

## **Name of Medicine**

### **ISENTRESS™**

*raltegravir*

400 mg tablet

## **Presentation**

ISENTRESS™ (raltegravir) 400 mg is a film-coated pink tablet with 227 on one side and plain on the other. Dimensions are 15.88 mm x 8.81 mm.

## **Therapeutic Class**

ISENTRESS is an HIV integrase strand transfer inhibitor active against the Human Immunodeficiency Virus (HIV-1).

## **Indications**

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

## **Dosage and Administration**

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

## **Contraindications**

ISENTRESS is contraindicated in patients who are hypersensitive to any component of this medicine.

## **Warnings and Precautions**

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

### **Medicine Interactions**

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

### **Severe Skin and Hypersensitivity Reactions**

Severe, potentially life-threatening, and fatal skin reactions have been reported in patients taking ISENTRESS concomitantly with other drugs associated with these reactions. These include cases of Stevens-Johnson syndrome and toxic epidermal necrolysis.

Hypersensitivity reactions have also been reported and were characterised 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 oedema, 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.

### **Pregnancy**

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/foetal survival or foetal weights were observed.

In rats, at a maternal dose of 600 mg/kg/day, mean drug concentrations in foetal plasma were approximately 1.5- to 2.5-fold greater than in maternal plasma at 1 hour and 24 hours post-dose, respectively. In rabbits, at a maternal dose of 1000 mg/kg/day, mean drug concentrations in foetal plasma were approximately 2% of the mean maternal concentration at both 1 and 24 hours post-dose. 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 in pregnant women is not known. ISENTRESS, like other antiretroviral agents, is not recommended for use in pregnancy.

### **Nursing Mothers**

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

### **Paediatric Use**

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

### **Use in Elderly**

Clinical studies of ISENTRESS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and 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 medicine therapy.

### **Animal Toxicology**

#### Acute Toxicity

In dogs, an intravenous 3 day rising dose escalation study caused mortality at high doses; 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, no adverse effects 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 4.4-fold above the exposure at the recommended human dose), but not at 120 mg/kg/day (exposure 1.6-fold above the exposure at the recommended human dose). In rats, inflammation of the nasal cavity and degeneration of the stomach mucosa occurred at 120 mg/kg/day and is suggestive of irritative properties of the drug.

### Carcinogenicity

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, tumours (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 ( $\geq 300$  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.

### Mutagenesis

All genotoxicity studies to evaluate mutagenicity and clastogenicity were negative.

### Reproduction

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.

### **Effects on the Ability to Drive and Use Machinery**

Certain side effects that have been reported with ISENTRESS may affect some patients' ability to drive or operate machinery. Individual responses to ISENTRESS may vary (see Adverse Effects).

## Adverse Effects

### Treatment-Experienced Adverse Experiences

The safety assessment of ISENTRESS in treatment-experienced patients is based on the pooled safety data from the randomised clinical studies, P018 and P019 reported using the recommended dose of ISENTRESS 400 mg twice daily in combination with optimised 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 receiving placebo + OBT (mean follow-up 71.0 weeks) in the pooled analysis for studies, P018 and P019, the most commonly reported clinical adverse experiences (>10% in either group), of all intensities and regardless of causality were: diarrhoea 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. In this pooled analysis, the rates of discontinuation of therapy due to adverse experiences (clinical and laboratory) were 4.5% in patients receiving ISENTRESS + OBT and 5.5% in patients receiving placebo + OBT.

### Medicine Related Adverse Experiences

The clinical adverse experiences listed below were considered by investigators to be of moderate to severe intensity and causally related to ISENTRESS or placebo alone or in combination with OBT.

Medicine-related clinical adverse experiences of moderate to severe intensity occurring in  $\geq 2\%$  of treatment-experienced adult patients in either treatment group are presented in Table 1.

