1 PRODUCT NAME

ISENTRESS® 400 mg tablet

ISENTRESS HD® 600 mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of ISENTRESS contains 400 mg of raltegravir (as potassium salt).

Each film-coated tablet of ISENTRESS HD contains 600 mg of raltegravir (as potassium salt).

3 PHARMACEUTICAL FORM

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.

ISENTRESS HD (raltegravir) 600 mg is a film-coated yellow, oval tablet with the MSD logo and "242" debossed on one side and plain on the other. Dimensions are 19.1 mm x 9.7 mm x 6.1 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of administration

ISENTRESS or ISENTRESS HD is to be given in a combination regimen with other antiretroviral agents.

ISENTRESS or ISENTRESS HD can be administered with or without food.

ISENTRESS is available in the following dose strength:

- 400 mg film coated tablet for twice daily use

ISENTRESS HD is available in the following dose strength:

- 600 mg film-coated tablet for once daily use

The formulations have different pharmacokinetic profiles, therefore do not substitute the 400 mg tablet for the 600 mg tablet to create a 1200 mg once daily dose.

It is not recommended to chew, crush or split the 400 mg tablet or 600 mg tablet.

For the treatment of adult patients with HIV-1 infection, the dosage of ISENTRESS or ISENTRESS HD is as follows:

Dosing Recommendations in Adults with HIV 1 Infection	
Population	**Recommended Dose**
Treatment-naïve patients or patients who are virologically suppressed on an initial regimen of ISENTRESS 400 mg twice daily	*1200 mg (2 x 600 mg) once daily or 400 mg twice daily
Treatment-experienced patients	400 mg twice daily
*Do not substitute the 400 mg tablet for the 600 mg tablet to create a 1200 mg once daily dose.	

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Severe Skin and Hypersensitivity Reactions

Severe, potentially life-threatening, and fatal skin reactions have been reported in patients taking ISENTRESS or ISENTRESS HD 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 or ISENTRESS HD 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 or ISENTRESS HD treatment or other suspect agents after the onset of severe rash may result in a life-threatening reaction.

Medicine Interactions

Antacids

Coadministration of ISENTRESS 400 mg twice daily with aluminium and magnesium antacids resulted in reduced raltegravir plasma levels. Coadministration of ISENTRESS 400 mg twice daily with aluminium and/or magnesium antacids is not recommended (see section 4.5).

Coadministration of ISENTRESS 1200 HD mg (2 x 600 mg) once daily with calcium carbonate and aluminum/magnesium containing antacids resulted in reduced raltegravir plasma levels therefore coadministration is not recommended (see section 4.5).

Atazanavir

Coadministration of ISENTRESS HD 1200 mg (2 x 600 mg) once daily with atazanavir resulted in increased raltegravir plasma levels therefore coadministration is not recommended (see section 4.5).

Tipranavir/ritonavir

Coadministration of ISENTRESS HD 1200 mg (2 x 600 mg) once daily with tipranavir/ritonavir could result in decreased raltegravir trough plasma levels therefore coadministration is not recommended (see section 4.5).

Strong Inducers of drug metabolising enzymes

Caution should be used when coadministering ISENTRESS 400 mg twice daily with strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 (e.g., rifampin) due to reduced plasma concentrations of raltegravir (see section 4.5).

Strong inducers of drug metabolising enzymes (e.g., rifampin) have not been studied with ISENTRESS HD 1200 mg (2 x 600 mg) once daily but could result in decreased raltegravir trough plasma level therefore coadministration with ISENTRESS HD 1200 mg (2 x 600 mg) once daily is not recommended (see section 4.5).

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.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reconstitution; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

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.

4.5 Interaction with other medicines and other forms of interaction

Effect of Raltegravir on the Pharmacokinetics of Other Agents

Raltegravir does not inhibit (IC_{50}>100 µM) CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A *in vitro*. Moreover, *in vitro*, raltegravir did not induce

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, and anti-erectile dysfunction agents).

In drug interaction studies performed using the 400 mg twice daily dose, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of the following: hormonal contraceptives, methadone, maraviroc, tenofovir disoproxil fumarate, midazolam, lamivudine, etravirine, darunavir/ritonavir and boceprevir. 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 disoproxil fumarate 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. Findings from clinical studies conducted for ISENTRESS 400 mg twice daily to evaluate the effect of raltegravir on coadministered drugs and presented in Table 1 can be extended to raltegravir 1200 mg once daily, unless otherwise noted.

Effect of Other Agents on the Pharmacokinetics of Raltegravir

Raltegravir is not a substrate of cytochrome P450 (CYP) enzymes.

