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PRODUCT INFORMATION

ISENTRESS™

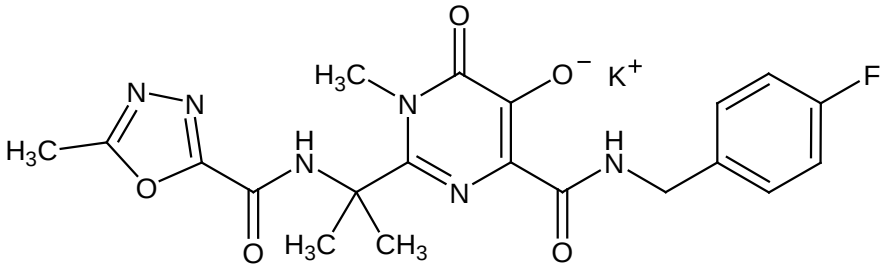
(raltegravir, MSD)

NAME OF THE MEDICINE

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

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 Registry Number: 871038-72-1

DESCRIPTION

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 400 mg Tablet

Each film-coated tablet of ISENTRESS contains 400 mg of raltegravir (as potassium salt) and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, calcium phosphate dibasic anhydrous, hypromellose 2208, poloxamer 407 (contains 0.01% butylated hydroxytoluene as antioxidant), sodium stearyl fumarate, magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, red iron oxide and black iron oxide.

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[1] TRADEMARK of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, N.J USA

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ISENTRESS 100 mg Chewable Tablet

Each chewable tablet contains 100 mg of raltegravir (as potassium salt) and 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 chewable tablet contains 25 mg of raltegravir (as potassium salt) and the following inactive ingredients: hydroxypropylcellulose, sucralose, saccharin sodium, sodium citrate, mannitol, yellow iron oxide, ammonium glycyrrhizinate, sorbitol, fructose, natural and artificial flavors (orange, banana and masking that contains aspartame), cospovidone, magnesium stearate, sodium stearyl fumarate, ethylcellulose 20 cP, ammonium hydroxide, medium chain triglycerides, oleic acid, hydroxypropylmethyl cellulose 2910/6cP, macrogol 400.

PHARMACOLOGY

Mechanism of action:

Raltegravir inhibits the catalytic activity of HIV integrase, an HIV-encoded enzyme that is required for viral replication. Inhibition of integrase prevents the covalent insertion, or integration, of the HIV genome into the host cell genome during the early phase of infection. HIV genomes that fail to integrate cannot direct the production of new infectious viral particles, so inhibiting integration prevents propagation of the viral infection. Raltegravir did not significantly inhibit human phosphoryltransferases including DNA polymerases α, β, and γ.

PHARMACODYNAMICS:

Microbiology

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

PHARMACOKINETICS:

Absorbtion - Adults

Raltegravir 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. With twice-daily dosing, pharmacokinetic steady state is achieved rapidly, within approximately the first 2 days of dosing. There is little to no accumulation in AUC and C_{max} and evidence of slight accumulation in C_{12hr}. The absolute bioavailability of raltegravir has not been established.

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

Effect of Food on Oral Absorption

Raltegravir was administered without regard to food in the pivotal safety and efficacy studies in HIV-infected patients. The effect of consumption of low-, moderate- and

high-fat meals on steady-state raltegravir pharmacokinetics was assessed in healthy volunteers. Administration of multiple doses of raltegravir following a moderate-fat meal did not affect raltegravir AUC to a clinically meaningful degree with an increase of 13% relative to fasting. Raltegravir $C_{12\ hr}$ was 66% higher and C_{max} was 5% higher following a moderate-fat meal compared to fasting. Administration of raltegravir following a high-fat meal increased AUC and C_{max} by approximately 2-fold and increased $C_{12\ hr}$ by 4.1-fold. Administration of 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.

Distribution - Adults

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

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

Metabolism and 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 radiolabeled raltegravir, approximately 51 and 32% of the dose was excreted in feces and urine, respectively. In feces, only raltegravir was present, most of which is likely derived from hydrolysis of raltegravir-glucuronide secreted in bile as observed in 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 was performed in young adult 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. No dosage adjustment is necessary.

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Age

The effect of age (18 years and older) 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 DOSAGE AND ADMINISTRATION) resulted in a pharmacokinetic profile of raltegravir similar to that observed in adults receiving 400 mg twice daily. Table 1 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 1: Raltegravir Pharmacokinetic Parameters IMPAACT P1066 Following Administration of Doses in DOSAGE AND ADMINISTRATION

Age (years)	**Formulation**	**Dose**	**N#**	**AUC $_{0-12hr}$ (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 15	10	22.6 (34%)	130 (88%)
2 to 5	Chewable tablet	Weight based dosing, see Table 15.	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.

