AUSTRALIAN PRODUCT INFORMATION

ISENTRESS® and ISENTRESS HD® (raltegravir potassium) tablets

1 NAME OF THE MEDICINE

ISENTRESS (raltegravir) 400 mg tablet, 25 mg chewable tablet and 100 mg chewable tablet.

ISENTRESS HD (raltegravir) 600 mg tablet.

2 AND 3 QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

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. The pKa is 6.6 in water. The octanol/water partition at pH 7.4 is 2.80.

ISENTRESS HD 600 mg Tablet

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

ISENTRESS 400 mg Tablet

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

ISENTRESS 100 mg Chewable Tablet

Each chewable tablet contains 100 mg of raltegravir (as potassium salt).

ISENTRESS 25 mg Chewable Tablet

Each chewable tablet contains 25 mg of raltegravir (as potassium salt).

For the full list of excipients, see Section 6.1 List of excipients.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ISENTRESS or ISENTRESS HD, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in adults, adolescents and children from the age of 2 years.

This indication is based on analyses of plasma HIV-1 RNA levels in controlled studies of ISENTRESS (see Section 5.1).

The indication in paediatric patients is based on the evaluation of safety, tolerability, pharmacokinetic parameters and efficacy of ISENTRESS through at least 24 weeks in a multicentre, open label, non-comparative study in HIV-1 infected, treatment-experienced children and adolescents 2 to 18 years of age.

The use of other active antiretroviral agents in combination with ISENTRESS is associated with a greater likelihood of treatment response (see Section 5.1).

There are no study results demonstrating the effect of ISENTRESS on clinical progression of 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 strengths:

- 400 mg film-coated tablet for twice daily use

- chewable tablet in 100 mg (scored) and 25 mg strengths 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. Do not substitute the chewable tablet for the 400 mg or 600 mg tablet.

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

Chewable tablets are to be chewed, not swallowed whole.

The maximum dose of chewable tablets is 300 mg twice daily.

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

Adults:

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

Paediatric Patients:

- If at least 40 kg in weight and either treatment naïve or virologically suppressed on an initial regimen of ISENTRESS 400 mg twice daily:
    - ISENTRESS HD 1200 mg (2x600 mg) once daily, or
    - ISENTRESS 400 mg twice daily, or
    - ISENTRESS 300 mg chewable tablets twice daily

    Note: do not substitute the 400 mg tablet for the 600 mg tablet to create a 1200 mg once daily dose.

- If at least 25 kg in weight:
    - one ISENTRESS 400 mg tablet twice daily, orally, or
    - weight based dosing for chewable tablets as specified in Table 1

- If between 7 and 25 kg in weight: weight-based dosing for chewable tablets as specified in Table 1.

Table 1: Recommended dose for ISENTRESS Chewable Tablets

Body Weight (kg)	Dose	Number of Chewable Tablets per dose
7 to < 10	50 mg twice daily	0.5 x 100 mg*
10 to < 14	75 mg twice daily	3 x 25 mg
14 to < 20	100 mg twice daily	1 x 100 mg
20 to < 28	150 mg twice daily	1.5 x 100 mg*
28 to < 40	200 mg twice daily	2 x 100 mg
At least 40	300 mg twice daily	3 x 100 mg

* The 100 mg chewable tablet can be divided into equal halves.

Note: the weight-based dosage recommendation for the chewable tablet of 6 mg/kg was derived from a clinical study where it was found to result in key pharmacokinetic values that closely approximate those in adults.

Renal Insufficiency
There were no clinically important pharmacokinetic differences between patients with severe renal insufficiency and healthy participants. No dosage adjustment is necessary. Because the extent to which ISENTRESS or ISENTRESS HD may be dialyzable is unknown, dosing before a dialysis session should be avoided.

Hepatic Insufficiency
There were no clinically important pharmacokinetic differences between patients with moderate hepatic insufficiency and healthy participants. 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.

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.

Drug 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 HD 1200 mg (2 x 600 mg) once daily with calcium carbonate and aluminium/magnesium containing antacids resulted in reduced raltegravir plasma levels therefore coadministration is not recommended.

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).

Iron Salts
Given simultaneously iron salts may reduce raltegravir plasma levels; taking iron salts at least two hours from the administration of raltegravir may limit this effect.

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.

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
IMPAACT (P1066) was conducted in treatment-experienced HIV infected children and adolescents aged 2 to 18 years of age. Given raltegravir exposures in children approximated that in adults, it is expected the safety and efficacy profile in treatment-naïve HIV infected children aged 2 to 18 years would not be substantially different from that seen in treatment-naïve adults.

ISENTRESS HD 1200 mg (2 x 600 mg) once daily has not been studied in paediatric patients. However, population PK modeling and simulation support the use of 1200 mg (2 x 600 mg) once daily in paediatric patients weighing at least 40 kg (see section 5.2).

Safety and effectiveness of ISENTRESS or ISENTRESS HD in children under 2 years of age have not been established.

Juvenile 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. The drug exposure (AUC) with this dose was approximately 1.5-fold the human value at the recommended dose of 400 mg twice daily. No additional toxicities were noted in juvenile rats and development to maturity was unaffected by treatment.

Use in the 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 drug therapy.

Use in Hepatic Impairment
The safety and efficacy of ISENTRESS have not been established in patients with severe underlying liver disorders.

Phenylketonurics
Chewable tablets contain phenylalanine as a component of aspartame. Each 25 mg chewable tablet contains approximately 0.05 mg phenylalanine. Each 100 mg chewable tablet contains approximately 0.10 mg phenylalanine. Phenylalanine can be harmful to patients with phenylketonuria.

Effects on Laboratory Tests
See section 4.8, *Laboratory Abnormalities.*

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 analgaesics, statins, azole antifungals, proton pump inhibitors, oral contraceptives, 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 3 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

Coadministration of ISENTRESS 400 mg twice daily with drugs 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 coadministering ISENTRESS 400 mg twice daily with rifampin or other strong inducers of UGT1A1 (see section 4.4). If coadministration with rifampin is unavoidable, a doubling of the dose of ISENTRESS can be considered. Until further pharmacokinetic data are available, rifampin coadministration with ISENTRESS chewable tablet is not recommended. The impact of other potent inducers of drug metabolising enzymes, such as phenytoin and phenobarbitone, on UGT1A1 is unknown. Other less potent inducers (e.g., efavirenz, etravirine, 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 metabolising 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

Coadministration of ISENTRESS 400 mg twice daily with drugs 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 HD 1200 mg (2 x 600 mg) once daily, is not recommended.

Iron salts

Given simultaneously iron salts may reduce raltegravir plasma levels; taking iron salts at least two hours from the administration of raltegravir may limit this effect.

Agents that Increase Gastric pH

Coadministration 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 coadministered 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 metabolising enzymes, caused a decrease in trough levels of raltegravir (see subsections Inducers of Drug Metabolising 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 2.

Table 2: Effect of Other Agents on the Pharmacokinetics of Raltegravir in Adults

Coadministered Drug	Coadministered Drug Dose/Schedule	Raltegravir Dose/Schedule	Ratio (90% Confidence Interval) of Raltegravir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00			
			n	C_{max}	AUC	C_{min}
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)
Aluminium and magnesium hydroxide antacid	20 mL single dose given 6 hours before raltegravir	400 mg twice daily	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

Effects on Fertility

No effect on fertility was seen in male and female rats at doses up to 600 mg/kg/day which resulted in a 3-fold higher drug exposure (based on AUC) than the human value with the recommended human dose.

Use in Pregnancy (Pregnancy Category A – 400mg only, B3 for all other strengths): The pregnancy classification of A only applies to the 2 x 400mg dose regimen. There are no adequate and well-controlled studies in pregnant women. As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account in order to characterize the safety for the fetus.

Antiretroviral Pregnancy Registry

The Antiretroviral Pregnancy Registry (APR) is an international, voluntary, prospective, exposure-registration, observational study that was established to detect major teratogenic effects resulting from the exposure of pregnant women to antiretroviral therapy.

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).

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 postmarketing 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 postmarketing 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.

There are limited data with other doses.

Animal Data

Developmental toxicity studies were conducted in rats and rabbits using oral doses of 600 and 1000 mg/kg/day, respectively. 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. An increased incidence of fetal supernumerary ribs was observed in rats at the highest dose of 600 mg/kg/day (exposures [adjusted for protein binding] 4.4-fold above the exposure at the recommended human dose), but not at a dose of 300 mg/kg/day (drug exposure [adjusted for protein binding] approximately 3-fold the human value). Fetal development was unaffected in rabbits. Placental transfer of raltegravir to the fetus was substantial in rats, but minimal in rabbits.