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

Inducers of Drug Metabolising Enzymes

Co-administration of ISENTRESS 400 mg twice daily with medicines that are potent inducers of UGT1A1, such as rifampin (an inducer of numerous drug metabolising enzymes), reduces plasma concentrations of raltegravir. Caution should be used when co-administering ISENTRESS 400 mg twice daily with rifampin or other strong inducers of UGT1A1 (see section 4.4). 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 400 mg twice daily.

The impact of drugs that are strong inducers of UGT1A1 such as rifampin on ISENTRESS HD 1200 mg (2 x 600 mg) once daily is unknown, but co-administration is likely to decrease raltegravir trough levels based on the reduction in trough concentrations observed with ISENTRESS 400 mg twice daily; therefore coadministration with ISENTRESS HD 1200 mg (2 x 600 mg) once daily is not recommended. The impact of other strong inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown therefore coadministration with ISENTRESS HD 1200 mg (2 x 600 mg) once daily is not

recommended. In drug interaction studies, efavirenz did not have a clinically meaningful effect on the pharmacokinetics of ISENTRESS HD 1200 mg (2 x 600 mg) once daily, therefore other less potent inducers (e.g., efavirenz, nevirapine, rifabutin, glucocorticoids, St. John's wort, pioglitazone) may be used with ISENTRESS HD 1200 mg (2 x 600 mg) once daily.

Inhibitors of UGT1A1

Co-administration of ISENTRESS 400 mg twice daily with medicines that are known to be potent UGT1A1 inhibitors (e.g., atazanavir) increases plasma levels of raltegravir. 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 for ISENTRESS 400 mg twice daily.

Coadministration of atazanavir with ISENTRESS HD 1200 mg (2 x 600 mg) once daily significantly increased plasma levels of raltegravir therefore coadministration of ISENTRESS HD 1200 mg (2 x 600 mg) once daily and atazanavir is not recommended.

Antacids

Coadministration of ISENTRESS 400 mg twice daily with antacids containing divalent metal cations may reduce raltegravir absorption by chelation, resulting in a decrease of raltegravir plasma levels. Taking an aluminium and magnesium antacid within 6 hours of ISENTRESS administration significantly decreased raltegravir plasma levels. Therefore, coadministration of ISENTRESS 400 mg twice daily with aluminium and/or magnesium containing antacids is not recommended. Coadministration of ISENTRESS 400 mg twice daily with a calcium carbonate antacid decreased raltegravir plasma levels; however, this interaction is not considered clinically meaningful. Therefore, when ISENTRESS 400 mg twice daily is coadministered with calcium carbonate containing antacids, no dose adjustment is recommended.

Coadministration of ISENTRESS HD 1200 mg (2 x 600 mg) once daily with aluminium/magnesium and calcium carbonate containing antacids are likely to result in clinically meaningful reductions in the plasma trough levels of raltegravir. Based on these findings, coadministration of aluminium/magnesium and calcium carbonate containing antacids with ISENTRESS 1200 mg (2 x 600 mg) once daily, is not recommended.

Agents that Increase Gastric pH

Co-administration of ISENTRESS 400 mg twice daily with drugs that are known to increase gastric pH (e.g., omeprazole) may increase raltegravir plasma levels based on increased solubility of ISENTRESS at higher pH. In subjects who received ISENTRESS 400 mg twice daily in combination with proton pump inhibitors (PPIs) 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 400 mg twice daily without dose adjustment.

Population pharmacokinetic analysis from ONCEMRK (Protocol 292) showed that co-administration of ISENTRESS HD 1200 mg (2 x 600 mg) once daily with PPIs or H2 blockers did not result in statistically significant changes in the pharmacokinetics of raltegravir.

Comparable efficacy and safety results were obtained in the absence or presence of these gastric pH-altering agents. Based on these data, proton pump inhibitors and H2 blockers may be coadministered with ISENTRESS HD 1200 mg (2 x 600 mg) once daily.

Additional Considerations

In drug interaction studies of ISENTRESS 400 mg twice daily, 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 (see subsections Inducers of Drug Metabolizing Enzymes and Inhibitors of UGT1A1 above).

No studies have been conducted to evaluate the drug interactions of ritonavir, tipranavir/ritonavir, boceprevir or etravirine with ISENTRESS HD 1200 mg (2 x 600 mg) once daily. While the magnitudes of change on raltegravir exposure from ISENTRESS 400 mg twice daily by ritonavir, boceprevir or etravirine were small, the impact from tipranavir/ritonavir was greater (GMR C_{trough}=0.45, GMR AUC=0.76). Coadministration of ISENTRESS HD 1200 mg (2 x 600 mg) once daily and tipranavir/ritonavir is not recommended.