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

Race

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

Body Mass Index (BMI)

The composite analysis assessed the effect of BMI on the pharmacokinetics of raltegravir in adults. There was no clinically meaningful effect of BMI on raltegravir pharmacokinetics. Additionally, no clinically meaningful effect of body weight on raltegravir pharmacokinetics was identified in the population PK analysis. No dosage adjustment is necessary.

Hepatic Insufficiency

Raltegravir is eliminated primarily by glucuronidation in the liver. A study of the pharmacokinetics of raltegravir was performed in adult 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. 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 adult 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. 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).

CLINICAL TRIALS

ADULTS

The evidence of durable efficacy of ISENTRESS is based on the analyses of 96 week data from 2 ongoing, randomized, double-blind, placebo-controlled trials, BENCHMRK 1 and BENCHMRK 2 (Protocols 018 and 019), in antiretroviral

treatment-experienced HIV-1 infected adult patients and the analysis of 156-week data from an ongoing, randomized, double-blind, active-control trial, STARTMRK (P021) in treatment-naïve HIV-1 infected 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. Randomization was stratified by degree of resistance to PI (1PI vs. >1PI) and the use of enfuvirtide in the OBT. Prior to randomization, OBT was selected by the investigator based on genotypic/phenotypic resistance testing and prior ART history.

Table 2 shows the demographic characteristics between patients in the group receiving ISENTRESS 400 mg b.i.d. and patients in the group receiving placebo.

Table 2: 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)

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BENCHMRK 1 and 2 Pooled	ISENTRESS 400 mg b.i.d. + OBT (N = 462)	Placebo + OBT (N = 237)
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 3 compares the characteristics of optimized background therapy at baseline in the group receiving ISENTRESS 400 mg b.i.d. and patients in the control group.

Table 3: Characteristics of Optimized 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 randomized 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 4.

Table 4: Outcomes by Treatment Group through Week 48 and 96

Randomized 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)

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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 changes 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).

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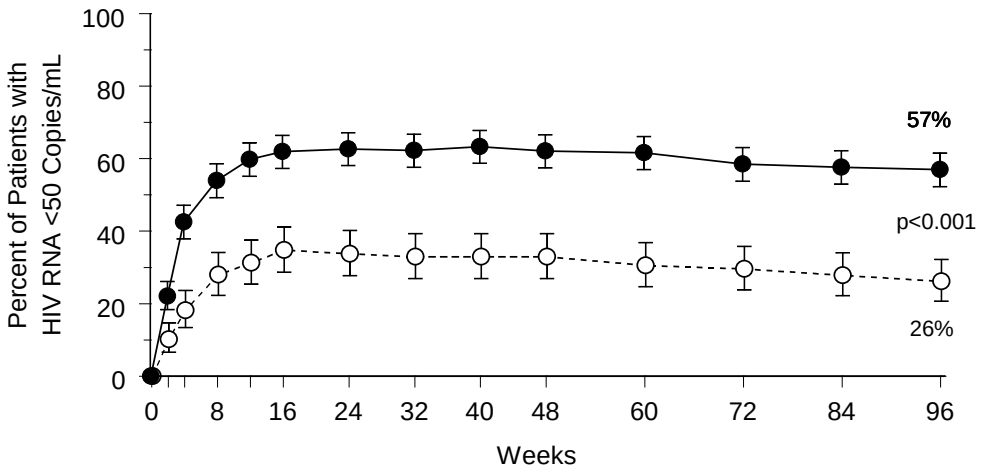
Figure 1: Proportion of Patients with HIV RNA <50 Copies/mL (95%CI) Over Time (NC=F)



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 5. 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 5: 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						

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BENCHMRK 1 and 2 Pooled	ISENTRESS 400 mg b.i.d. + OBT (N =425)			Placebo + OBT (N =219)		
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 randomized them 1:1 to continue lopinavir (+) ritonavir 2 tablets twice daily (n=174 and n=178, respectively) or replace lopinavir (+) ritonavir with raltegravir 400 mg twice daily (n=174 and n=176, respectively). Patients with a prior history of virological failure were not excluded and the number of previous antiretroviral therapies was not limited.