Use in Lactation

It is not known whether raltegravir is secreted in human milk. However, raltegravir is secreted in the milk of lactating rats, in which 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Certain side effects that have been reported with ISENTRESS or ISENTRESS HD may affect some patients' ability to drive or operate machinery. Individual responses to ISENTRESS or ISENTRESS HD may vary (see section 4.8).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials Experience - Adults

Treatment - Experienced

The safety assessment of ISENTRESS in treatment-experienced patients is based on the pooled safety data from the randomised clinical studies, BENCHMRK 1 and BENCHMRK 2 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.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

For patients in the group receiving ISENTRESS 400 mg twice daily + OBT and the comparator group receiving placebo + OBT in the pooled analysis for studies BENCHMRK 1 and BENCHMRK 2, the most commonly reported clinical adverse experiences (>10%) 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%, pyrexia in 9.7% and 13.9%, vomiting in 8.9% and 11.0% of patients respectively.

Drug Related Adverse Experiences- treatment experienced
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:

Common Adverse Reactions
Drug-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 3.

Table 3: Percentage of Patients with Drug-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, BENCHMRK 1 and BENCHMRK 2	
	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 drug
† n=total number of patients per treatment group

Less Common Adverse Reactions
Drug 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:

Cardiac Disorders:

ventricular extrasystoles

Ear and Labyrinth Disorders:
Vertigo

Eye Disorders:
visual impairment

Gastrointestinal Disorders:
diarrhoea, nausea, abdominal pain, abdominal distension, abdominal pain upper, vomiting, constipation abdominal discomfort, dyspepsia, flatulence, gastritis, gastro-oesophageal reflux disease, dry mouth, eructation

General Disorders and Administration Site Conditions:
asthenia, fatigue, pyrexia, chills, face oedema, peripheral oedema

Hepatobiliary Disorders:
hepatitis

Immune System Disorders:
drug hypersensitivity

Infections and Infestations:
herpes simplex, genital herpes, gastroenteritis

Investigations:
weight decreased, weight increased

Metabolism and Nutrition Disorders:
diabetes mellitus, dyslipidaemia, increased appetite, decreased appetite

Musculoskeletal and Connective Tissue Disorders:
arthralgia, myalgia, back pain, musculoskeletal pain, osteoporosis, polyarthritis

Nervous System Disorders:
dizziness, neuropathy peripheral, paraesthesia, somnolence, tension headache, tremor

Psychiatric disorders:
depression, insomnia, anxiety

Renal and urinary disorders:
nephritis, nephrolithiasis, nocturia, renal failure, tubulointerstitial nephritis

Reproductive System and Breast Disorders:
Gynaecomastia

Respiratory, Thoracic and Mediastinal Disorders:
epistaxis

Skin and Subcutaneous Tissue Disorders:
lipodystrophy acquired, rash, hyperhidrosis, dermatitis acneiform, erythema, lipohypertrophy, night sweats, rash macular, rash maculopapular, rash pruritic, xeroderma, prurigo, lipoatrophy, pruritis

Discontinuations

In the pooled analyses for studies P018 and P019, the rates of discontinuation of therapy due to adverse experiences (clinical and laboratory) were 4.5% in patients receiving ISENTRESS + OBT and 5.4% in patients receiving placebo + OBT.

Serious Events
The following serious drug-related clinical adverse experiences were reported in the clinical studies, gastritis, hepatitis, renal failure, genital herpes, accidental overdose.

In a Phase I study of healthy volunteers, one patient developed a serious rash that required hospitalisation and treatment with oral and topical corticosteroids. This rash occurred several days after darunavir was added to ISENTRESS. The patient discontinued study therapy and the rash eventually resolved.

Clinical Trials Experience - Treatment Naive
The safety of ISENTRESS was evaluated in HIV-1 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. 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.

Table 4: Percentage of Patients 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 STARTMRK	
	ISENTRESS 400 mg b.i.d. + Emtricitabine (+) Tenofovir disoproxil fumarate (n = 281)† %	Efavirenz 600 mg at bedtime+ 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
Musculoskeletal and Connective Tissue Disorders		
Back pain	12.1	9.9

Arthralgia	8.5	11.7
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 Medastinal 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 individuals per treatment group.

CNS Events

In treatment naïve patients (STARTMRK) 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, and 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.

Drug Related Adverse Experiences- treatment naive

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.

Drug-related clinical adverse reactions of moderate to severe intensity occurring in ≥2% of treatment-naïve adult patients are presented in Table 5.

Table 5: Percentage of Patients with Drug-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 STARTMRK	
	ISENTRESS 400 mg b.i.d. + Emtricitabine (+) Tenofovir disoproxil fumarate N = 281 %	Efavirenz 600 mg at bedtime + 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	1.8	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		

Less Common Adverse Reactions
Drug 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.

Blood and Lymphatic System Disorders:
lymph node pain, neutropenia, anaemia, lymphadenopathy

Ear and Labyrinth Disorders:
tinnitus, vertigo

Gastrointestinal Disorders:
diarrhoea, abdominal pain, vomiting, abdominal pain upper, dyspepsia, erosive duodenitis, gastro-oesophageal reflux disease, abdominal distension

General Disorders and Administration Site Conditions:
fatigue, asthenia, submandibular mass

Hepatobiliary Disorders:
Hepatitis alcoholic

Immune System Disorders:
immune reconstitution syndrome

Infections and Infestations:
herpes zoster, gastroenteritis, folliculitis, lymph node abscess

Metabolism and Nutrition Disorders:
decreased appetite, hypercholesterolaemia, body fat disorder

Musculoskeletal and Connective Tissue Disorders:
arthritis, neck pain

Nervous System Disorders:
dizziness, hypersomnia, somnolence, memory impairment

Psychiatric Disorders:
abnormal dreams, nightmare, anxiety, mental disorder, confusional state, depression, major depression, suicide attempt

Renal and Urinary Disorders:
nephrolithiasis

Reproductive System and Breast Disorders:
erectile dysfunction

Skin and Subcutaneous Tissue Disorders:

acne, alopecia, skin lesion, lipoatrophy

Serious Events
The following serious drug-related adverse experiences were reported in the clinical study, STARTMRK 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 randomised 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 (16.0% 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 – Adults - Treatment experienced and naive:

Cancers:
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.

Creatine Kinase laboratory abnormalities:
Grade 2-4 creatine kinase laboratory abnormalities were observed in individuals treated with ISENTRESS (see Table 6). 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.

Rash:
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 drug related occurred at similar rates for all three groups. These rashes were mild to moderate in severity and did not limit therapy; there were no discontinuations due to rash. 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 enroll 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 to 18 years of age, in combination with other antiretroviral agents in IMPAACT P1066 (see section 5.1). Of the 126 patients, 96 received the recommended dose of ISENTRESS.

In these 96 children and adolescents, frequency, type and severity of drug related adverse reactions through week 24 were comparable to those observed in adults. These safety data reflect 24 weeks of treatment.

One patient experience 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.

Laboratory Abnormalities

Treatment-Experienced
The percentages of treatment experienced adult patients receiving either ISENTRESS 400 mg twice daily or placebo (both with OBT), in BENCHMRK 1 and BENCHMRK 2 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-Experienced Adult Patients

Laboratory Parameter Preferred Term (Unit)	Limit	Randomised Studies, BENCHMRK 1 and BENCHMRK 2 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 7.

Table 7: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Naïve Adult Patients

		Randomised Study STARTMRK	
Laboratory Parameter Preferred Term (Unit)	**Limit**	**ISENTRESS 400 mg b.i.d. + Emtricitabine (+) Tenofovir disoproxil fumarate (N = 281) %(n/m)**	**Efavirenz 600 mg at bedtime + Emtricitabine (+) Tenofovir disoproxil fumarate (N = 282) %(n/m)**
Blood chemistry			
Fasting (non-random) serum glucose test (mg/dL)			
Grade 2	126 – 250	6.6% (18/274)	6.0% (16/266)
Grade 3	251 – 500	1.8% (5/274)	0.8% (2/266)
Grade 4	>500	0.0% (0/274)	0.0% (0/266)
Total serum bilirubin			
Grade 2	1.6 - 2.5 x ULN	4.6% (13/281)	0.4% (1/279)
Grade 3	2.6 - 5.0 x ULN	0.7% (2/281)	0.0% (0/279)
Grade 4	>5.0 x ULN	0.4% (1/281)	0.0% (0/279)
Serum aspartate aminotransferase			
Grade 2	2.6 - 5.0 x ULN	7.5% (21/281)	10.4% (29/279)
Grade 3	5.1 - 10.0 x ULN	4.6% (13/281)	2.9% (8/279)
Grade 4	>10.0 x ULN	1.1% (3/281)	0.4% (1/279)

Serum alanine aminotransferase			
Grade 2	2.6 - 5.0 x ULN	11.0% (31/281)	11.8% (33/279)
Grade 3	5.1 - 10.0 x ULN	1.8% (5/281)	2.2% (6/279)
Grade 4	>10.0 x ULN	1.8% (5/281)	0.7% (2/279)
Serum alkaline phosphatase			
Grade 2	2.6 - 5.0 x ULN	1.1% (3/281)	3.2% (9/279)
Grade 3	5.1 - 10.0 x ULN	0.0% (0/281)	0.7% (2/279)
Grade 4	>10.0 x ULN	0.4% (1/281)	0.4% (1/279)
ULN = Upper limit of normal range m = number of patients with baseline values for that laboratory test.			

