2)
	Week 48	241/280	86.1 (81.5, 89.9)	230/281	81.9 (76.8, 86.2)	4.2 (-1.9, 10.3)
	Week 60	231/281	82.2 (77.2, 86.5)	225/282	79.8 (74.6, 84.3)	2.4 (-4.1, 8.9)
	Week 72	241/281	85.8 (81.1, 89.6)	231/282	81.9 (76.9, 86.2)	3.8 (-2.3, 10.0)
	Week 84	234/280	83.6 (78.7, 87.7)	223/281	79.4 (74.2, 83.9)	4.2 (-2.3, 10.7)
	Week 96	228/281	81.1 (76.1, 85.5)	222/282	78.7 (73.5, 83.4)	2.4 (-4.3, 9.0)
	Week 108	228/281	81.1 (76.1, 85.5)	211/279	75.6 (70.2, 80.5)	5.4 (-1.4, 12.2)
	Week 120	220/277	79.4 (74.2, 84.0)	213/281	75.8 (70.4, 80.7)	3.5 (-3.4, 10.4)
	Week 132	214/279	76.7 (71.3, 81.5)	207/281	73.7 (68.1, 78.7)	2.9 (-4.2, 10.1)
Week 144	217/280	77.5 (72.2, 82.3)	197/281	70.1 (64.4, 75.4)	7.3 (0.0, 14.5)	
Week 156	212/281	75.4 (70.0, 80.4)	192/282	68.1 (62.3, 73.5)	7.3 (-0.2, 14.7)	

<sup>†</sup> Approach to handling missing values: Non-Completer = Failure (NC=F) Approach.

<sup>‡</sup> A positive value means ISENTRESS<sup>®</sup> is better than Efavirenz. The 95% CIs were calculated using Miettinen and Nurminen's method with weights proportional to the size of each stratum (screen HIV RNA >50,000 copies/mL or ≤50,000 copies/mL).

Note: ISENTRESS<sup>®</sup> and Efavirenz were administered with emtricitabine (+) tenofovir.

N = Number of patients in each treatment group.

n = Number of patients in each subcategory.

## TOXICOLOGY

### Acute Toxicity

In dogs, an intravenous 3-day rising dose escalation study caused mortality at high doses; this is considered to result from cardiac arrhythmia secondary to the excessive potassium salt administered in the drug formulation. Mild physical signs were noted at lower doses. In a 7-day intravenous study in dogs, at 100 mg/kg/day (exposure approximately 23-fold above the exposure at the recommended human dose), treatment-related effects were limited to physical signs which included body weight loss; minimal increases in serum urea nitrogen; increases in alanine aminotransferase activity, alkaline phosphatase activity, and cholesterol; and very slight renal tubular dilatation.

### **Chronic Toxicity**

Chronic repeat dose toxicity studies were conducted in rats (6 month duration) and dogs (1 year duration). In dogs, transient and/or intermittent emesis and weight loss were observed at 360 mg/kg/day (exposure 9 fold above the exposure at the recommended human dose). In rats, mortality, preceded by physical signs of drug intolerance, was seen at 600 mg/kg/day (exposures 4.8 fold above the exposure at the recommended human dose), but not at 120 mg/kg/day. In rats, inflammation of the nasal cavity and degeneration of the stomach mucosa occurred at 120 mg/kg/day (exposures 1.6 fold above the exposure at the recommended human dose) and is suggestive of irritative properties of the drug.

### **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 approximately 2-fold greater (females) or equal to (males) the AUC (54  $\mu\text{M}\cdot\text{hr}$ ) at the 400-mg twice daily dose. In rats, carcinogenic potential considered to be specific for this species was identified, but is regarded as having minimal relevance for humans. In rats, tumors (squamous cell carcinoma) of the nose/nasopharynx were identified in high- and mid-dose group animals. These neoplasms are considered to result from local deposition and/or aspiration of drug on the mucosa of the nose/nasopharynx during dosing and are an expected consequence of chronic irritation and inflammation. Consistent with this, the increased incidence of these neoplasms correlated with oral dosing of high concentrations of raltegravir (>300 mg/kg) instead of systemic exposure. However, at the NOAEL, systemic exposure was 1.4 to 1.7 fold greater than the AUC (54  $\mu\text{M}\cdot\text{hr}$ ) at the clinical 400-mg twice daily dose.

All genotoxicity studies to evaluate mutagenicity and clastogenicity were negative.