Previous studies of ISENTRESS 400 mg twice daily showed that coadministration of tenofovir disoproxil fumarate (a component of TRUVADA™) increased raltegravir exposure. TRUVADA™ was identified to increase raltegravir 1200 mg (2 x 600 mg) once daily bioavailability by 12%, however its impact is not clinically meaningful. Therefore, coadministration of TRUVADA™ and ISENTRESS HD 1200 mg (2 x 600 mg) once daily is permitted.

All interaction studies were performed in adults. Drug interactions are further described below in Table 1.

Table 1: 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_{max}	AUC	C_{min}
aluminium and magnesium hydroxide antacid	20 mL single dose given with raltegravir	400 mg twice daily	25	0.56 (0.42, 0.73)	0.51 (0.40, 0.65)	0.37 (0.29, 0.48)
	20 mL single dose given 2 hours before raltegravir		23	0.49 (0.33, 0.71)	0.49 (0.35, 0.67)	0.44 (0.34, 0.55)
	20 mL single dose given 2 hours after raltegravir		23	0.78 (0.53, 1.13)	0.70 (0.50, 0.96)	0.43 (0.34, 0.55)
	20 mL single dose given 6 hours before raltegravir		16	0.90 (0.58, 1.40)	0.87 (0.64, 1.18)	0.50 (0.39, 0.65)
	20 mL single dose given 6 hours after raltegravir		16	0.90 (0.58, 1.41)	0.89 (0.64, 1.22)	0.51 (0.40, 0.64)
aluminium and magnesium hydroxide antacid	20 mL single dose given 12 hours after raltegravir	1200 mg single dose	19	0.86 (0.65, 1.15)	0.86 (0.73, 1.03)	0.42 (0.34, 0.52)
Calcium carbonate antacid	3000 mg single dose given with raltegravir	1200 mg single dose	19	0.26 (0.21, 0.32)	0.28 (0.24, 0.32)	0.52 (0.45, 0.61)
	3000 mg single dose given 12 hours after raltegravir			0.98 (0.81, 1.17)	0.90 (0.80, 1.03)	0.43 (0.36, 0.51)
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	400 mg daily	1200 mg single dose	14	1.16 (1.01, 1.33)	1.67 (1.34, 2.10)	1.26 (1.08, 1.46)
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)
boceprevir	800 mg three times daily	400 mg single dose	22	1.11 (0.91, 1.36)	1.04 (0.88, 1.22)	0.75 (0.45, 1.23)
calcium carbonate antacid	3000 mg single dose	400 mg twice daily	24	0.48 (0.36, 0.63)	0.45 (0.35, 0.57)	0.68 (0.53, 0.87)
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)
efavirenz	600 mg daily	1200 mg single dose	21	0.91 (0.70, 1.17)	0.86 (0.73, 1.01)	0.94 (0.76, 1.17)
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 disoproxil fumarate	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)

*Compared to 400 mg twice daily administered alone.

4.6 Fertility, pregnancy and lactation

Pregnancy

Antiretroviral Pregnancy Registry (APR) Data:

To monitor maternal-fetal outcomes of pregnant patients exposed to ISENTRESS, an International Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients via email at SM_APR@INCResearch.com or via facsimile at +1-910-256-0637.

Risk Summary

Available prospective data from ~2700 exposures to raltegravir 400 mg twice daily during pregnancy (including ~1000 first trimester exposures) show no difference in the rates of miscarriage, fetal death/stillbirth or congenital defects (including neural tube defects) compared to background rates in the general population (see *Human Data*).

In animal reproduction studies in rats and rabbits, no evidence of adverse developmental outcomes was observed with oral administration of raltegravir during organogenesis at doses that produced exposures up to approximately 4 times the maximum recommended human dose (MRHD) of 1200 mg (see *Animal Data*).

Human Data

Prospective reports of 1166 exposures to raltegravir during pregnancy resulting in 1096 live births are available from the antiretroviral pregnancy registry (APR) (870 reports), clinical trials, and post-marketing data. These reports include 586 first trimester exposures (386 exposures in the periconception period). Overall, the rates of spontaneous abortion and fetal death/stillbirths following exposure to raltegravir were 3.5% (95% CI: 2.5% to 4.7%) and 1.0% (95% CI: 0.5% to 1.7%), respectively. The background rates of spontaneous abortion and fetal death/stillbirth in the US general population are 15-20% and ~3%, respectively. The rate of congenital defects was 2.3% (95% CI: 1.2% to 4.0%) following first trimester exposure to raltegravir and 4.2% (95% CI: 2.7% to 6.2%) following second or third trimester exposure to raltegravir. The background birth defect rate is 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP).