**Table 1: Percentage of Patients with Medicine-Related\* Adverse Experiences of Moderate to Severe Intensity Occurring in  $\geq 2\%$  of Treatment-Experienced Adult Patients in Either Treatment Group\*\***

System Organ Class, Preferred Term	Randomised Studies P018 and P019	
	ISENTRESS 400 mg b.i.d. + OBT N = 462	Placebo + OBT N = 237
	Mean Follow-up (weeks) 118.7 %	Mean Follow-up (weeks) 71.0%
<b>Gastrointestinal Disorders</b>		
Diarrhoea	1.5	2.1
<b>Nervous System Disorders</b>		
Headache	2.2	0.4
* Includes adverse experiences at least possibly, probably, or very likely related to the medicine		
**N=total number of patients per treatment group		

Medicine-related clinical adverse experiences, occurring in less than 2% of treatment-experienced patients (n=462) receiving ISENTRESS + OBT and of moderate to severe intensity are listed below by System Organ Class.

[Common ( $\geq 1/100$ ,  $< 1/10$ ), Uncommon ( $\geq 1/1,000$ ,  $< 1/100$ )]

### *Cardiac Disorders*

*Uncommon:* ventricular extrasystoles

### *Ear and Labyrinth Disorders*

*Uncommon:* vertigo

### *Eye Disorders*

*Uncommon:* visual impairment

### *Gastrointestinal Disorders*

*Common:* diarrhoea, nausea

*Uncommon:* abdominal pain, abdominal distension, abdominal pain upper, vomiting, constipation, abdominal discomfort, dyspepsia, flatulence, gastritis, gastroesophageal reflux disease, dry mouth, eructation

### *General Disorders and Administration Site Conditions*

*Common:* asthenia, fatigue

*Uncommon:* pyrexia, chills, face oedema, peripheral oedema

### *Hepatobiliary Disorders*

*Uncommon:* hepatitis

### *Immune System Disorders*

*Uncommon:* medicine hypersensitivity

### *Infections and Infestations*

*Uncommon:* herpes simplex, genital herpes, gastroenteritis

### *Investigations*

*Uncommon:* weight increased, weight decreased

### *Metabolism and Nutrition Disorders*

*Uncommon:* diabetes mellitus, dyslipidaemia, increased appetite, decreased appetite

### *Musculoskeletal and Connective Tissue Disorders*

*Uncommon:* arthralgia, myalgia, back pain, musculoskeletal pain, osteoporosis, polyarthritis

### *Nervous System Disorders*

*Uncommon:* dizziness, neuropathy peripheral, paraesthesia, somnolence, tension headache, tremor

### *Psychiatric disorders*

*Uncommon:* depression, insomnia, anxiety

### *Renal and urinary disorders*

*Uncommon:* nephritis, nephrolithiasis, nocturia, renal failure, tubulointerstitial nephritis

### *Reproductive System and Breast Disorders*

*Uncommon:* gynaecomastia

### *Respiratory, Thoracic and Mediastinal Disorders*

*Uncommon:* epistaxis

## Skin and Subcutaneous Tissue Disorders

*Uncommon:* lipodystrophy acquired, rash, hyperhidrosis, dermatitis acneiform, erythema, lipohypertrophy, night sweats, rash macular, rash maculopapular, rash pruritic, xeroderma, prurigo, lipoatrophy, pruritus

## Serious Events

The following serious medicine-related clinical adverse experiences were reported in clinical studies: gastritis, hepatitis, renal failure, genital herpes, and accidental overdose.

## Treatment Naïve Adverse Experiences

The following safety assessment of ISENTRESS in treatment-naïve patients is based on the randomised double-blind active controlled study of treatment-naïve patients, protocol 021 (STARTMRK) 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 with ISENTRESS 400 mg twice daily + emtricitabine (+) tenofovir was 830 patient-years and 788 patient-years for patients with 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, were less frequent than in the group receiving efavirenz based on the nominal p-values (0.109 and <0.001, respectively). In this study, the rates of discontinuation of therapy due to adverse experiences (clinical and laboratory) were 4.6% in patients receiving ISENTRESS + emtricitabine (+) tenofovir and 8.5% in patients receiving efavirenz + emtricitabine (+) tenofovir.

