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 HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

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).
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

Long-term (2-year) carcinogenicity studies of raltegravir in rodents are ongoing but have not been completed. Fifty rats per sex per group are receiving raltegravir at 50 (male and female), 150 (male), 300 (male and female) or 600 (female) mg/kg/day. Tumours (squamous cell carcinoma) of the nose/nasopharynx were identified in 2 of 26 High-Dose rats sacrificed early following 49 weeks of dosing from the ongoing carcinogenicity study (n=100 total High-Dose 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. Systemic exposure at the High-Dose is approximately 1.7- to 10.3-fold greater than the AUC (54 μM•hr) at the clinical 400 mg/b.i.d. dose. In addition to the squamous cell carcinomas described above, a single nasal chondrosarcoma was observed in one-mid dose rat and likely resulted from similar chronic irritation.

Mutagenesis

No evidence of mutagenicity or genotoxicity was observed in *in vitro* microbial mutagenesis (Ames) tests, *in vitro* alkaline elution assays for DNA breakage and *in vitro* and *in vivo* chromosomal aberration studies.

Reproduction

No effect on fertility was seen in male and female rats at doses up to 600 mg/kg/day which resulted in 4.4-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, P005, P018 and P019 reported using the recommended dose of ISENTRESS 400 mg twice daily in combination with optimised background therapy (OBT) in 507 patients, in comparison to 282 patients taking placebo in combination with OBT. During double-blind treatment, the total follow-up was 332.2 patient-years in the ISENTRESS 400 mg b.i.d. group and 150.2 patient-years in the placebo group.

For patients in the ISENTRESS 400 mg twice daily + OBT arm and the comparator placebo + OBT arm in the pooled analysis for studies P005, P018 and P019, the most commonly reported adverse experiences (>10% in either group), of all intensities and regardless of causality were: diarrhoea in 16.6% and 19.5%, nausea in 9.9% and 14.2%, headache in 9.7% and 11.7%, pyrexia in 4.9% and 10.3% of patients respectively. In this pooled analysis, the rates of discontinuation of therapy due to adverse experiences were 2.0% in patients receiving ISENTRESS + OBT and 1.4% in patients receiving placebo + OBT.

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

Medicine-related clinical adverse events of moderate to severe intensity occurring in ≥2% of patients treated with ISENTRESS + OBT are presented in Table 1.

Table 1: Percentage of Patients with Medicine-Related* Adverse Events of Moderate to Severe Intensity Occurring in ≥2% of Treatment-Experienced Adult Patients**

System Organ Class, Preferred Term, %	Randomised Studies P005, P018 and P019	
	ISENTRESS 400 mg b.i.d. + OBT N = 507	Placebo + OBT N = 282
Gastrointestinal Disorders		
Diarrhoea	3.7%	4.6%
Nausea	2.2%	3.2%
Nervous System Disorders		
Headache	2.4%	1.4%
* Includes adverse events at least possibly, probably, or very likely related to the medicine **N=total number of patients per treatment group		

Medicine-related adverse experiences, occurring in less than 2% of treatment-experienced patients (n=507) receiving ISENTRESS + OBT and of moderate to severe intensity are listed below by System Organ Class.

[Common (≥1/100, <1/10), Uncommon (≥ 1/1,000, <1/100)]

Blood and Lymphatic System Disorders

Uncommon: anaemia, anaemia macrocytic, neutropenia

Cardiac Disorders
Uncommon: myocardial infarction, palpitations, ventricular extrasystoles
Ear and Labyrinth Disorders
Uncommon: vertigo
Eye Disorders
Uncommon: visual disturbance
Gastrointestinal Disorders
Common: abdominal pain
Uncommon: vomiting, abdominal distension, abdominal pain upper, constipation, gastrointestinal pain, abdominal discomfort, dyspepsia, flatulence, gastritis, glossitis, gastroesophageal reflux disease
General Disorders and Administration Site Conditions
Common: asthenia, fatigue
Uncommon: pyrexia, chest discomfort, chills, feeling hot, irritability
Hepatobiliary Disorders
Uncommon: hepatitis, hepatomegaly, hyperbilirubinaemia
Immune System Disorders
Uncommon: drug hypersensitivity, hypersensitivity
Infections and Infestations
Uncommon: cellulitis, herpes simplex
Investigations
Uncommon: weight decreased, weight increased
Metabolism and Nutrition Disorders
Uncommon: diabetes mellitus, body fat disorder, central obesity, dyslipidaemia, facial wasting, hyperlactacidaemia, hyperlipidaemia, hypertriglyceridaemia, increased appetite, lipomatosis
Musculoskeletal and Connective Tissue Disorders
Uncommon: arthralgia, myalgia, pain in extremity, back pain, muscle spasms, musculoskeletal pain, myositis, muscle atrophy
Nervous System Disorders
Common: dizziness
Uncommon: neuropathy peripheral, allodynia, neuropathy, paraesthesia polyneuropathy, somnolence, tension headache
Psychiatric disorders
Uncommon: depression, insomnia, abnormal dreams, anxiety
Renal and urinary disorders
Uncommon: nephropathy toxic, nephrotic syndrome, nocturia, pollakiuria, renal failure, renal failure chronic, renal impairment, renal tubular necrosis
Reproductive System and Breast Disorders
Uncommon: erectile dysfunction, gynaecomastia
Respiratory, Thoracic and Mediastinal Disorders
Uncommon: epistaxis
Skin and Subcutaneous Tissue Disorders
Uncommon: lipodystrophy acquired, rash, hyperhidrosis, dermatitis acneiform, erythema, fat atrophy, lipoatrophy, night sweats, rash macular, rash maculopapular, xeroderma, prurigo
Serious Events
Medicine-Related
The following serious medicine-related adverse experiences were reported in the clinical studies P005, P018 and P019: hypersensitivity[1], anaemia, neutropenia, myocardial infarction, gastritis, hepatitis, drug hypersensitivity, nephropathy toxic, and renal failure, herpes simplex, accidental overdose, renal failure chronic and renal tubular necrosis.