Additional prospective data have been reported from two European cohorts, including 1578 exposures to raltegravir during pregnancy (440 exposures in the periconception period). There was no increase in the rate of congenital defect compared to the background rate of 2.5% in the EU population as reported by the European network of population-based registries.

Combining all prospective data, the rate of neural tube defects following raltegravir exposure was not increased compared to the background rate in the general population (there were no reports of neural tube defects among live births following ~ 800 exposures to raltegravir in the periconception period). The estimated world-wide rate of neural tube defects is 0.09%-0.16%.

ISENTRESS 400 mg twice daily can be used during pregnancy, if clinically needed. Existing post-marketing data suggest that tolerability and safety of ISENTRESS 400 mg twice daily in pregnant women is consistent with that observed in other populations.

There are limited data on the use of ISENTRESS HD 1200 mg (2 x 600 mg) once daily in pregnant women.

Animal Data

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 post-dose, 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 post-dose. Toxicokinetic studies demonstrated placental transfer of drug in both species.

Breast-feeding

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.

Fertility

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.

4.7 Effects on ability to drive and use machines

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 section 4.8).

4.8 Undesirable 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 ≥2% of treatment-experienced adult patients in either treatment group are presented in Table 2.

Table 2: Percentage of Patients with Medicine-Related* Adverse Experiences of Moderate to Severe Intensity Occurring in ≥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%
Gastrointestinal Disorders		
Diarrhoea	1.5	2.1
Nervous System Disorders		
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 (≥1/100, <1/10), Uncommon (≥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 safety of ISENTRESS was evaluated in HIV-infected treatment-naïve subjects in 2 Phase III studies; STARTMRK (Protocol 021) evaluated ISENTRESS 400 mg twice daily versus efavirenz, both in combination with emtricitabine (+) tenofovir disoproxil fumarate and ONCEMRK (Protocol 292) evaluated ISENTRESS HD 1200 mg (2 x 600 mg) once daily versus ISENTRESS 400 mg twice daily, both in combination with emtricitabine (+) tenofovir disoproxil fumarate.

STARTMRK (Protocol 021; ISENTRESS 400 mg twice daily)

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 disoproxil fumarate 245 mg, (N=281) versus efavirenz (EFV) 600 mg at bedtime in combination with emtricitabine (+) tenofovir disoproxil fumarate (N=282). During double-blind treatment, the total follow-up for patients with ISENTRESS 400 mg twice daily + emtricitabine (+) tenofovir disoproxil fumarate was 1104 patient-years and 1036 patient-years for patients with efavirenz 600 mg at bedtime + emtricitabine (+) tenofovir disoproxil fumarate.

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 (0.325 and <0.001, respectively). In this study, the rates of discontinuation of therapy due to adverse experiences (clinical and laboratory) were 5.0% in patients receiving ISENTRESS + emtricitabine (+) tenofovir disoproxil fumarate and 10.0% in patients receiving efavirenz + emtricitabine (+) tenofovir disoproxil fumarate.

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 disoproxil fumarate, the most commonly reported clinical adverse experiences (>10% in either group), of all intensities and regardless of causality are shown in Table 3.

Table 3: 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 Disoproxil Fumarate (n = 281)† %	Efavirenz 600 mg q.h.s. + Emtricitabine (+) Tenofovir Disoproxil Fumarate (n = 282)† %
Gastrointestinal Disorders		
Diarrhoea	25.6	27.0
Nausea	16.7	14.5
Vomiting	8.2	10.6
General Disorders and Administration Site Conditions		
Fatigue	9.3	13.5
Pyrexia	15.7	13.8
Infections and Infestations		
Influenza	11.7	13.5
Nasopharyngitis	26.7	22.3
Upper respiratory tract infection	21.4	20.2
Muscular and Connective Tissue Disorders		
Arthralgia	8.5	11.7
Back pain	12.1	9.9
Nervous System Disorders		
Dizziness	16.4	38.3
Headache	26.0	28.4
Psychiatric Disorders		
Abnormal dreams	8.2	13.1
Anxiety	8.9	11.0
Depression	10.3	11.7
Insomnia	15.7	14.9
Respiratory, Thoracic and Mediastinal Disorders		
Cough	16.7	12.1
Skin and Subcutaneous Tissue Disorder		
Rash	7.8	13.8

*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.

CNS Events

In treatment-naïve patients (P021) central nervous system (CNS) adverse experiences, as measured by proportion of patients with 1 or more CNS symptoms (described below), were reported significantly less frequently in the group receiving ISENTRESS + emtricitabine (+) tenofovir disoproxil fumarate as compared with the group receiving efavirenz + emtricitabine (+) tenofovir disoproxil fumarate, $p < 0.001$, < 0.001 and < 0.001 for cumulative events through Weeks 8, 48 and 96, respectively. In the group receiving ISENTRESS, 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, 26.3% compared to 58.5% by Week 48 and 28.8% compared to 60.6% by Week 96. CNS adverse experiences 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.