For patients in the group receiving ISENTRESS 400 mg twice daily + emtricitabine (+) tenofovir and the group receiving the comparator, efavirenz 600 mg at bedtime + emtricitabine (+) tenofovir, the most commonly reported clinical adverse experiences (>10% in either group), of all intensities and regardless of causality are shown in Table 2.

**Table 2: Percentage of Subjects with the Most Commonly Reported (>10%) Adverse Experiences of All Intensities\* and Regardless of Causality Occurring in Treatment-Naïve Adult Patients in Either Treatment Group**

System Organ Class, Adverse Experiences	Randomised Study P021	
	ISENTRESS 400 mg b.i.d. + Emtricitabine (+) Tenofovir (n = 281)† %	Efavirenz 600 mg q.h.s. + Emtricitabine (+) Tenofovir (n = 282)† %
<b>Gastrointestinal Disorders</b>		
Diarrhoea	23.1	27.0
Nausea	16.4	13.5
Vomiting	7.5	10.3
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	8.2	12.8
Pyrexia	13.5	12.1
<b>Infections and Infestations</b>		
Influenza	9.3	12.8
Nasopharyngitis	22.1	18.1
Upper respiratory tract infection	18.9	18.4
<b>Muscular and Connective Tissue Disorders</b>		
Arthralgia	7.8	11.0
<b>Nervous System Disorders</b>		

Dizziness	8.9	37.6
Headache	23.5	27.0
<b>Psychiatric Disorders</b>		
Abnormal dreams	7.1	13.1
Insomnia	13.9	12.4
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Cough	14.9	10.3
<b>Skin and Subcutaneous Tissue Disorder</b>		
Rash	7.5	13.1
*Intensities are defined as follows: Mild (awareness of sign or symptom, but easily tolerated); Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity). †n=total number of subjects per treatment group.		

### Medicine Related Adverse Experiences

The clinical adverse reactions listed below were considered by investigators to be of moderate to severe intensity and causally related to ISENTRESS or efavirenz alone or in combination with emtricitabine (+) tenofovir .

Medicine-related clinical adverse reactions of moderate to 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 Medicine-Related\* Adverse Experiences of Moderate to Severe Intensity Occurring in  $\geq 2\%$  of Treatment- Naïve Adult Patients in Either Treatment Group\*\***

System Organ Class, Preferred Term	Randomised Study P021	
	ISENTRESS 400 mg b.i.d. + Emtricitabine (+) Tenofovir (n = 281)† %	Efavirenz 600 mg q.h.s. + Emtricitabine (+) Tenofovir (n = 282)† %
<b>Gastrointestinal Disorders</b>		
Diarrhoea	1.1	2.8
Nausea	2.8	3.5
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	1.8	2.8
<b>Nervous System Disorders</b>		
Dizziness	1.4	6.4
Headache	3.9	5.0
<b>Psychiatric Disorders</b>		
Insomnia	3.6	3.9
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash	0.0	2.8
Rash Maculo-Papular	0.0	2.5
* Includes adverse experiences at least possibly, probably, or very likely related to the drug **N=total number of patients per treatment group		

Medicine related clinical adverse experiences, 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.