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

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

Patients co-infected with hepatitis B and/or hepatitis C virus
In Phase III studies, patients with chronic (but not acute) active hepatitis B and/or hepatitis C co-infection (N=113/699 or 16.2%) were permitted to enroll provided that baseline liver function tests did not exceed 5 times the upper limit of normal. In general the

[1] Hypersensitivity was seen in 2 patients with ISENTRESS. Therapy was interrupted and upon rechallenge the patients were able to resume drug.

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.

Treatment Naïve Adverse Experiences

In a dose-ranging double-blind study of treatment-naïve patients (P004) with ISENTRESS 400 mg twice daily plus tenofovir (TFV) and lamivudine (3TC) (N=41) versus efavirenz (EFV) plus TFV and 3TC (N=38), the following medicine-related adverse experiences of moderate to severe intensity were reported in one or more patients with ISENTRESS: insomnia, nausea, abnormal dreams, dizziness, headache, anxiety, depression, fatigue, lichen planus, oral lichen planus, vomiting, and renal impairment.

Post-marketing Experience

The following additional adverse experiences have been reported in post-marketed experience without regard to causality:

Skin and Subcutaneous Tissue Disorders

Stevens-Johnson syndrome

Laboratory Test Findings

Laboratory Abnormalities

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

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

Laboratory Parameter Preferred Term (Unit)	Limit	Randomised Studies P005, P018 and P019 ISENTRESS 400 mg b.i.d. + OBT (N = 507)	Placebo + OBT (N = 282)
Blood chemistry			
Fasting (non-random) serum glucose test (mg/dL)			
Grade 2	126 – 250	9.3%	6.8%
Grade 3	251 – 500	1.4%	1.4%
Grade 4	>500	0.0%	0.0%
Total serum bilirubin			
Grade 2	1.6 - 2.5 x ULN	5.3%	6.7%
Grade 3	2.6 - 5.0 x ULN	3.2%	2.5%
Grade 4	>5.0 x ULN	0.8%	0.0%
Serum aspartate aminotransferase			
Grade 2	2.6 - 5.0 x ULN	9.1%	5.7%
Grade 3	5.1 - 10.0 x ULN	2.2%	2.1%
Grade 4	>10.0 x ULN	0.4%	0.7%
Serum alanine aminotransferase			
Grade 2	2.6 - 5.0 x ULN	6.9%	7.8%
Grade 3	5.1 - 10.0 x ULN	3.0%	1.4%
Grade 4	>10.0 x ULN	0.6%	1.1%
Serum alkaline phosphatase			
Grade 2	2.6 - 5.0 x ULN	2.0%	0.4%
Grade 3	5.1 - 10.0 x ULN	0.4%	1.1%
Grade 4	>10.0 x ULN	0.4%	0.4%
Serum creatine kinase			
Grade 2	6.0 - 9.9 x ULN	2.2%	1.4%
Grade 3	10.0 - 19.9 x ULN	2.4%	1.8%
Grade 4	≥20.0 x ULN	2.2%	0.7%
ULN = Upper limit of normal range			

Lipids, Change from Baseline

In a double-blind study of 198 treatment-naïve patients (P004), raltegravir was studied at several doses including 400 mg twice daily. ISENTRESS at 400 mg in combination with TFV and 3TC does not increase serum cholesterol, LDL-cholesterol, or triglyceride levels based upon *post hoc* analysis of lipids. Results for other doses (100, 200, 600 mg) were similar. Percent changes from baseline for 400 mg are shown in Table 3.