Lipids, Change from Baseline - Adults

Through 240 weeks of therapy, ISENTRESS demonstrated minimal effects on serum lipids with small increases in total cholesterol, HDL-C, LDL-C, triglycerides and non-HDL-C. The group treated with efavirenz had a significantly higher mean change from baseline in total cholesterol, HDL-C, LDL-C, triglycerides, and non-HDL-C (see Table 8- Lipids, Change from Baseline)**.**

Changes from baseline in fasting lipids are shown in Table 8.

Table 8: STARTMRK Lipid Values, Change from Baseline in Serum Lipids at Week 240 - Adults

Laboratory Parameter Preferred Term (Unit)	**ISENTRESS 400 mg b.i.d. N = 207**		**Efavirenz 600 mg at bedtime. N = 187**	
		Change from Baseline at Week 240		**Change from Baseline at Week 240**
	Baseline Mean (N)	**Mean Change (95% CI)†**	**Baseline Mean (N)**	**Mean Change (95% CI)†**
Total Cholesterol (mg/dL)‡	1158.8 (207)	16.0 (11.5, 20.6)	157.1 (187)	44.0 (37.7, 50.4)
HDL-Cholesterol (mg/dL)‡	37.9 (207))	5.7 (4.3, 6.9)	38.4 (187)	12.6 (10.9, 14.4)
LDL-Cholesterol (mg/dL)‡	96.2 (204)	9.92 (6.1, 13.8)	92.5 (182)	25.4 (20.1, 30.7)
Triglyceride (mg/dL)‡	128.3 (207)	1.5 (-9.9, 13.0)	140.6(187)	37.3 (14.3, 60.2)
Total: HDL-C ratio	4.4 (207)	-0.2 (-0.4, -0.1)	4.4 (187)	0.1 (-0.3, 0.2)
Non-HDL-C (mg/dL)	121.0 (207)	10.3 (6.13, 14.6)	118.7 (187)	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 patients 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 P292 with selected Grade 2 to 4 laboratory abnormalities that represent a worsening Grade from baseline are presented in Table 9.

Table 9: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Naïve Patients

Laboratory Parameter Preferred Term (Unit)	Limit	Randomised Study P292 Raltegravir 1200 mg Once Daily (N = 531)	Randomised Study P292 Raltegravir 400 mg Twice Daily (N = 266)
Haematology			
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™).

Postmarketing Experience

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

Blood and Lymphatic System Disorders:
thrombocytopenia

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)

Reporting Suspected Adverse Effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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 disoproxil fumarate 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 information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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.

Microbiology

Raltegravir at concentrations of 31 ± 20 nM resulted in 95% inhibition (IC_{95}) of viral replication (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 replication 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.

Drug Resistance

The mutations observed in HIV-1 integrase that contributed to raltegravir resistance (evolved either *in vitro* or in patients treated with raltegravir) generally included a substitution at either Y143 (changed to C, H or R) or Q148 (changed to H, K, or R) or N155 (changed to H) plus one or more additional mutations (e.g., L74I/M, E92Q, 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 decrease susceptibility to raltegravir and sometimes acted as compensatory mutations for viral replication capacity. In phase 3 studies, integrase genotype data were obtained from about half of the patients experiencing virologic failure by 16 weeks while taking raltegravir. Viruses isolated from the majority of these patients had a signature raltegravir resistance mutation (N155H or Q148H, K, or R) along with one or more additional integrase mutations conferring higher-level raltegravir resistance.

Cardiac Electrophysiology

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

Clinical Trials

Adults

The evidence of durable efficacy of ISENTRESS 400 mg twice daily is based on the analyses of 96 week data from 2 randomized, double-blind, placebo-controlled trials, BENCHMRK1 and BENCHMRK 2 (Protocols 018 and 019), in antiretroviral treatment-experienced HIV-1 infected adult patients, analysis of 240-week data from a randomized, double-blind, active-control trial, STARTMRK (P021) evaluating ISENTRESS 400 mg twice daily in treatment-naïve adult patients, and analysis of 96-week data from a randomized, doubled-blind, active-control trial, ONCEMRK (P292) evaluating ISENTRESS HD 1200 mg (2 x 600 mg) once daily in treatment-naïve adult patients.

Treatment-Experienced Patients

BENCHMRK 1 and BENCHMRK 2 are Phase III studies to evaluate the safety and antiretroviral activity of ISENTRESS 400 mg b.i.d. in combination with an optimized background therapy (OBT), versus OBT alone, in HIV-infected patients, 16 years or older, with documented resistance to at least 1 drug in each of 3 Classes (NRTIs, NNRTIs, PIs) of antiretroviral therapies. Randomisation was

stratified by degree of resistance to PI (1PI vs. >1PI) and the use of enfuvirtide in the OBT. Prior to randomisation, OBT was selected by the investigator based on genotypic/phenotypic resistance testing and prior ART history.

Table 10 shows the demographic characteristics between patients in the group receiving ISENTRESS 400 mg b.i.d. and patients in the group receiving placebo.

Table 10: Baseline Characteristics

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

† Hepatitis B surface antigen positive or hepatitis C antibody positive.

Table 11 compares the characteristics of optimised background therapy at baseline in the group receiving ISENTRESS 400 mg b.i.d. and patients in the control group.

Table 11: Characteristics of Optimised Background Therapy at Baseline

BENCHMRK 1 and 2 Pooled	ISENTRESS 400 mg b.i.d. + OBT (N = 462)	Placebo + OBT (N = 237)
Number of ARTs in OBT		
Median (min, max)	4.0 (1 to 7)	4.0 (2 to 7)
Number of Active PI in OBT by Phenotypic Resistance Test†		
0	165 (35.7)	96 (40.5)
1 or more	278 (60.2)	137 (57.8)
Phenotypic Sensitivity Score (PSS)‡		
0	67 (14.5)	43 (18.1)
1	144 (31.2)	71 (30.0)
2	142 (30.7)	66 (27.8)
3 or more	85 (18.4)	48 (20.3)
Genotypic Sensitivity Score (GSS)‡		
0	116 (25.1)	65 (27.4)
1	177 (38.3)	95 (40.1)
2	111 (24.0)	49 (20.7)
3 or more	51 (11.0)	23 (9.7)

† Darunavir use in OBT in darunavir naïve patients was counted as one active PI.

‡ The Phenotypic Sensitivity Score (PSS) and the Genotypic Sensitivity Score (GSS) were defined as the total oral ARTs in OBT to which a patient's viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide-naïve patients was counted as one active drug in OBT in the GSS and PSS. Similarly, darunavir use in OBT in darunavir-naïve patients was counted as one active drug in OBT.

Week 48 and 96 outcomes for the 699 patients randomised and treated with the recommended dose of ISENTRESS 400 mg b.i.d. or comparator in the pooled BENCHMRK 1 and 2 studies are shown in Table 12.

Table 12: Outcomes by Treatment Group through Week 48 and 96

Randomised Studies Protocol 018 and 019	Outcome at Week 48		Outcome at Week 96	
	ISENTRESS 400 mg b.i.d. (N=462) n (%)	Placebo (N=237) n (%)	ISENTRESS 400 mg b.i.d. (N=462) n (%)	Placebo (N=237) n (%)
Patients with HIV RNA less than 400 copies/mL*	332 (72.3)	88 (37.1)	283 (61.5)	67 (28.3)
Patients with HIV RNA less than 50 copies/mL*	285 (62.1)	78 (32.9)	262 (57.0)	62 (26.2)
Patients with greater than 1 log_{10} drop in HIV RNA or HIV RNA less than 400 copies/mL*	348 (75.8)	94 (39.7)	294 (63.9)	69 (29.1)
Mean HIV RNA change from baseline (log_{10} copies/mL)*	-1.71	-0.78	-1.51	-0.60
Mean CD4 cell count change from baseline (cells/mm^3)*	109.4	44.6	123.4	48.9
Virologic Failure (confirmed)†	105 (22.7)	136 (57.4)	150 (32.5)	148 (62.4)
Non responder	13 (2.8)	77 (32.5)	12 (2.6)	72 (30.4)
Rebound	92 (19.9)	59 (24.9)	138 (29.9)	76 (32.1)
Death‡	10 (2.2)	6 (2.5)	13 (2.8)	6 (2.5)
Adjudicated AIDS-Defining Conditions (ADC)‡	17 (3.7)	11 (4.6)	18 (3.9)	11 (4.6)
Discontinuation due to clinical adverse experiences‡	10 (2.2)	7 (3.0)	16 (3.5)	10 (4.2)
Discontinuation due to laboratory adverse experiences‡	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Discontinuation due to other reasons‡§	11 (2.4)	4 (1.7)	38 (8.2)	19 (8.0)

*Approach to handling missing values: For binary endpoints (proportions), Non-Completer = Failure. For change from baseline in log_{10} HIV RNA and change from baseline in CD4 cell counts, Observed Failure (OF) approach assumes baseline value was carried forward for patients who discontinued assigned therapy due to lack of efficacy.