[Common ( $\geq 1/100$ ,  $< 1/10$ ), Uncommon ( $\geq 1/1,000$ ,  $< 1/100$ )]

### *Blood and Lymphatic System Disorders*

*Uncommon:* lymph node pain, neutropenia, anaemia, lymphadenopathy

#### *Ear and Labyrinth Disorders*

*Uncommon:* tinnitus, vertigo

#### *Gastrointestinal Disorders*

*Common:* diarrhoea, abdominal pain

*Uncommon:* vomiting, abdominal pain upper, dyspepsia, erosive duodenitis, gastroesophageal reflux disease, abdominal distension

#### *General Disorders and Administration Site Conditions*

*Common:* fatigue, asthenia

*Uncommon:* submandibular mass

#### *Hepatobiliary Disorders*

*Uncommon:* hepatitis alcoholic

#### *Immune System Disorders*

*Uncommon:* immune reconstitution syndrome

#### *Infections and Infestations*

*Uncommon:* herpes zoster, gastroenteritis, folliculitis, lymph node abscess

#### *Metabolism and Nutrition Disorders*

*Uncommon:* decreased appetite, hypercholesterolemia

#### *Musculoskeletal and Connective Tissue Disorders*

*Uncommon:* arthritis, neck pain

#### *Nervous System Disorders*

*Common:* dizziness

*Uncommon:* hypersomnia, somnolence, memory impairment

#### *Psychiatric disorders*

*Common:* abnormal dreams, nightmare

*Uncommon:* anxiety, mental disorder, confusional state, depression, major depression

#### *Renal and Urinary Disorders*

*Common:* nephrolithiasis

#### *Reproductive System and Breast Disorders*

*Uncommon:* erectile dysfunction

#### *Skin and Subcutaneous Tissue Disorders*

*Uncommon:* acne, alopecia, skin lesion, lipoatrophy

#### Serious Events

The following serious medicine-related adverse experiences were reported in the clinical study, P021 in treatment-naïve patients receiving ISENTRESS + emtricitabine (+) tenofovir: anaemia, immune reconstitution syndrome, mental disorder, suicide attempt.

#### **Selected Adverse Experiences**

Cancers were observed in treatment-experienced patients who initiated ISENTRESS or placebo, both with OBT, and in treatment-naïve patients 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<sup>3</sup> 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 4). 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 occurred more commonly in treatment-experienced patients receiving regimens containing ISENTRESS + darunavir compared to patients receiving ISENTRESS without darunavir or darunavir without ISENTRESS. However, rash that was considered medicine 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. Rash occurred less commonly in treatment-naïve patients receiving ISENTRESS compared with efavirenz, each in combination with emtricitabine (+) tenofovir.

#### 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. In general, the safety profile of ISENTRESS in patients with hepatitis B and/or hepatitis C co-infection was similar to that in patients without hepatitis B and/or hepatitis C co-infection, although the rates of AST and ALT abnormalities were somewhat higher in the subgroup with hepatitis B and/or hepatitis C co-infection for both treatment groups.

#### **Paediatric Adverse Experiences**

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. Of the 126 patients, 96 received the recommended dose of ISENTRESS.

In these 96 children and adolescents, the 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 behaviour 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.

#### **Post-marketing Experience**

The following additional adverse experiences have been reported in post-marketed 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* behaviours.

## Skin and Subcutaneous Tissue Disorders

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

## **Laboratory Test Findings**

### Laboratory Abnormalities

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

**Table 4: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Experienced Patients**

Laboratory Parameter Preferred Term (Unit)	Limit	Randomised Studies P018 and P019	
		ISENTRESS 400 mg b.i.d. + OBT (N = 462)	Placebo + OBT (N = 237)
<b>Blood chemistry</b>			
Fasting (non-random) serum glucose test (mg/dL)			
Grade 2	126 - 250	11.3%	7.5%
Grade 3	251 - 500	2.9%	1.3%
Grade 4	>500	0.0%	0.0%
Total serum bilirubin			
Grade 2	1.6 - 2.5 x ULN	5.6%	3.0%
Grade 3	2.6 - 5.0 x ULN	3.0%	2.5%
Grade 4	>5.0 x ULN	0.9%	0.0%
Serum aspartate aminotransferase			
Grade 2	2.6 - 5.0 x ULN	9.5%	8.5%
Grade 3	5.1 - 10.0 x ULN	4.3%	3.0%
Grade 4	>10.0 x ULN	0.7%	1.3%
Serum alanine aminotransferase			
Grade 2	2.6 - 5.0 x ULN	10.8%	9.7%
Grade 3	5.1 - 10.0 x ULN	4.8%	2.5%
Grade 4	>10.0 x ULN	1.3%	1.7%
Serum alkaline phosphatase			
Grade 2	2.6 - 5.0 x ULN	2.2%	0.4%
Grade 3	5.1 - 10.0 x ULN	0.4%	1.3%
Grade 4	>10.0 x ULN	0.7%	0.4%
Serum creatine kinase			
Grade 2	6.0 - 9.9 x ULN	2.6%	2.1%
Grade 3	10.0 - 19.9 x ULN	4.1%	2.5%
Grade 4	≥20.0 x ULN	3.0%	1.3%
ULN = Upper limit of normal range			