Table 3: Protocol 004 Lipid Values, Percent (%) Change from Baseline

Laboratory Parameters	Week 24		Week 48	
	ISENTRESS*	Efavirenz*	ISENTRESS*	Efavirenz*
Total Cholesterol	-2.2	11.5	1.4	13.4
LDL	0.4	6.5	4.2	3.1
HDL	7.2	15.3	14.3	30.0

Triglycerides	2.0	39.6	2.7	45.2
* ISENTRESS 400 mg b.i.d and efavirenz 600 mg gd were administered with tenofovir and lamivudine.				

Interactions
Raltegravir is not a substrate of cytochrome P450 (CYP) enzymes and does not inhibit (IC_{50}>100 µM) CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A *in vitro*. Moreover, *in vitro*, raltegravir did not induce CYP3A4. A midazolam drug interaction study confirmed the low propensity of raltegravir to alter the pharmacokinetics of agents 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 µM) 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, oral contraceptives, 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.

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: lamivudine, tenofovir and midazolam. 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 4.

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

Coadministered Drug	**Coadministered Drug Dose/Schedule**	**Raltegravir Dose/Schedule**	**Ratio (90% Confidence Interval) of Raltegravir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00**			
			n	**C_{max}**	**AUC**	**C_{min}**
atazanavir	400 mg daily	100 mg single dose	10	1.53 (1.11, 2.12)	1.72 (1.47, 2.02)	1.95 (1.30, 2.92)
atazanavir/ritonavir	300 mg/100 mg daily	400 mg twice daily	10	1.24 (0.87, 1.77)	1.41 (1.12, 1.78)	1.77 (1.39, 2.25)
efavirenz	600 mg daily	400 mg single dose	9	0.64 (0.41, 0.98)	0.64 (0.52, 0.80)	0.79 (0.49, 1.28)
rifampin	600 mg daily	400 mg single dose	9	0.62 (0.37, 1.04)	0.60 (0.39, 0.91)	0.39 (0.30, 0.51)
ritonavir	100 mg twice daily	400 mg single dose	10	0.76 (0.55, 1.04)	0.84 (0.70, 1.01)	0.99 (0.70, 1.40)
tenofovir	300 mg daily	400 mg twice daily	9	1.64 (1.16, 2.32)	1.49 (1.15, 1.94)	1.03 (0.73, 1.45)
tipranavir/ritonavir	500 mg/200 mg twice daily	400 mg twice daily	15 (14 for C_{min})	0.82 (0.46, 1.46)	0.76 (0.49, 1.19)	0.45 (0.31, 0.66)

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 α, β, and γ.

Pharmacodynamics

Microbiology

Raltegravir at concentrations of 31 ± 20 nM resulted in 95% inhibition (IC95) of viral spread (relative to an untreated virus-infected culture) in human T-lymphoid cell cultures infected with the cell-line adapted HIV-1 variant H9IIIB. In addition, raltegravir at concentrations of 6 to 50 nM resulted in 95% inhibition of viral spread in cultures of mitogen-activated human peripheral blood mononuclear cells infected with diverse, primary clinical isolates of HIV-1, including isolates resistant to reverse transcriptase inhibitors and protease inhibitors. Raltegravir also inhibited replication of an HIV-2 isolate when tested in CEMx174 cells (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 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). Amino acid substitution at Y143C/H/R is another pathway to raltegravir resistance.

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 $AUC_{0\text{-}12hr}$ of 14.3 μM•hr and C_{12hr} of 142 nM.

Effect of Food on Oral Absorption

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

Distribution

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

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 α-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 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

In an ongoing clinical trial, there is no evidence that UGT1A1 polymorphism alters raltegravir pharmacokinetics based on limited data. In a comparison of 7 subjects with *28/*28 genotype to 4 subjects with wild-type genotype, the geometric mean ratio (90% CI) of AUC was 0.94 (0.36, 2.49).

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

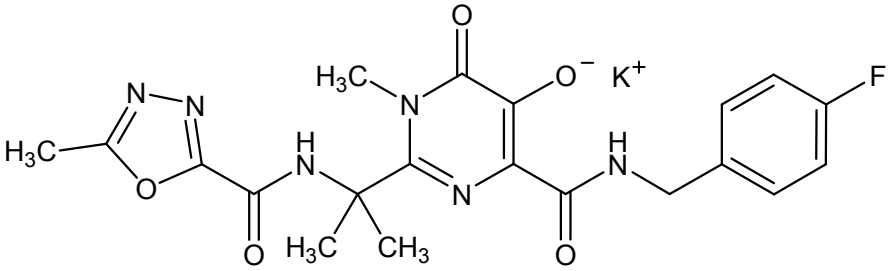
ISENTRESS 400 mg tablets are available in bottles of 60 tablets.

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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