†Virologic failure: defined as non-responders who did not achieve >1.0 log_{10} HIV RNA reduction or <400 HIV RNA copies/mL by Week 16, or viral rebound, which was defined as: (a) HIV RNA >400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA <400 copies/mL, or (b) >1.0 log_{10} increase in HIV RNA above nadir level (on 2 consecutive measurements at least 1 week apart).

‡Outcome at Week 48 included data for at least 48 Weeks. Outcome at Week 96 included data up to Week 96.

§ Includes loss to follow-up, patient withdrew consent, noncompliance, protocol violation and other reasons.

Note: ISENTRESS and Placebo were administered with Optimized Background Therapy (OBT).

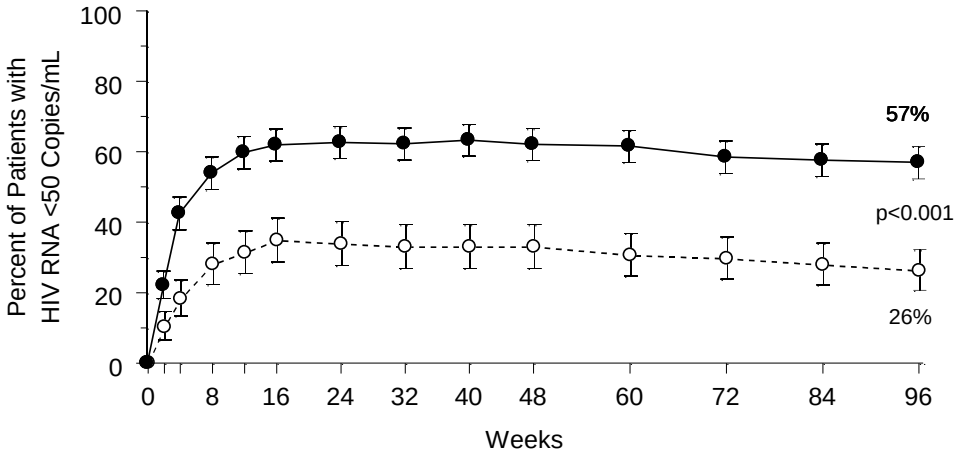
N = Number of patients in each treatment group.

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

The percent (95% confidence interval) of patients achieving HIV RNA <50 copies/mL over time is displayed in Figure 1 as Non-Completer = Failure Approach (NC=F).

Figure 1

Proportion of Patients with HIV RNA <50 Copies/mL (95%CI) Over Time (NC=F)



Number of Contributing Patients

● ISENTRESS + OBT	462	458	457	461	453	458	459	456	460	460	460
○ Placebo + OBT	237	236	236	237	237	237	237	236	237	237	237

Virologic responses at Week 96 by baseline genotypic and phenotypic sensitivity score are shown in Table 13. Higher response rates were observed in patients with Genotypic Sensitivity Score (GSS) > 0. Patients with GSS or Phenotypic Sensitivity Score (PSS) = 0 had a higher risk of developing resistance to raltegravir. Raltegravir should be used in combination with at least one other active agent to enhance benefit and to reduce the risk of virologic failure and development of resistance to raltegravir.

Table 13: Virologic Response (95% confidence interval) at Week 96 by Baseline Genotypic/Phenotypic Sensitivity Score

BENCHMRK 1 and 2 Pooled	**ISENTRESS 400 mg b.i.d. + OBT (N =425)**			**Placebo + OBT (N =219)**		
	n	**Percent with HIV RNA <400 copies /mL at Week 96**	**Percent with HIV RNA <50 copies/ mL at Week 96**	**n**	**Percent with HIV RNA <400 copies/ mL at Week 96**	**Percent with HIV RNA <50 copies/mL at Week 96**
Phenotypic Sensitivity Score(PSS)‡						
0	63	51	48	43	5	5
1	131	69	65	68	26	24
2	134	74	69	60	37	35
3 or more	74	62	54	40	53	48
Genotypic						

Sensitivity Score(GSS)‡						
0	111	46	41	64	5	5
1	160	76	72	89	31	28
2	102	75	70	41	61	61
3 or more	45	62	53	21	48	38

†Observed Failure Approach
‡The Phenotypic Sensitivity Score (PSS) and the Genotypic Sensitivity Score (GSS) were defined as the total oral ARTs in OBT to which a patient's viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide-naïve patients was counted as one active drug in OBT in the GSS and PSS. Similarly, darunavir use in OBT in darunavir-naïve patients was counted as one active drug in OBT.

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

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

Treatment-Naïve Patients
STARTMRK (Protocol 021; ISENTRESS 400 mg twice daily)
STARTMRK (Protocol 21) is a Phase III study to evaluate the safety and antiretroviral activity of ISENTRESS 400 mg b.i.d. + emtricitabine (+) tenofovir disoproxil fumarate versus efavirenz + emtricitabine (+) tenofovir disoproxil fumarate in treatment-naïve HIV-infected patients aged 18 years or older, with HIV RNA >5000 copies/mL and with no baseline resistance to efavirenz, tenofovir disoproxil fumarate, or emtricitabine. Randomisation was stratified by screening HIV RNA level (≤50,000 copies/mL; and >50,000 copies/mL) and by hepatitis B or C co-infection status.

Table 14 shows the demographic characteristics between patients in the group receiving ISENTRESS 400 mg b.i.d and patients in the group receiving efavirenz.

Table 14: Patient Baseline Characteristics

	ISENTRESS 400 mg b.i.d. (N = 281)	Efavirenz 600 mg at bedtime. (N = 282)	Total (N = 563)
Gender n (%)			
Male	227 (80.8)	231 (81.9)	458 (81.3)
Female	54 (19.2)	51 (18.1)	105 (18.7)
Race n (%)			
White	116 (41.3)	123 (43.6)	239 (42.5)
Black	33 (11.7)	23 (8.2)	56 (9.9)
Asian	36 (12.8)	32 (11.3)	68 (12.1)

Hispanic	60 (21.4)	67 (23.8)	127 (22.6)
Native American	1 (0.4)	1 (0.4)	2 (0.4)
Multiracial	35 (12.5)	36 (12.8)	71 (12.6)
Region n (%)			
Latin America	99 (35.2)	97 (34.4)	196 (34.8)
Southeast Asia	34 (12.1)	29 (10.3)	63 (11.2)
North America	82 (29.2)	90 (31.9)	172 (30.6)
EU/Australia	66 (23.5)	66 (23.4)	132 (23.4)
Age (years)			
18-64 n (%)	279 (99.3)	278 (98.6)	557 (98.9)
≥65 n (%)	2 (0.7)	4 (1.4)	6 (1.1)
Mean (SD)	37.6 (9.0)	36.9 (10.0)	37.2 (9.5)
Median (min, max)	37.0 (19 to 67)	36.0 (19 to 71)	37.0 (19 to 71)
CD4 Cell Count (cells/microL)			
N[†]	281	281	562
Mean (SD)	218.9 (124.2)	217.4 (133.6)	218.1 (128.8)
Median (min, max)	212.0 (1 to 620)	204.0 (4 to 807)	207.5 (1 to 807)
Plasma HIV RNA (log10 copies/mL)			
N[†]	281	282	563
Mean (SD)	5.0 (0.6)	5.0 (0.6)	5.0 (0.6)
Median (min, max)	5.1 (2.6 to 5.9)	5.0 (3.6 to 5.9)	5.0 (2.6 to 5.9)
Plasma HIV RNA (copies/mL)			
N[†]	281	282	563
Geometric Mean	103,205	106,215	104,702
Median (min, max)	114,000 (400 to 750,000)	104,000 (4,410 to 750,000)	110,000 (400 to 750,000)
History of AIDS n (%)			
Yes	52 (18.5)	59 (20.9)	111(19.7)
Stratum n (%)			
Screening HIV RNA≤50,000	75 (26.7)	80 (28.4)	155 (27.5)
Hepatitis B or C Positive[‡]	18 (6.4)	16 (5.7)	34 (6.0)
Viral Subtype n (%)			
Clade B	219 (77.9)	230 (81.6)	449 (79.8)
Non-Clade B[§]	59 (21.0)	47 (16.7)	106 (18.8)
Missing	3 (1.1)	5 (1.8)	8 (1.4)
Baseline Plasma HIV RNA[†] n (%)			
≤50,000 copies/mL	79 (28.1)	84 (29.8)	163 (29.0)
>50,000 copies/mL	202 (71.9)	198 (70.2)	400 (71.0)
≤100,000 copies/mL	127 (45.2)	139 (49.3)	266 (47.2)
>100,000 copies/mL	154 (54.8)	143 (50.7)	297 (52.8)
Baseline CD4 Cell Counts n (%)			
≤50 cells/mm^3	27 (9.6)	31 (11.0)	58 (10.3)
>50 cells/mm^3 and ≤200 cells/mm^3	104 (37.0)	105 (37.2)	209 (37.1)
>200 cells/mm^3	150 (53.4)	145 (51.4)	295 (52.4)
Missing	0 (0.0)	1 (0.4)	1 (0.2)

[†]Patients with missing results excluded.