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

**Table 5: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Naïve Patients**

Laboratory Parameter Preferred Term (Unit)	Limit	Randomised Study P021	
		ISENTRESS 400 mg b.i.d. + Emtricitabine (+) Tenofovir (N = 281)	Efavirenz 600 mg q.h.s. + Emtricitabine (+) Tenofovir (N = 282)
<b>Blood chemistry</b>			
<i>Fasting (non-random) serum glucose test (mg/dL)</i>			
Grade 2	126 - 250	4.4%	5.3%
Grade 3	251 - 500	1.5%	0.8%
Grade 4	>500	0.0%	0.0%
<i>Total serum bilirubin</i>			
Grade 2	1.6 - 2.5 x ULN	4.6%	0.0%
Grade 3	2.6 - 5.0 x ULN	0.7%	0.0%
Grade 4	>5.0 x ULN	0.4%	0.0%
<i>Serum aspartate aminotransferase</i>			
Grade 2	2.6 - 5.0 x ULN	5.3%	7.2%
Grade 3	5.1 - 10.0 x ULN	3.2%	2.5%
Grade 4	>10.0 x ULN	1.1%	0.4%
<i>Serum alanine aminotransferase</i>			
Grade 2	2.6 - 5.0 x ULN	10.3%	9.7%
Grade 3	5.1 - 10.0 x ULN	1.1%	1.8%
Grade 4	>10.0 x ULN	1.1%	0.7%
<i>Serum alkaline phosphatase</i>			
Grade 2	2.6 - 5.0 x ULN	1.1%	2.9%
Grade 3	5.1 - 10.0 x ULN	0.4%	0.4%
Grade 4	>10.0 x ULN	0.0%	0.4%
ULN = Upper limit of normal range			

### Lipids, Change from Baseline

For P021, changes from baseline in fasting lipids are shown in Table 6.

**Table 6: P021 Lipid Values, Change from Baseline in Serum Lipids at Week 144**

Laboratory Parameter Preferred Term (Unit)	ISENTRESS 400 mg b.i.d. N = 281		Efavirenz 600 mg q.h.s. N = 282	
		Change from Baseline at Week 144		Change from Baseline at Week 144
	Baseline Mean	Mean Change (95% CI)†	Baseline Mean	Mean Change (95% CI)†
Total Cholesterol (mg/dL)‡	159.5	12.6 (8.3, 16.9)	155.5	39.8 (34.8, 44.8)
HDL-Cholesterol (mg/dL)‡	38.4	4.5 (3.3, 5.6)	37.9	10.5 (9.0, 12.1)
LDL-Cholesterol (mg/dL)‡	97.0	7.6 (3.9, 11.3)	92.0	22.4 (18.2, 26.5)
Triglyceride (mg/dL)‡	125.9	1.0 (-10.1, 12.1)	138.8	45.2 (16.8, 73.7)
Total: HDL-C ratio	4.4	-0.2 (-0.3, -0.1)	4.4	0 (-0.2, 0.2)