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

TREATMENT-NAÏVE PATIENTS

STARTMRK (Protocol 21) is a Phase III study to evaluate the safety and antiretroviral activity of ISENTRESS 400 mg b.i.d. + emtricitabine (+) tenofovir versus efavirenz + emtricitabine (+) tenofovir 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, or emtricitabine. Randomization was stratified by screening HIV RNA level (≤50,000 copies/mL; and >50,000 copies/mL) and by hepatitis B or C coinfection status.
Table 6 shows the demographic characteristics between patients in the group receiving ISENTRESS 400 mg b.i.d and patients in the group receiving efavirenz.

Table 6: Patient Baseline Characteristics

	ISENTRESS 400 mg b.i.d. (N = 281)	Efavirenz 600 mg at bedtime. (N = 282)	Total (N = 563)

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	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)

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	ISENTRESS 400 mg b.i.d. (N = 281)	Efavirenz 600 mg at bedtime. (N = 282)	Total (N = 563)
>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.
N = Number of patients in each group.
n (%) = Number (percent) of patients in each sub-category.

Week 48 and 156 outcomes in STARTMRK are shown in Table 7.

Table 7: Outcomes by Treatment Group through Week 48 and 156

Randomized Study Protocol 021	Outcome at Week 48			Outcome at Week 156		
	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)	212 (75.4)	192 (68.1)	7.3% (-0.2, 14.7)
Patients with HIV RNA less than 400 copies/mL[†]	252 (90.0)	241 (85.8)	4.1% (-1.3, 9.7)	224 (79.7)	203 (72.0)	7.6% (0.5, 14.6)
Mean CD4 cell count change from baseline (cells/mm^3)[†]	189.1	163.3	25.8 (4.4, 47.2)	331.7	295.2	36.6 (3.9, 69.2)
Virologic Failure (confirmed)[‡] (<50)	27 (9.6)	39 (13.8)		49 (17.4)	52 (18.4)	
Non responder	10 (3.6)	24 (8.5)		10 (3.6)	23 (8.2)	
Rebound	17 (6.0)	15 (5.3)		39 (13.9)	29 (10.3)	
Death	2 (0.7)	0 (0.0)		4 (1.4)	1 (0.4)	
Discontinuation due to clinical adverse experiences	8 (2.8)	17 (6.0)		13 (4.6)	21 (7.4)	
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)		38 (13.5)	47 (16.7)	

[†]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.

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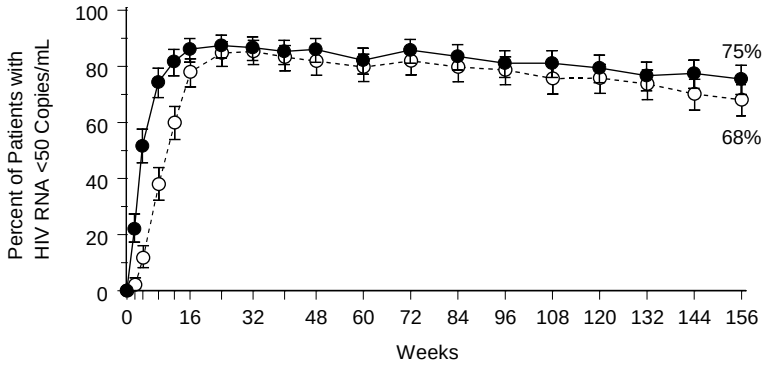
Randomized Study Protocol 021	Outcome at Week 48			Outcome at Week 156		
	ISENTRESS 400 mg b.i.d. (N=281) n (%)	Efavirenz 600 mg q.h.s. (N=282) n (%)	Difference (ISENTRESS – Efavirenz) (CI†)	ISENTRESS 400 mg b.i.d. (N=281) n (%)	Efavirenz 600 mg q.h.s. (N=282) n (%)	Difference (ISENTRESS – Efavirenz) (CI†)
Note: ISENTRESS and Efavirenz were administered with 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. Through 156 weeks of treatment 75% in the group receiving ISENTRESS 400 mg b.i.d. and 68% 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

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

At week 156, the treatment difference (raltegravir – efavirenz) was 7.3% favouring raltegravir with an associated 95% CI of (-0.2, 14.7). 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.

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In the STARTMRK trial of combination antiretroviral therapy in treatment-naive patients, ISENTRESS with emtricitabine (+) tenofovir demonstrated consistent virologic and immunologic efficacy relative to efavirenz with emtricitabine (+) tenofovir 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 88.0% (162/184) and 94.0% (47/50) of patients with B and non-B subtypes respectively, achieving HIV RNA <50 copies/mL at week 156 (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 optimized 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 DOSAGE AND ADMINISTRATION).

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%).

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INDICATIONS

ISENTRESS, 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 CLINICAL TRIALS).

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 CLINICAL TRIALS).

There are no study results demonstrating the effect of ISENTRESS on clinical progression of HIV-1 infection.