[‡]Evidence of hepatitis B surface antigen or evidence of HCV RNA by polymerase chain reaction (PCR) quantitative test for hepatitis C Virus.

[§]Non-Clade B Subtypes (# of patients): Clade A (4), A/C (1), A/G (2), A1(1), AE (29), AG (12), BF (6), C (37), D (2), F (2), F1 (5), G (2), Complex (3)

Notes:

ISENTRESS and efavirenz were administered with emtricitabine (+) tenofovir disoproxil fumarate.

N = Number of patients in each group.

n (%) = Number (percent) of patients in each sub-category.

Results 48-week and 240-week analyses

With respect to the primary efficacy endpoint (based on a Non-Completer=Failure approach), the proportion (%) of patients achieving HIV RNA < 50 copies/mL at Week 48 was 241/280 (86.1%) in the group receiving ISENTRESS and 230/281 (81.9%) in the group receiving efavirenz. The treatment difference (ISENTRESS-efavirenz) was 4.2% with an associated 95% CI of (-1.9, 10.3) establishing that ISENTRESS is non-inferior to efavirenz (p-value for non-inferiority <0.001). At Week 240, the treatment difference (ISENTRESS-efavirenz) was 9.5% with an associated 95% CI of (1.7, 17.3).

Week 48 and Week 240 outcomes for patients on the recommended dose of ISENTRESS 400 mg twice daily from STARTMRK are shown in Table 15.

Table 15: Outcomes by Treatment Group through Week 48 and 240

Randomised Study Protocol 021	Outcome at Week 48			Outcome at Week 240		
	ISENTRESS 400 mg b.i.d. (N=281) n (%)	Efavirenz 600 mg q.h.s. (N=282) n (%)	Difference (ISENTRESS - Efavirenz) (CI†)	ISENTRESS 400 mg b.i.d. (N=281) n (%)	Efavirenz 600 mg q.h.s. (N=282) n (%)	Difference (ISENTRESS - Efavirenz) (CI†)
Patients with HIV RNA less than 50 copies/mL*†	241 (86.1)	230 (81.9)	4.2% (-1.9, 10.3)	198 (71.0)	171 (61.3)	9.5 %(1.7, 17.3)
Patients with HIV RNA less than 400 copies/mL*†	252 (90.0)	241 (85.8)	4.1% (-1.3, 9.7)	206 (73.8)	181 (64.9)	8.8% (1.2, 16.4)
Mean CD4 cell count change from baseline (cells/mm^3)†	189.1	163.3	25.8 (4.4, 47.2)	373.7	311.6	62.1 (21.9, 102.2)
Virologic Failure (confirmed)‡ (<50)	27 (9.6)	39 (13.8)		55 (19.6)	59 (20.9)	
Non responder	10 (3.6)	24 (8.5)		10 (3.6)	24 (8.5)	
Rebound	17 (6.0)	15 (5.3)		45 (16.0)	35 (12.4)	
Death	2 (0.7)	0 (0.0)		5 (1.8)	5 (1.8)	
Discontinuation due to clinical adverse experiences	8 (2.8)	17 (6.0)		14 (5.0)	25 (8.9)	
Discontinuation due to laboratory adverse experiences	0 (0.0)	1 (0.4)		0 (0.0)	3 (1.1)	
Discontinuation due to other reasons§	12 (4.3)	15 (5.3)		51 (18.1)	60 (21.3)	

*ISENTRESS is concluded non-inferior to efavirenz if the lower bound of the 95% CI for the difference in percent response is above -12 percentage points. It can be further concluded that ISENTRESS is superior to efavirenz if the lower bound exceeds zero.

†Approach to handling missing values: For binary endpoints (proportions), Non-Completer = Failure. For change from baseline in CD4 cell counts, Observed Failure (OF) approach assumes baseline value was carried forward for patients who discontinued assigned therapy due to lack of efficacy.

‡Virologic failure: defined as non responders for those with (1) HIV RNA > 50 copies/mL at the time of discontinuation for patients who prematurely discontinue study therapy or (2) HIV RNA > 50 copies/mL at Week 24; or virologic rebound for those with HIV RNA > 50 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA < 50 copies/mL.

§Includes loss to follow-up, patient withdrew consent, noncompliance, protocol violation and other reasons.

Note: ISENTRESS and Efavirenz were administered with emtricitabine (+) tenofovir disoproxil fumarate (TRUVADA™).

n (%) = Number (Percent) of patients in each category.

Efficacy by Viral Subtypes

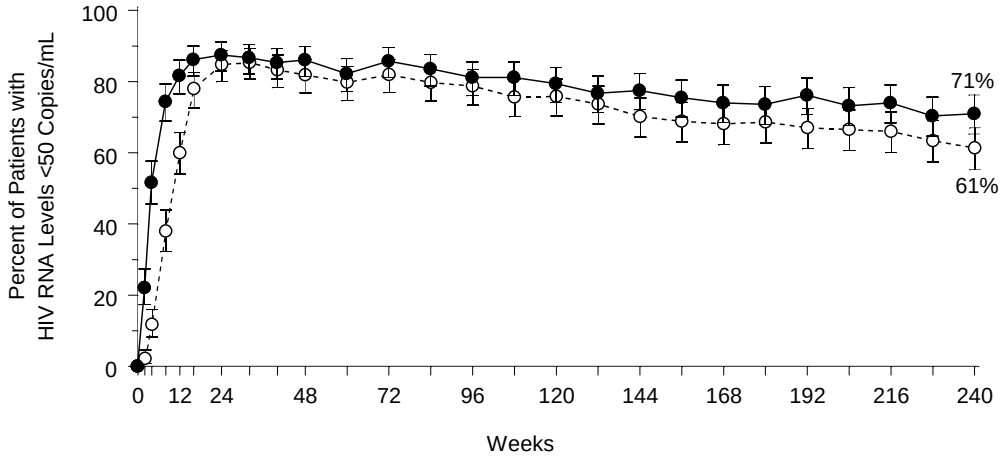
A total of 52 non-Clade B subtypes were identified: Clade A (4), A/C (1) A/G (2), A1 (1), AE (29), AG (12), BF (6), C (37), D (2), F (2), F1 (5), G (2), Complex (3). Efficacy in terms of the proportion of patients achieving HIV-RNA <50 copies/mL at Week 96 was achieved by 52/55 (94.5%) of patients with non-B subtypes and 173/195 (88.7%) of patients with B subtype.

Figure 2 presents the proportion of patients with plasma HIV RNA <50 copies/mL over time by treatment group. Patients on ISENTRESS achieved viral suppression (HIV RNA <50 copies/mL) earlier than those receiving EFV, both in combination with emtricitabine (+) tenofovir disoproxil

fumarate. Through 240 weeks of treatment 71% in the group receiving ISENTRESS 400 mg b.i.d. and 61% in the comparator group achieved HIV RNA <50 copies/mL (NC=F approach).

Figure 2

Proportion of Patients with HIV RNA <50 Copies/mL (95% CI) Over Time (NC=F)



Number of Contributing Patients

● Raltegravir 400 mg b.i.d.	281	278	279	280	281	281	277	280	281	281	277	279
○ Efavirenz 600 mg q.h.s.	282	282	282	281	282	282	281	281	282	282	282	279

At week 240, the treatment difference (raltegravir – efavirenz) was 9.5% favouring raltegravir with an associated 95% CI of (1.7, 17.3). Therefore, the proportion of patients achieving HIV RNA < 50 copies/mL in raltegravir treatment group was non-inferior to that of efavirenz, as the lower bound of the 95% CI for treatment difference exceeded the pre-defined non-inferiority bound of -12 percentage points.