Non-HDL-C (mg/dL)	121.0	8.0 (4.0, 11.9)	117.8	29.3 (24.2, 34.3)
†Within group 95% CIs were based on t-distribution. ‡Fasting (non-random) laboratory tests at Week 144. Notes: ISENTRESS and efavirenz were administered with emtricitabine (+) tenofovir. N = Number of patients in the treatment group. The analysis is based all available data. P≤0.001 for comparison of ISENTRESS vs. efavirenz except Total: HDL-C ratio (p-value=0.061) and triglyceride (p-value=0.004). The Last Obs. Carry Forward (LOCF) approach is applied for the missing data when the missing is due to increased lipids (e.g., use of rescue therapy).				

## Interactions

Raltegravir is not a substrate of cytochrome P450 (CYP) enzymes and does not inhibit ( $IC_{50}>100\ \mu\text{M}$ ) 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 metabolised 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 ( $IC_{50}>50\ \mu\text{M}$ ) of the UDP-glucuronosyltransferases (UGTs) tested (UGT1A1, UGT2B7), and raltegravir does not inhibit P-glycoprotein-mediated transport. Based on these data, ISENTRESS is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or P-glycoprotein (e.g., protease inhibitors, NNRTIs, methadone, opioid analgesics, statins, azole anti-fungals, 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.

Co-administration of ISENTRESS with medicines that are potent inducers of UGT1A1, such as rifampin (an inducer of numerous drug metabolising enzymes), reduces plasma concentrations of ISENTRESS. Caution should be used when co-administering ISENTRESS with rifampin or other strong inducers of UGT1A1 (see Warnings and Precautions). The impact of other potent inducers of drug metabolising 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.

Co-administration of ISENTRESS with medicines that are known to be potent UGT1A1 inhibitors (e.g., atazanavir) increases plasma levels of ISENTRESS. 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.

Co-administration of ISENTRESS with drugs that are known to increase gastric pH (e.g., omeprazole) may increase ISENTRESS plasma levels based on increased solubility of ISENTRESS at higher pH. In subjects who received ISENTRESS in combination with proton pump inhibitors or H2 blockers in Protocols 018 and 019, comparable safety profiles were observed in this subgroup relative to subjects not receiving proton pump inhibitors or H2 blockers. Based on these data, proton pump inhibitors and H2 blockers may be co-administered with ISENTRESS without dose adjustment.

### 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 co-administered with raltegravir as compared to when administered without raltegravir. In a multiple-dose drug interaction study, tenofovir AUC and trough concentrations when co-administered with raltegravir were 90% and 87% of values obtained with tenofovir monotherapy. In another drug interaction study, midazolam AUC from co-administration 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 metabolising enzymes, caused a decrease in trough levels of raltegravir. Drug interactions are further described below in Table 7.

**Table 7: Effect of Other Agents on the Pharmacokinetics of Raltegravir**

Co-administered Drug	Co-administered Drug Dose/Schedule	Raltegravir Dose/Schedule	Ratio (90% Confidence Interval) of Raltegravir Pharmacokinetic Parameters with/without Co-administered Drug; No Effect = 1.00			
			n	C <sub>max</sub>	AUC	C <sub>min</sub>
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)
darunavir /ritonavir	600 mg/100 mg twice daily	400 mg twice daily	6	0.67 (0.33-1.37)	0.71 (0.38-1.33)	1.38 (0.16-12.12)
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	800 mg twice daily	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 <sub>min</sub> )	0.82 (0.46, 1.46)	0.76 (0.49, 1.19)	0.45 (0.31, 0.66)

\*Compared to 400 mg twice daily administered alone.

### Overdosage

No specific information is available on the treatment of overdosage with ISENTRESS. 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). Raltegravir had a wide therapeutic margin; thus the potential for toxicity as a result of overdose is limited.

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 dialysable is unknown.