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 disoproxil fumarate.

Medicine-related clinical adverse reactions of moderate to severe intensity occurring in ≥2% of treatment-naïve adult patients in either treatment group are presented in Table 4.

Table 4: Percentage of Patients with Medicine-Related* Adverse Experiences of Moderate to Severe Intensity Occurring in ≥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 Disoproxil Fumarate (n = 281)† %	Efavirenz 600 mg q.h.s. + Emtricitabine (+) Tenofovir Disoproxil Fumarate (n = 282)† %
Gastrointestinal Disorders		
Diarrhoea	1.1	2.8
Nausea	2.8	3.5
General Disorders and Administration Site Conditions		
Fatigue	1.8	2.8
Nervous System Disorders		
Dizziness	1.4	6.4
Headache	3.9	5.0
Psychiatric Disorders		
Insomnia	3.6	3.9
Skin and Subcutaneous Tissue Disorders		
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 disoproxil fumarate 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: 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, body fat disorder

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, depression
Uncommon: anxiety, mental disorder, confusional state, major depression, suicide attempt

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 disoproxil fumarate: anaemia, immune reconstitution syndrome, mental disorder, suicide attempt, depression.

ONCEMRK (Protocol 292; ISENTRESS HD 1200 mg [2 x 600 mg] once daily)

The safety of ISENTRESS HD 1200 mg (2 x 600 mg) once daily was assessed in one randomized double-blind active controlled study in 797 treatment-naïve HIV-1 infected patients, comparing 531 patients receiving ISENTRESS HD 1200 mg (2 x 600 mg) once

daily with 266 patients receiving ISENTRESS 400 mg twice daily, each in combination with emtricitabine (+) tenofovir disoproxil fumarate. The total follow-up for patients on ISENTRESS HD 1200 mg (2 x 600 mg) once daily was 913 patient-years and for ISENTRESS 400 mg twice daily was 450 patient-years.

The proportion of patients with drug-related clinical and laboratory adverse experiences in the group receiving ISENTRESS HD 1200 mg (2 x 600 mg) once daily, and the group receiving ISENTRESS 400 mg twice daily were generally similar (26%, 1.3% versus 26.7%, 2.3%, respectively).

The rates of discontinuation of therapy due to clinical and laboratory adverse experiences were 0.9% and 0.4% in patients receiving ISENTRESS HD 1200 mg (2 x 600 mg) once daily and 2.3% and 0% in patients receiving ISENTRESS 400 mg twice daily.

The most commonly reported clinical adverse experiences (>10% in either treatment group), of all intensities and regardless of causality, respectively, were headache (16% versus 13.9%), nausea (13.6% versus 12.8%), diarrhoea (13.4% versus 12.8%), upper respiratory tract infection (12.6% versus 10.2%) and nasopharyngitis (12.2% versus 9.8%).

There were no drug-related clinical adverse reactions of moderate to severe intensity occurring in ≥2% of patients reported in either treatment group.

The rates of serious clinical adverse experiences were similar between patients receiving ISENTRESS HD 1200 mg (2 x 600 mg) once daily and in patients receiving ISENTRESS 400 mg twice daily (9.2% versus 15.8%, respectively). The rates of serious drug related clinical adverse experiences were also similar between the treatment groups (0.2% versus 0.8%, respectively).

Selected Adverse Experiences

In studies of ISENTRESS 400 mg twice daily, 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 disoproxil fumarate; several were recurrent. The types and rates of specific cancers were those expected in a highly immunodeficient population (many had CD4+ counts below 50 cells/mm^3 and most had prior AIDS diagnoses). The risk of developing cancer in these studies was similar in the group receiving ISENTRESS and the group receiving the comparator.

Grade 2-4 creatine kinase laboratory abnormalities were observed in subjects treated with ISENTRESS (see Table 5). 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 disoproxil fumarate.

Patients with Co-existing conditions

Patients Co-infected with hepatitis B and/or hepatitis C virus

In Phase III studies of ISENTRESS, patients with chronic (but not acute) active hepatitis B and/or hepatitis C co-infection were permitted to enrol provided that baseline liver function tests did not exceed 5 times the upper limit of normal. In the treatment experienced studies, BENCHMRK 1 and BENCHMRK 2 (Protocol 018 and Protocol 019), 16% of all patients (114/699) were co-infected; in the treatment-naïve studies, STARTMRK (Protocol 021) and ONCEMRK (Protocol 292), 6% (34/563) and 2.9% (23/797), respectively, were co-infected. 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
Thrombocytopaenia

Hepatobiliary Disorders
Hepatic failure (with and without associated hypersensitivity) in patients with underlying liver disease and/or concomitant medications

Musculoskeletal and Connective Tissue Disorders
Rhabdomyolysis

Nervous System Disorders
Cerebellar ataxia

Psychiatric Disorders
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

Treatment-Experienced

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 5.