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

In the STARTMRK trial of combination antiretroviral therapy in treatment-naive patients, ISENTRESS with emtricitabine (+) tenofovir disoproxil fumarate demonstrated consistent virologic and immunologic efficacy relative to efavirenz with emtricitabine (+) tenofovir disoproxil fumarate across demographic and baseline prognostic factors, including: baseline plasma HIV RNA level >100,000 copies/mL, baseline CD4 cells ≤50 cells/mm3, demographic groups (including age, gender, region, and race), viral hepatitis co-infection status (hepatitis B and/or C) and viral subtypes (comparing non-clade B as a group to clade B).

Consistent efficacy of ISENTRESS was observed in all HIV subtypes with 89.6% (155/173) and 87.0% (40/46) of patients with B and non-B subtypes respectively, achieving HIV RNA <50 copies/mL at week 240 (OF approach).

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

ONCEMRK is a Phase III study to evaluate the safety and antiretroviral activity of ISENTRESS HD 1200 mg (2 x 600 mg) once daily versus ISENTRESS 400 mg twice daily, both in combination with emtricitabine (+) tenofovir disoproxil fumarate, in treatment-naïve HIV-infected patients with HIV RNA ≥ 1000 copies/mL. Randomisation was stratified by screening HIV RNA level (≤100,000 copies/mL; and >100,000 copies/mL) and by hepatitis status.

Table 16 shows the demographic characteristics for both treatment groups.

Table 16: Subject Baseline Characteristics by Treatment Group

	Raltegravir 1200 mg Once daily (N = 531) n (%)	Raltegravir 400 mg Twice daily (N = 266) n (%)	Total (N = 797) n (%)
Gender n (%)			
Male	440 (82.9)	234 (88.0)	674 (84.6)
Female	91(17.1)	32 (12.0)	123 (15.4)
Race n (%)			
American Indian or Alaska Native	3 (0.6)	3 (1.1)	6 (0.8)
Asian	83 (15.6)	40 (15.0)	123 (15.4)
Black or African American	98 (18.5)	36 (13.5)	134 (16.8)
Multiple	46 (8.7)	14 (5.3)	60 (7.5)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.4)	1 (0.1)
White	301 (56.7)	172 (64.7)	473 (59.3)
Ethnicity n (%)			
Hispanic or Latino	126 (23.7)	52 (19.5)	178 (22.3)
Not Hispanic or Latino	380 (71.6)	205 (77.1)	585 (73.4)
Not Reported	19 (3.6)	8 (3.0)	27 (3.4)
Unknown	6 (1.1)	1 (0.4)	7 (0.9)
Region n (%)			
Africa	43 (8.1)	13 (4.9)	56 (7.0)
Asia/Pacific	86 (16.2)	46 (17.3)	132 (16.6)
Europe	199 (37.5)	112 (42.1)	311 (39.0)
Latin America	77 (14.5)	26 (9.8)	103 (12.9)
North America	126 (23.7)	69 (25.9)	195 (24.5)
Age (years)			
18 to 64	527 (99.2)	263 (98.9)	790 (99.1)
>=65	4 (0.8)	3 (1.1)	7 (0.9)
Mean (SD)	35.4 (10.3)	36.9 (11.0)	35.9 (10.5)
Median (min, max)	34.0 (18,66)	35.0 (19,84)	34.0 (18,84)
Baseline CD4 Cell Count (cells/mm^3)			
N†	531	266	797
Mean (SD)	407.6 (213.7)	428.9 (217.3)	414.7 (215.0)
Median (min, max)	380.0 (19,1836)	415.5 (19,1130)	390.0 (19,1836)
Baseline CD4 Cell Counts n (%)			
<=50 cells/mm^3	9 (1.7)	6 (2.3)	15 (1.9)

>50 cells/mm^3 and <=200 cells/mm^3	60 (11.3)	31 (11.7)	91 (11.4)
>200 cells/mm^3	462 (87.0)	229 (86.1)	691 (86.7)
Baseline Plasma HIV RNA (log10 copies/mL)			
N†	531	266	797
Mean (SD)	4.6 (0.7)	4.6 (0.7)	4.6 (0.7)
Median (min, max)	4.6 (1.6, 6.6)	4.6 (2.7, 6.2)	4.6 (1.6, 6.6)
Baseline Plasma HIV RNA (copies/mL)			
N†	531	266	797
Geometric Mean	40518.8	40733.2	40590.2
Median (min, max)	43890.0 (39, 3910386)	40631.0 (454, 1466713)	42424.0 (39,3910386)
Baseline Plasma HIV RNA n (%)			
<=100,000 copies/mL	382 (71.9)	189 (71.1)	571 (71.6)
>100,000 copies/mL	149 (28.1)	77 (28.9)	226 (28.4)
Baseline Plasma HIV RNA n (%)			
<=500,000 copies/mL	506 (95.3)	251 (94.4)	757 (95.0)
>500,000 copies/mL	25 (4.7)	15 (5.6)	40 (5.0)
History of AIDS n (%)			
Yes	79 (14.9)	29 (10.9)	108 (13.6)
No	452 (85.1)	237 (89.1)	689 (86.4)
Stratum n (%)			
Screening HIV RNA<= 100,000	382 (71.9)	190 (71.4)	572 (71.8)
Hepatitis B and/or C Positive††	15 (2.8)	8 (3.0)	23 (2.9)
Baseline Hepatitis Status			
Hep B Positive Only	11 (2.1)	3 (1.1)	14 (1.8)
Hep C Positive Only	4 (0.8)	4 (1.5)	8 (1.0)
Both Hep B and Hep C Positive	0 (0.0)	1 (0.4)	1 (0.1)
Viral Subtype n (%)			
Clade B	335 (63.1)	186 (69.9)	521 (65.4)
Non-Clade B	194 (36.5)	77 (28.9)	271 (34.0)
Missing	2 (0.4)	3 (1.1)	5 (0.6)

† Subjects with missing results excluded.

†† Evidence of hepatitis B surface antigen or evidence of HCV RNA by polymerase chain reaction (PCR) quantitative test for hepatitis C Virus. Nineteen subjects previously classified as hepatitis B or C positive were subsequently identified based on lab tests as being hepatitis B or C negative. Three subjects previously classified as hepatitis B or C negative were subsequently identified based on lab tests as being hepatitis B or C positive.

Note: Raltegravir 1200 mg once daily and raltegravir 400 mg twice daily were administered with emtricitabine (+) tenofovir disoproxil fumarate (TRUVADA™).
N = Number of patients randomized and treated in each treatment group. n (%) = Number (percent) of patients in each sub-category.

The ISENTRESS HD 1200 mg (2 x 600 mg) once daily regimen was non-inferior to the ISENTRESS 400 mg twice daily regimen at both Weeks 48 and 96. At Week 48 88.9% versus 88.3% of once-daily and twice-daily patients, respectively had HIV RNA <40 copies/mL. A summary of antiretroviral response and immunologic effect at Week 96 is shown in Table 17.

Table 17: Efficacy Analysis by Treatment Group at Week 96

	Unadjusted Data Summary by Treatment Group		**Treatment Difference (once daily – twice daily)***
Parameter	**Raltegravir 1200 mg once daily n/N (%)**	**Raltegravir 400 mg twice daily n/N (%)**	**Estimated Difference (95% CI)**
Primary			
Proportion of Patients with HIV RNA <40 copies/mL†	433/531 (81.5)	213/266 (80.1)	1.4 (-4.4, 7.3)§
Supportive			
Proportion of Patients with HIV RNA <50 copies/mL†	439/531 (82.7)	215/266 (80.8)	1.8 (-3.9, 7.5)
Proportion of Patients with HIV RNA <200 copies/mL†	453/531 (85.3)	220/266 (82.7)	2.6 (-2.9, 8.1)
	Mean (95% CI)	Mean (95% CI)	Mean Difference (95% CI)
Secondary			
Change from Baseline in CD4 Cell Count (cells/mm^3) ‡	262 (243, 280)	262 (236, 288)	-0.6 (-32.8, 31.6)

* The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (screening HIV-1 RNA <=100,000 copies/mL or HIV-1 RNA >100,000 copies/mL). The 95% CI for mean difference in CD4 change was based on t-distribution.

† NC=F: Non-Completer=Failure as defined by FDA snapshot approach.

‡ OF: Observed Failure approach.

§ Raltegravir 1200 mg once daily is concluded non-inferior to raltegravir 400 mg twice daily if the lower bound of the 95% CI for the difference in percent response is above -10 percentage points.