## **Actions**

### **Mechanism of Action**

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 ( $IC_{95}$ ) of viral spread (relative to an untreated virus-infected culture) in human T-lymphoid cell cultures infected with the cell-line adapted HIV-1 variant H9IIIB. In addition, raltegravir at concentrations of 6 to 50 nM resulted in 95% inhibition of viral spread in cultures of mitogen-activated human peripheral blood mononuclear cells infected with diverse, primary clinical isolates of HIV-1, including isolates 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  $IC_{50}$  values ranging from 5 to 12 nM. Raltegravir also inhibited replication of an HIV-2 isolate when tested in CEMx174 cells ( $IC_{95} = 6$  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.

#### Medicine 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, E138A/K, G140A/S, or V151I).

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.

#### Cardiac Electrophysiology

In a randomised, placebo-controlled, crossover study, 31 healthy subjects were administered a single oral supra-therapeutic 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

### Absorption

Raltegravir is rapidly absorbed with a  $T_{max}$  of approximately 3 hours post-dose 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 rapidly, within approximately the first 2 days of dosing. There is little to no accumulation in AUC and  $C_{max}$  and evidence of slight accumulation in  $C_{12hr}$ . The absolute bioavailability of raltegravir has not been established.

In patients on 400 mg twice daily monotherapy, raltegravir drug exposures were characterised by a geometric mean  $AUC_{0-12hr}$  of 14.3  $\mu M \cdot hr$  and  $C_{12hr}$  of 142 nM.

### Effect of Food on Oral Absorption

ISENTRESS may be administered with or without food. Raltegravir was administered without regard to food in the pivotal safety and efficacy studies in HIV-infected patients. The effect of consumption of low-, moderate- and high-fat meals on steady-state raltegravir pharmacokinetics was assessed in healthy volunteers. Administration of multiple doses of raltegravir following a moderate-fat meal 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 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 decreased AUC and  $C_{max}$  by 46% and 52%, respectively;  $C_{12hr}$  was essentially unchanged. Food appears to increase pharmacokinetic variability relative to fasting.

### Distribution

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

Raltegravir readily crossed the placenta in rats, but did not penetrate the brain to any appreciable extent.

### Metabolism and Elimination

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 radiolabelled raltegravir, approximately 51 and 32% of the dose was excreted in faeces and urine, respectively. In faeces, 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.

## Characteristics in Patients

### 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 pharmacokinetic (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.

### Age

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

### Paediatric

The pharmacokinetics of raltegravir in paediatric patients less than 16 years of age has not been established.

### 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 may be dialysable is unknown, dosing before a dialysis session should be avoided.

### UGT1A1 Polymorphism

There is no evidence that common UGT1A1 polymorphisms alter raltegravir pharmacokinetics to a clinically meaningful extent. In a comparison of 30 subjects with

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

## Pharmaceutical Precautions

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

## Medicine Classification

Prescription Medicine

## Package Quantities

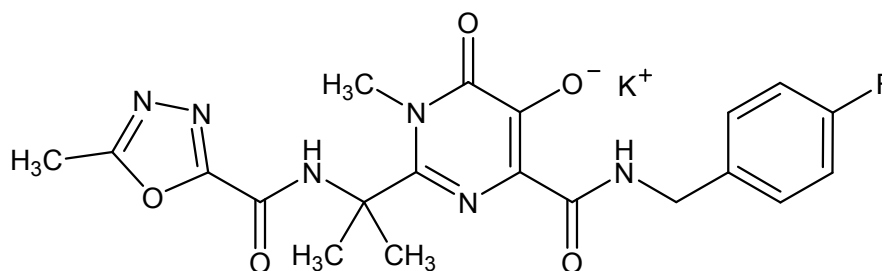
ISENTRESS 400 mg tablets are available in bottles of 60 tablets.

## Further Information

### Chemistry

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.

### Active Ingredients

Each film-coated tablet of ISENTRESS contains 434.4 mg of raltegravir potassium (as salt), equivalent to 400 mg of raltegravir (free phenol).

### Inactive Ingredients

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

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