Table 5: 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)
Blood chemistry			
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			

Treatment-Naïve

STARTMRK (Protocol 021; ISENTRESS 400 mg twice daily)

The percentages of treatment-naïve adult patients receiving either ISENTRESS 400 mg twice daily or efavirenz (both with emtricitabine (+) tenofovir disoproxil fumarate), in P021

with selected Grade 2 to 4 laboratory abnormalities that represent a worsening Grade from baseline are presented in Table 6.

Table 6: 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 Disoproxil Fumarate (N = 281)	Efavirenz 600 mg q.h.s. + Emtricitabine (+) Tenofovir Disoproxil Fumarate (N = 282)
Blood chemistry			
Fasting (non-random) serum glucose test (mg/dL)			
Grade 2	126 - 250	6.6 %	6.0 %
Grade 3	251 - 500	1.8 %	0.8%
Grade 4	>500	0.0%	0.0%
Total serum bilirubin			
Grade 2	1.6 - 2.5 x ULN	4.6%	0.4%
Grade 3	2.6 - 5.0 x ULN	0.7%	0.0%
Grade 4	>5.0 x ULN	0.4%	0.0%
Serum aspartate aminotransferase			
Grade 2	2.6 - 5.0 x ULN	7.5 %	10.4 %
Grade 3	5.1 - 10.0 x ULN	4.6 %	2.9 %
Grade 4	>10.0 x ULN	1.1%	0.4%
Serum alanine aminotransferase			
Grade 2	2.6 - 5.0 x ULN	11.0 %	11.8 %
Grade 3	5.1 - 10.0 x ULN	1.8 %	2.2 %
Grade 4	>10.0 x ULN	1.8 %	0.7%
Serum alkaline phosphatase			
Grade 2	2.6 - 5.0 x ULN	1.1%	3.2 %
Grade 3	5.1 - 10.0 x ULN	0.0 %	0.7 %
Grade 4	>10.0 x ULN	0.4%	0.4%
ULN = Upper limit of normal range			

Lipids, Change from Baseline

For P021, changes from baseline in fasting lipids are shown in Table 7.

Table 7: P021 Lipid Values, Change from Baseline in Serum Lipids at Week 240

Laboratory Parameter Preferred Term (Unit)	ISENTRESS 400 mg b.i.d. N = 207		Efavirenz 600 mg q.h.s. N = 187	
		Change from Baseline at Week 240		Change from Baseline at Week 240
	Baseline Mean	Mean Change (95% CI)†	Baseline Mean	Mean Change (95% CI)†
Total Cholesterol (mg/dL)‡	158.8	16.0 (11.5, 20.6)	157.1	44.0 (37.7, 50.4)
HDL-Cholesterol (mg/dL)‡	37.9	5.7 (4.3, 6.9)	38.4	12.6 (10.9, 14.4)
LDL-Cholesterol (mg/dL)‡	96.2	9.92 (6.1, 13.8)	92.5	25.4 (20.1, 30.7)
Triglyceride (mg/dL)‡	128.3	1.5 (-9.9, 13.0)	140.6	37.3 (14.3, 60.2)
Total: HDL-C ratio	4.4	-0.2 (-0.4, -0.1)	4.4	0.1 (-0.3, 0.2)
Non-HDL-C (mg/dL)	121.0	10.3 (6.13, 14.6)	118.7	31.4 (25.1, 37.7)

†Within group 95% CIs were based on t-distribution.
‡Fasting (non-random) laboratory tests at Week 240.
Notes:
ISENTRESS and efavirenz were administered with emtricitabine (+) tenofovir disoproxil fumarate.
N =Total number of subjects per treatment group with at least one lipid test result available. 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).

ONCEMRK (Protocol 292; ISENTRESS HD 1200 mg [2 x 600 mg] once daily)

The percentages of patients receiving either ISENTRESS HD 1200 mg (2 x 600 mg) once daily or ISENTRESS 400 mg twice daily in ONCEMRK (P292) with selected Grade 2 to 4 laboratory abnormalities that represent a worsening Grade from baseline are presented in Table 8.