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

N = Number of subjects in each treatment group

Week 96 outcomes by the Snapshot Approach at Week 96 are shown in Table 18.

Table 18: Virologic Outcome by Treatment Group at Week 96 Snapshot Approach

Outcome	Raltegravir 1200 mg once daily (N=531) n (%)	Raltegravir 400 mg twice daily (N=266) n (%)
HIV RNA <40 copies/mL	433 (81.5)	213 (80.1)
HIV RNA ≥ 40 copies/mL*	49 (9.2)	22 (8.3)
No Virologic Data at Week 96 Window	49 (9.2)	31 (11.7)
Reasons		
Discontinued study due to AE or Death†	7 (1.3)	7 (2.6)
Discontinued study for Other Reasons‡	36 (6.8)	20 (7.5)
On study but missing data in window	6 (1.1)	4 (1.5)

*Includes subjects who changed any component of background therapy to a new drug class or changed background components that were not permitted per protocol or changed any background drug in the regimen because of lack of efficacy (perceived or documented) before Week 96, subjects who discontinued study drug or study before Week 96 for lack or loss of efficacy and subjects with HIV RNA equal to or above 40 copies/mL in the Week 96 window (relative day 631-714).

†Includes subjects who discontinued because of adverse event (AE) or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

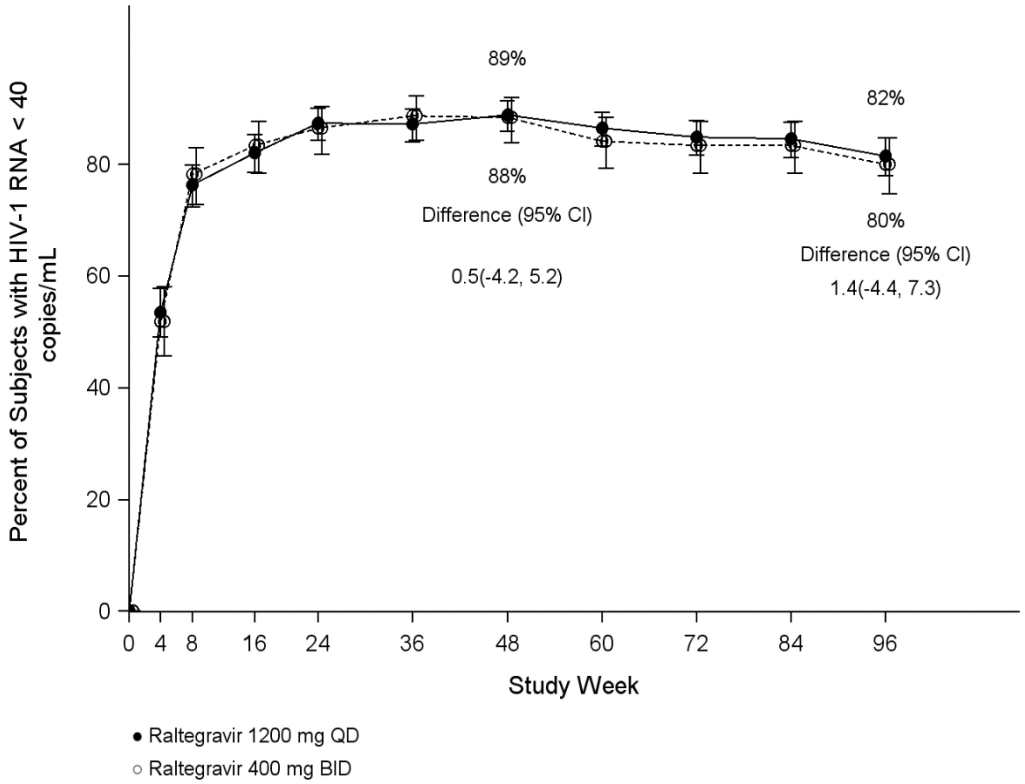
‡Other Reasons includes: lost to follow-up, non-compliance with study drug, physician decision, pregnancy, withdrawal by subject.

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

n (%) = Number (Percent) of subjects in each category.

Figure 3 presents the proportion of patients with HIV RNA <40 copies/mL over time by treatment group. Through 96 weeks of treatment 81.5% in the group receiving ISENTRESS HD 1200 mg (2 x 600 mg) once daily and 80.1% in the group receiving ISENTRESS 400 mg twice daily achieved HIV RNA <40 copies/mL (NC=F approach).

Figure 3: Proportion of Subjects With HIV RNA < 40 copies/mL Over Time (95% CI) Snapshot Approach (Non-Completer=Failure)



In the ONCEMRK trial, ISENTRESS HD 1200 mg (2 x 600 mg) once daily demonstrated consistent virologic and immunologic efficacy relative to ISENTRESS 400 mg twice daily, both in combination with emtricitabine (+) tenofovir disoproxil fumarate, across demographic and baseline prognostic factors, including: baseline HIV RNA levels >100,000 copies/mL and >500,000 copies/mL, demographic groups (including age, gender, race, ethnicity and region), viral hepatitis co-infection status (hepatitis B and/or C), concomitant proton pump inhibitors/H2 blockers use and viral subtypes (comparing non-clade B as a group to clade B).

In the sub-group efficacy analysis by baseline CD4 cell counts at week 96, ISENTRESS HD demonstrated consistent virologic efficacy relative to ISENTRESS 400 mg twice daily. In patients with baseline CD4 cell counts >200 cells/mm^3, 91.4% and 92.2% in the once daily group and twice daily group, respectively, achieved HIV-1 RNA <40 copies/mL [treatment difference of -0.8 (95%CI: -5.1, 4.3)]. In patients with baseline CD4 cell counts >50 and ≤200 cells/mm^3, 81.1% and 80.0% in the once daily group and twice daily group, respectively, achieved HIV-1 RNA <40 copies/ mL [treatment difference of 1.1 (95%CI: -16.2, 22.4)]. The efficacy in patients with baseline CD4 cell counts of less than 50 cells/mm^3 was numerically lower for the once daily regimen (66.7% (6/9) versus 80.0% (4/5) with a treatment difference of -13.3% (95%CI:-53.7, 38.9)); however, the sample size was small (nine patients in the raltegravir once daily group and five in the twice daily group) and the findings were not statistically significant, hence it is difficult to draw meaningful conclusions.

Consistent efficacy in patients receiving ISENTRESS HD 1200 mg (2 x 600 mg) once daily was observed across HIV subtypes with 90.0% (270/300) and 89.5% (162/181) of patients with B and non-B subtypes, respectively, achieving HIV RNA <40 copies/mL at week 96 (OF approach).

Paediatric Patients

IMPAACT P1066 is a Phase I/II open label multicentre trial to evaluate the pharmacokinetic profile, safety, tolerability, and efficacy of raltegravir in HIV infected, children. This study enrolled 126 antiretroviral treatment experienced children and adolescents 2 through to 18 years of age. Patients were stratified by age, enrolling adolescents first and then successively younger children. Patients received either the 400 mg tablet formulation (6 through 18 years of age) or the chewable tablet formulation (2 through 11 years of age). Raltegravir was administered with an optimised background regimen.

The initial dose finding stage included intensive pharmacokinetic evaluation. Dose selection was based upon achieving similar raltegravir exposure and trough concentration as seen in adults, and acceptable short term safety. After dose selection, additional patients were enrolled for evaluation of long term safety, tolerability and efficacy. Of the 126 patients, 96 received the recommended dose of ISENTRESS (see section 4.2).

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

Ninety-three (97%) patients 2 to 18 years of age completed 24 weeks of treatment (3 discontinued due to non-compliance). At week 24, using observed failure (OF) approach to handle missing data, 72% (68/95) achieved $\geq$ 1 $\log_{10}$ HIV RNA drop from baseline or $\leq$ 400 copies/mL (a composite outcome) with 95% CI of (61.4%, 80.4%); 54% (51/95) achieved HIV RNA <50 copies/mL with 95% CI of (43.2%, 64%). The mean CD4 count (percent) increase from baseline to Week 24 was 119 cells/mm^3 (3.8%).

Seventy-two (95%) patients 6 to 18 years of age completed 48 weeks of treatment (4 discontinued due to non-compliance). At week 48, using OF approach to handle missing data, 77% (55/71) achieved $\geq$ 1 $\log_{10}$ HIV RNA drop from baseline or <400 copies/mL with 95% CI of (66.0%, 86.5%); 56% (40/71) achieved HIV RNA <50 copies/mL with 95% CI of (44.0%, 68.1%). The mean CD4 count (percent) increase from baseline to Week 48 was 155 cells mm^3 (4.7%).