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

### **Development**

Oral administration of up to 600 mg/kg/day to juvenile rats resulted in drug irritation effects in the stomach which were similar to those seen in adult rats. No additional toxicities were noted in juvenile rats indicating that juvenile rats were no more sensitive to drug effects than adult rats.

Treatment-related increases over controls in the incidence of supernumerary ribs were seen in rats at 600 mg/kg/day (exposures 4.4-fold above the exposure at the recommended human dose).

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**PART III: CONSUMER INFORMATION****ISENTRESS<sup>®</sup>  
raltegravir tablets (as raltegravir potassium)**

This leaflet is part III of a three-part "Product Monograph" published when ISENTRESS<sup>®</sup> was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ISENTRESS<sup>®</sup>. Contact your physician or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION**What is HIV?

HIV is a disease that destroys the body's ability to protect itself from infection.

- It is caused by a virus (called HIV) that attacks certain white blood cells and weakens the immune system.
- HIV is spread by contact with blood of or sexual contact with an infected person.

What the medication is used for:

- ISENTRESS<sup>®</sup> is a medicine that helps control HIV infection, in combination with other antiretroviral medications.
- Your physician has prescribed ISENTRESS<sup>®</sup> to help control your HIV infection.

ISENTRESS<sup>®</sup> has not been studied in children less than 16 years of age.

What it does:

ISENTRESS<sup>®</sup> is a medicine that helps to control HIV infection. The term HIV stands for Human Immunodeficiency Virus. It is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

**How does ISENTRESS<sup>®</sup> work?**

- ISENTRESS<sup>®</sup> blocks an enzyme which the virus (HIV) needs in order to make more virus. The enzyme that ISENTRESS<sup>®</sup> blocks is called HIV integrase.
- ISENTRESS<sup>®</sup> is used along with other HIV medicines. Anti-HIV medicines are also called "antiretroviral medicines" or an-ti-re-tro-vi-ral medicines.

**When used with other anti-HIV medicines, ISENTRESS<sup>®</sup> may do two things:**

1. It may reduce the amount of HIV in your blood. This is called your "viral load".
  - Reducing the amount of HIV in the blood may keep your immune system healthy.
  - This in turn, can help your immune system to fight infection.
2. It may also increase the number of white blood cells that help fight the virus (HIV).
  - Physicians call them CD4 (T) cells.

ISENTRESS<sup>®</sup> may not have these effects in all patients.

When it should not be used:

- Do not take ISENTRESS<sup>®</sup> if you are hypersensitive to any of its ingredients (see What the non-medicinal ingredients are).

What the medicinal ingredient is:

Raltegravir potassium

What the non-medicinal ingredients are:

calcium phosphate dibasic anhydrous, hypromellose 2208, lactose monohydrate, magnesium stearate, microcrystalline cellulose, poloxamer 407 (contains 0.01% butylated hydroxytoluene as antioxidant), sodium stearyl fumarate.

In addition, the film coating contains the following inactive ingredients: black iron oxide, polyethylene glycol 3350, polyvinyl alcohol, talc, red iron oxide and titanium dioxide.

What dosage forms it comes in:

ISENTRESS<sup>®</sup> is available as pink, oval shaped, with 227 on one side, film-coated tablets containing 400 mg raltegravir (as raltegravir potassium), as the active ingredient.

**WARNINGS AND PRECAUTIONS****Tell your physician about all the medicines you take (see INTERACTIONS WITH THIS MEDICATION)**

BEFORE you use ISENTRESS<sup>®</sup> talk to your physician or pharmacist if:

- You have any allergies.
- You are pregnant or plan to become pregnant.
  - ISENTRESS<sup>®</sup> is not recommended for use during pregnancy. ISENTRESS<sup>®</sup> has not been studied in pregnant women.
- You are breast-feeding or plan to breast-feed.
  - It is recommended that HIV-infected women should not breast-feed their infants. This is because their babies could be infected with HIV through their breast milk.
  - Talk with your physician about the best way to feed your baby.

Other Warnings**Does ISENTRESS<sup>®</sup> lower the chance of passing HIV to other people?**

No. ISENTRESS<sup>®</sup> does not reduce the chance of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood.

- Continue to practice safer sex.
- Use latex or polyurethane condoms or other barrier methods to lower the chance of sexual contact with any body fluids. This includes semen from a man, vaginal secretions from a woman, or blood.
- Never re-use, or share needles.
- Ask your physician if you have any questions about safer sex or how to prevent passing HIV to other people.

**What else is there to know?**

- ISENTRESS<sup>®</sup> does not cure HIV infection or AIDS.
- It is very important that you stay under the care of your physician during treatment with ISENTRESS<sup>®</sup>.