Table 8: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Naïve Patients

Laboratory Parameter Preferred Term (Unit)	Limit	Randomized Study P292 Raltegravir 1200 mg Once Daily (N = 531)	Randomized Study P292 Raltegravir 400 mg Twice Daily (N = 266)
Hematology			
Neutrophils (10[3]/microL)			
Grade 2	0.75-0.999	1.5%	0.8%
Grade 3	0.50-0.749	1.3%	1.1%
Grade 4	<0.50	0.2%	0.0%
Platelets (10[3]/microL)			
Grade 2	50-99.999	1.1%	0.4%
Grade 3	25-49.999	0.0%	0.0%
Grade 4	<25	0.0%	0.4%
Chemistry			
Total bilirubin			
Grade 2	1.6-2.5 x ULN	2.8%	1.5%
Grade 3	2.6-5.0 x ULN	0.6%	0.4%
Grade 4	>5.0 x ULN	0.2%	0.0%
Creatinine			
Grade 2	1.4-1.8 x ULN	0.0%	0.4%
Grade 3	1.9-3.4 x ULN	0.0%	0.0%
Grade 4	≥3.5 x ULN	0.0%	0.0%
Aspartate aminotransferase			
Grade 2	2.6-5.0 x ULN	4.5%	2.6%
Grade 3	5.1-10.0 x ULN	2.1%	0.4%
Grade 4	>10.0 x ULN	0.6%	0.4%
Alanine aminotransferase			
Grade 2	2.6-5.0 x ULN	4.2%	1.5%
Grade 3	5.1-10.0 x ULN	1.1%	0.4%
Grade 4	>10.0 x ULN	1.1%	0.4%
Alkaline phosphatase			
Grade 2	2.6-5.0 x ULN	1.1%	0.0%
Grade 3	5.1-10.0 x ULN	0.2%	0.0%
Grade 4	>10.0 x ULN	0.0%	0.0%
Lipase			
Grade 2	1.6-3.0 x ULN	7.0%	5.3%
Grade 3	3.1-5.0 x ULN	1.5%	0.8%
Grade 4	>5.0 x ULN	1.7%	0.8%
Creatine Kinase			
Grade 2	6.0-9.9 x ULN	4.3%	4.9%
Grade 3	10.0-19.9 x ULN	3.2%	2.6%
Grade 4	≥20.0 x ULN	3.4%	1.9%

ULN = Upper limit of normal range

Note: Raltegravir 1200 mg once daily and raltegravir 400 mg twice daily were administered with emtricitabine (+) tenofovir disoproxil fumarate (TRUVADA™).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

No specific information is available on the treatment of overdosage with ISENTRESS or ISENTRESS HD. Multiple doses as high as 1800 mg (3 x 600 mg) q.d. for 28 days and 800 mg b.i.d. were studied in Phase I without evidence of toxicity. Occasional doses of 2400 mg per day were taken in Phase 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 or ISENTRESS HD may be dialyzable is unknown.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

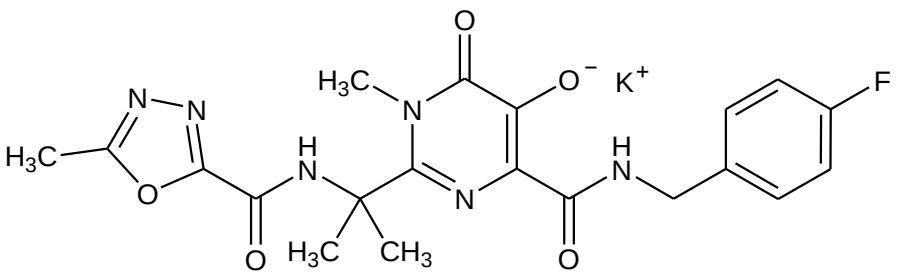
Pharmacotherapeutic group: Antivirals for systemic use, other antivirals, ATC code: J05A X08.

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

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.

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 (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.

Mutations conferring resistance to raltegravir generally also confer resistance to the integrase strand transfer inhibitor elvitegravir. Mutations at amino acid 143 confer greater resistance to raltegravir than to elvitegravir, and the E92Q mutation confers greater resistance to elvitegravir than to raltegravir. Viruses harbouring a mutation at amino acid 148, along with one or more other than resistance mutations, may also have clinically significant resistance to dolutegravir.

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.

5.2 Pharmacokinetic properties

Absorption

As demonstrated in healthy volunteers administered single oral doses of raltegravir (400 mg film coated tablet) in the fasted state, raltegravir 400 mg twice daily 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 $C12_{hr}$ 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. In patients on 400 mg twice daily monotherapy, raltegravir drug exposures were characterized by a geometric mean $AUC_{0\text{-}12hr}$ of 14.3 μM●hr and C_{12hr} of 142 nM. 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 $C12_{hr}$. The absolute bioavailability of raltegravir has not been established.