5.2 PHARMACOKINETIC PROPERTIES

Absorption - Adults

As demonstrated in healthy volunteers administered single oral doses of raltegravir (400 mg film coated tablet) in the fasted state, raltegravir 400mg twice daily is rapidly absorbed with a T_{max} of approximately 3 hours postdose in the fasted state. Raltegravir AUC and C_{max} increase dose proportionally over the dose range 100 mg to 1600 mg. Raltegravir C_{12hr} increases dose proportionally over the dose range of 100 to 800 mg and increases slightly less than dose proportionally over the dose range 100 mg to 1600 mg. 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. 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.

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

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 400 mg twice daily 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 - Adults

Raltegravir is approximately 83% bound to human plasma proteins *in vitro* over the concentration range of 2 to 10 µM.

In three studies in HIV-infected pregnant women who received raltegravir 400 mg twice daily, raltegravir was found to readily cross the placenta, with median cord blood/maternal blood raltegravir concentration ratios reported as 1.5, 1.21 and 1.48. (see section 5.2 *Pregnancy*).

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.

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

Metabolism and excretion - Adults

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 feces and urine, respectively. In feces, only raltegravir was present, most of which is likely derived from hydrolysis of raltegravir glucuronide secreted in bile as observed in laboratory animal 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 400mg 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 individuals 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 individuals 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
Based on a formulation comparison study in healthy adult volunteers, the chewable tablet has higher oral bioavailability compared to the 400 mg tablet. In this study, administration of the chewable tablet with a high fat meal led to an average 6% decrease in AUC, 62% decrease in C_{max}, and 188% increase in C_{12hr} compared to administration in the fasted state. Administration of the chewable tablet with a high fat meal does not affect raltegravir pharmacokinetics to a clinically meaningful degree and the chewable tablet can be administered without regard to food. The doses recommended for HIV-infected children and adolescents 2 to 18 years of age (see section 4.2) resulted in a pharmacokinetic profile of raltegravir similar to that observed in adults receiving 400 mg twice daily. Table 20 displays pharmacokinetic parameters in the 400 mg tablet (6 to 18 years of age) and the chewable tablet (2 to 11 years of age).

Table 20: Raltegravir Pharmacokinetic Parameters IMPAACT P1066 Following Administration of Doses in DOSAGE AND ADMINISTRATION

Age (years)	Formulation	Dose	N#	AUC $_{0\text{-}12hr}$ (µM*hr) Geometric Mean (%CV)	C_{12h} (nM) Geometric Mean (% CV)
12 to 18	400 mg tablet	400 mg twice daily regardless of weight¥	11	15.7 (98%)	333 (78%)
6 to 11	400 mg tablet	400 mg twice daily for patients ≥ 25 kg	11	15.8 (120%)	246 (221%)
6 to 11	Chewable tablet	Weight based dosing, see Table 1	10	22.6 (34%)	130 (88%)
2 to 5	Chewable tablet	Weight based dosing, see Table 1	12	18.0 (59%)	71 (55%)

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

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

ISENTRESS HD 1200 mg (2 x 600 mg) once daily was not evaluated in a paediatric clinical study, however, population PK modeling and simulation analyses were conducted. Given that all the

paediatric simulated exposures are within the adult exposures observed from Phase III ONCEMRK (Protocol 292), and that there are no safety concerns at the same exposure values, a weight cutoff of 40 kg is deemed adequate to achieve a safe administration of ISENTRESS HD 1200 mg (2 x 600 mg) once daily while maintaining clinical efficacy. These results support the use of ISENTRESS HD 1200 mg (2 x 600 mg) once daily in paediatric patients weighing at least 40 kg.

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 HD 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 individuals. 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 individuals. 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 dialyzable is unknown, dosing before a dialysis session should be avoided.

UGT1A1 Polymorphism

There is no evidence that common UGT1A1 polymorphisms alter raltegravir pharmacokinetics to a clinically meaningful extent. In a comparison of 30 adult individuals with *28/*28 genotype (associated with reduced activity of UGT1A1) to 27 adult individuals with wild-type genotype, the geometric mean ratio (90% CI) of AUC was 1.41 (0.96, 2.09).

Pregnancy

The pharmacokinetics of raltegravir during pregnancy has been investigated in two clinical studies in which HIV-infected pregnant women received raltegravir-based antiretroviral therapy, at the dose of raltegravir 400mg twice daily. One study of 42 HIV-infected pregnant women with PK sampling performed at 0-26 weeks and 30- 36 weeks of gestation and 6-12 weeks postpartum found that raltegravir exposure during the second and third trimester was approximately half that post-partum. The second study of 22 HIV-infected pregnant women in which PK sampling was performed in the third trimester and more than 2 weeks post-partum found that 11 of 17 patients with complete paired pharmacokinetic curves showed a decrease in raltegravir exposure in the third trimester compared with postpartum; exposure in the third trimester was increased in the other 6 women. As most women had undetectable HIV RNA levels at delivery and mother-to-child-transmission of HIV was not observed among the limited number of maternal–infant pairs, dose modification is not routinely recommended. Decisions based on individual patient monitoring under specialist care are recommended as required.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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* tests for clastogenic activity

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 than (females) or equal to (males) the clinical AUC (54 µM●hr) at the 400-mg twice daily dose. In rats, treatment-related squamous cell carcinomas of the nose/nasopharynx were identified in high- and mid-dose group animals treated with raltegravir for two years. No tumors of the nose/nasopharynx were observed in rats dosed with 50 mg/kg/day in females and 150 mg/kg/day in males at which systemic exposure was approximately 1.5 fold greater than the AUC (54 µM●hr) at the clinical 400-mg twice daily dose.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ISENTRESS HD 600 mg Tablet

Each tablet 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.

ISENTRESS 400 mg Tablet

Each tablet 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.

ISENTRESS 100 mg Chewable Tablet

Each tablet contains the following inactive ingredients: hydroxypropylcellulose, sucralose, saccharin sodium, sodium citrate, mannitol, red iron oxide, yellow iron oxide, ammonium glycyrrhizinate, sorbitol, fructose, natural and artificial flavours (orange, banana and masking that contains aspartame),

crospovidone, magnesium stearate, sodium stearyl fumarate, ethylcellulose 20 cP, ammonium hydroxide, medium chain triglycerides, oleic acid, hydroxypropylmethyl cellulose 2910/6cP, macrogol 400.

ISENTRESS 25 mg Chewable Tablet
Each tablet contains the following inactive ingredients: hydroxypropylcellulose, sucralose, saccharin sodium, sodium citrate, mannitol, yellow iron oxide, ammonium glycyrrhizinate, sorbitol, fructose, natural and artificial flavours (orange, banana and masking that contains aspartame), crospovidone, magnesium stearate, sodium stearyl fumarate, ethylcellulose 20 cP, ammonium hydroxide, medium chain triglycerides, oleic acid, hydroxypropylmethyl cellulose 2910/6cP, macrogol 400.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

ISENTRESS and ISENTRESS HD film-coated and ISENTRESS chewable tablets should be stored below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Film-Coated Tablets
ISENTRESS HD

- 600 mg yellow, oval tablet debossed with the corporate logo and “242” on one side and plain on the other.

ISENTRESS

- 400 mg pink, oval, biconvex tablet debossed with "227" on one side and plain on the other.

Available in HDPE bottles of 60.

Chewable Tablets
ISENTRESS

- 100 mg pale orange, oval-shaped, orange-banana flavoured, scored chewable tablets with the corporate logo and "477" on opposite sides of the score and scored on the reverse sside.
- 25 mg pale yellow, round, orange-banana flavoured, chewable tablets with the corporate logo on one side and "473" on the other side.

Available in HDPE bottles of 60.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

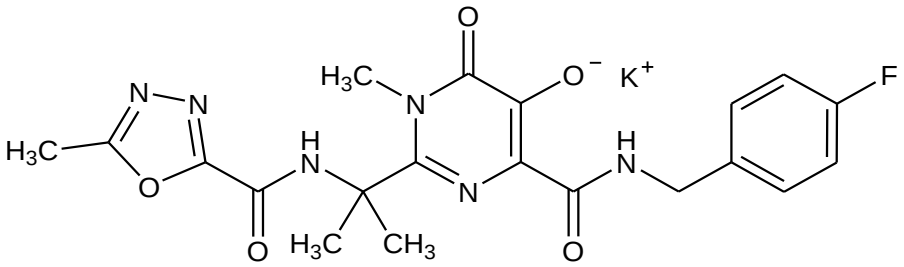
6.7 PHYSICOCHEMICAL PROPERTIES

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

Chemical structure

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:



CAS number

871038-72-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (schedule 4)

8 SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A,
26 Talavera Road
Macquarie Park, NSW 2113
Australia

9 DATE OF FIRST APPROVAL

30 January 2008

10 DATE OF REVISION

2 November 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
Various	Minor editorial changes throughout the Product Information
	Update to Company Copyright Statement

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