**INTERACTIONS WITH THIS MEDICATION**

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

- prescription medicines, including rifampin, which may interact with ISENTRESS<sup>®</sup>
- non-prescription medicines
- vitamins
- herbal supplements

Know the medicines you take.

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

**PROPER USE OF THIS MEDICATION**Usual adult dose:

Take ISENTRESS<sup>®</sup> exactly as your physician has prescribed. The recommended dose is as follows:

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

Do not change your dose or stop taking ISENTRESS<sup>®</sup> or your other anti-HIV medicines without first talking with your physician.

**IMPORTANT: Take ISENTRESS<sup>®</sup> exactly as your physician prescribed and at the right times of day because if you don't:**

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

Overdose:

In case of drug overdose, contact a health care practitioner (e.g. doctor), hospital emergency department or the regional poison control centre, even if there are no symptoms.

Missed Dose:

If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do NOT take two tablets of ISENTRESS<sup>®</sup> at the same time. In other words, do NOT take a double dose.

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

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

- When your ISENTRESS<sup>®</sup> supply starts to run low, get more from your physician or pharmacy.
- Do not wait until your medicine runs out to get more.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Like all medicines, ISENTRESS<sup>®</sup> can cause side effects, although not everybody gets them. In studies, side effects usually were mild and did not cause patients to stop taking ISENTRESS<sup>®</sup>. The side effects reported in patients taking ISENTRESS<sup>®</sup> were similar to side effects in patients treated with a tablet containing no medication (a placebo).

The most common side effects of ISENTRESS<sup>®</sup> include:

- nausea
- headache
- diarrhea
- fever
- vomiting
- fatigue
- dizziness
- difficulty sleeping
- cough
- rash
- tiredness
- upper respiratory tract infection
- inflammation of the nasal passages and throat
- bronchitis

Additionally, while the medicine has been on the market, some further reactions have occurred:

- Depression and suicidal thoughts have been reported. If you develop these feelings, discuss this with your physician.
- Other side effects that have been reported include low blood platelet count, clumsiness and lack of coordination, rash with or without an increase in some white blood cells and severe skin reaction. If you develop any of these reactions, discuss with your physician.

In some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from opportunistic infections may occur when combination antiretroviral treatment is started. Tell your physician immediately if you notice any symptoms of infection.

Contact your physician promptly if you experience unexplained muscle pain, tenderness, or weakness while taking ISENTRESS<sup>®</sup>.

Contact your physician promptly if you develop a rash. Severe and life-threatening skin reactions and allergic reactions have been reported in some patients taking ISENTRESS<sup>®</sup>.

Tell your physician if you develop any unusual side effect or if any known side effect does not go away or gets worse. For more information, ask your physician or pharmacist.

*This is not a complete list of side effects. For any unexpected effects while taking ISENTRESS<sup>®</sup>, contact your physician or pharmacist.*

**HOW TO STORE IT**

Store ISENTRESS<sup>®</sup> at room temperature (15°C–30°C).

Keep ISENTRESS<sup>®</sup> and all medicines out of the reach of children.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701E  
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

or at Merck Canada Inc. by one of the following 2 ways:

- Call toll-free at 1-800-567-2594
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-800-369-3090, or
  - Mail to: Merck Canada Inc.  
Pharmacovigilance  
P.O. Box 1005  
Pointe-Claire–Dorval, QC H9R 4P8

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program or Merck do not provide medical advice.*

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptoms / effects	Talk with your physician or pharmacist		Stop taking drug and call your physician or pharmacist
	Only if severe	In all cases	
<b>Un-common</b>			✓
<u>Severe skin reactions and allergic reactions:</u> occasionally life-threatening, with symptoms such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing			
persistent fatigue	✓		
<u>lack of white blood cells:</u> frequent infections such as fever, severe chills, sore throat or mouth ulcers	✓		
<u>lack of red blood cells:</u> tiredness, headaches, being short of breath when exercising, dizziness and looking pale	✓		
severe chest pain			✓
<u>stomach problems:</u> pain, nausea, vomiting, heartburn	✓		
<u>liver disease:</u> liver disease with nausea, vomiting, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, and dark coloured urine		✓	
<u>kidney disease:</u> nausea, loss of appetite and weakness, pass little or no urine, breathlessness			✓
depression, suicidal thoughts and actions		✓	
shaking		✓	
speech disorders		✓	
disturbance in attention		✓	

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.merck.ca>

or by contacting the sponsor, Merck Canada Inc., at: 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

Last revised: February 10, 2012

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