Raltegravir 1200 mg (2 x 600 mg) once daily is also rapidly absorbed with median T_{max} ~1.5 to 2 hours in the fasted state, and generates a sharper absorption peak with a tendency to higher C_{max} in comparison to raltegravir twice daily (1 x 400 mg tablet twice daily). In addition, relative to the raltegravir 400 mg formulation the raltegravir 600 mg formulation used in the 1200 mg (2 x 600 mg) once daily dosing regimen has higher relative bioavailability (by 21 to 66%), Once absorbed, both formulations of raltegravir exhibit similar systemic pharmacokinetics. In patients, after 1200 mg once daily raltegravir dosing, steady state $AUC_{0\text{-}24hr}$ was 53.7 h·μM, C_{24} was 75.6 nM, and median T_{max} was 1.50 h. Steady-state is generally reached in 2 days, with little to no accumulation with multiple dose administration.

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 400 mg twice daily 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 $C_{12\ hr}$ 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 $C_{12\ hr}$ by 4.1-fold. Administration of 400 mg twice daily raltegravir following a low-fat meal decreased AUC and C_{max} by 46% and 52%, respectively; $C_{12\ hr}$ was essentially unchanged. Food appears to increase pharmacokinetic variability relative to fasting.

A single dose food effect study demonstrated that 1200 mg (2 x 600 mg) once daily had similar or smaller food effects when studied under high-fat and low-fat meal conditions when

compared to 400 mg twice daily. Administration of a low fat meal with ISENTRESS HD 1200 mg (2 x 600 mg) once daily resulted in a 42% decrease in $AUC_{0\text{-last}}$, 52% decrease in C_{max}, and 16% decrease in C_{24hr}. Administration of a high fat meal resulted in a 1.9% increase in $AUC_{0\text{-last}}$, 28% decrease in C_{max}, and 12% decrease in C_{24hr}.

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.

In two studies of HIV-1 infected patients who received raltegravir 400 mg twice daily, raltegravir was readily detected in the cerebrospinal fluid. In the first study (n=18), the median cerebrospinal fluid concentration was 5.8% (range 1 to 53.5%) of the corresponding plasma concentration. In the second study (n=16), the median cerebrospinal fluid concentration was 3% (range 1 to 61%) of the corresponding plasma concentration. These median proportions are approximately 3- to 6-fold lower than the free fraction of raltegravir in plasma.

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 400 mg twice daily 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. For raltegravir 1200 mg (2 x 600 mg) once daily, based on population pharmacokinetic analysis, 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 for ISENTRESS 400 mg twice daily, and no clinically meaningful effect of race on raltegravir pharmacokinetics was concluded. For ISENTRESS HD 1200 mg (2 x 600 mg) once daily, population PK analysis also demonstrated that the impacts of race and ethnicity are not clinically meaningful. No dosage adjustment is necessary.

Body Mass Index (BMI) and Body Weight

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 for both ISENTRESS 400 mg twice daily and ISENTRESS 1200 mg (2 x 600 mg) once daily. 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. No hepatic impairment study has been conducted with ISENTRESS HD 1200 mg (2 x 600 mg) once daily; however, based on results with ISENTRESS 400 mg twice daily tablet, no clinically meaningful effect is expected for mild and moderate hepatic impairment. 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. No renal impairment study was conducted with ISENTRESS HD 1200 mg (2 x 600 mg) once daily; however, based on results with ISENTRESS 400 mg twice daily tablet, no clinically meaningful effect is anticipated. 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).

5.3 Preclinical safety data

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 µM•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 (≥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 µM•hr) at the clinical 400-mg twice daily dose.

Mutagenesis

All genotoxicity studies to evaluate mutagenicity and clastogenicity were negative.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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.

Each 600 mg film-coated tablet of ISENTRESS HD contains the following inactive ingredients: microcrystalline cellulose, hypromellose 2910, croscarmellose sodium, magnesium stearate. In addition, the film coating contains the following inactive ingredients: lactose monohydrate, hypromellose 2910, titanium dioxide, triacetin, iron oxide yellow, and iron oxide black. The tablet may also contain trace amounts of carnauba wax.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

ISENTRESS 400 mg tablet: 30 months

ISENTRESS HD 600 mg tablet: 24 months

6.4 Special precautions for storage

ISENTRESS and ISENTRESS HD film-coated tablets should be stored at or below 30°C (86°F).

6.5 Nature and contents of container

ISENTRESS 400 mg and ISENTRESS HD 600 mg tablets are available in HDPE bottles with a child-resistant closure and a pack size of 60 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Merck Sharp & Dohme (New Zealand) Limited
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Newmarket
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SUMMARY TABLE OF CHANGES

Sections Revised	Summary of Changes
Various Sections	Minor editorial updates throughout the Datasheet
	Update to company copyright statement

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