CONTRAINDICATIONS

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

PRECAUTIONS

Certain side effects that have been reported with ISENTRESS may affect some patients' ability to drive or operate machinery. Individual responses to ISENTRESS may vary (See: ADVERSE EFFECTS).

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.

SEVERE SKIN AND HYPERSENSITIVITY REACTIONS

Severe, potentially life-threatening, and fatal skin reactions have been reported in patients taking ISENTRESS concomitantly with other drugs associated with these reactions. These include cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. Hypersensitivity reactions have also been reported and were characterised by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure. Discontinue ISENTRESS and other suspect agents immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy

initiated. Delay in stopping ISENTRESS treatment or other suspect agents after the onset of severe rash may result in a life-threatening reaction.

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 B3*)*:

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 resulted in exposures (based on AUC) that were approximately 3- (rats) to 4- (rabbits) fold the human value at the standard recommended clinical dose of 400 mg twice daily. An increased incidence of foetal supernumerary ribs was observed in rats the highest dose, but not at a dose of 300 mg/kg/day (drug exposure approximately 2-fold the human value). Foetal development was unaffected in rabbits. Placental transfer of raltegravir to the foetus was substantial in rats, but minimal in rabbits.

There are no adequate and well-controlled studies in pregnant women; therefore, the safety of ISENTRESS in pregnant women is not known. ISENTRESS is not recommended for use in pregnancy.

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.

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.

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

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.

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USE IN PATIENTS WITH IMPAIRED HEPATIC FUNCTION

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.

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.

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.

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.

Interactions with other medicines

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

Similarly, raltegravir is not an inhibitor (IC_{50}>50 µM) of the UDP-glucuronosyltransferases (UGTs) tested (UGT1A1, UGT2B7), and raltegravir does not inhibit P-glycoprotein-mediated transport. Based on these data, ISENTRESS is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or P-glycoprotein (e.g., protease inhibitors, NNRTIs, methadone, opioid

analgesics, statins, azole antifungals, proton pump inhibitors, oral contraceptives, and anti-erectile dysfunction agents).

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

Coadministration of ISENTRESS with drugs that are potent inducers of UGT1A1, such as rifampin (an inducer of numerous drug metabolizing enzymes), reduces plasma concentrations of ISENTRESS. Caution should be used when coadministering ISENTRESS with rifampin or other strong inducers of UGT1A1. If co-administration with rifampin is unavoidable, a doubling of the dose of ISENTRESS can be considered. Until further pharmacokinetic data are available, rifampin co-administration with ISENTRESS chewable tablet is not recommended. The impact of other potent inducers of drug metabolizing 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.

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

Effect of Raltegravir on the Pharmacokinetics of Other Agents

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

Effect of Other Agents on the Pharmacokinetics of Raltegravir

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

All interaction studies were performed in adults.

In healthy individuals, co-administration of ISENTRESS with omeprazole increases raltegravir plasma levels. As the effects of increasing gastric pH on the absorption of raltegravir in HIV-infected patients are uncertain, use ISENTRESS with medicinal products that increase gastric pH (e.g., proton pump inhibitors and H2 antagonists) only if unavoidable.

Drug interactions are further described below in Table 8.

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Table 8: 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}
atazanavir	400 mg daily	100 mg single dose	10	1.53 (1.11, 2.12)	1.72 (1.47, 2.02)	1.95 (1.30, 2.92)
atazanavir/ritonavir	300 mg/100 mg daily	400 mg twice daily	10	1.24 (0.87, 1.77)	1.41 (1.12, 1.78)	1.77 (1.39, 2.25)
darunavir /ritonavir	600 mg/100 mg twice daily	400 mg twice daily	6	0.67 (0.33-1.37)	0.71 (0.38-1.33)	1.38 (0.16-12.12)
efavirenz	600 mg daily	400 mg single dose	9	0.64 (0.41, 0.98)	0.64 (0.52, 0.80)	0.79 (0.49, 1.28)
Etravirine	200 mg twice daily	400 mg twice daily	19	0.89 (0.68, 1.15)	0.90 (0.68, 1.18)	0.66 (0.34, 1.26)
omeprazole	20 mg daily	400 mg single dose	14 (10 for AUC)	4.15 (2.82, 6.10)	3.12 (2.13, 4.56)	1.46 (1.10, 1.93)
rifampin	600 mg daily	400 mg single dose	9	0.62 (0.37, 1.04)	0.60 (0.39, 0.91)	0.39 (0.30, 0.51)
rifampin	600 mg daily	800 mg twice daily	14	1.62* (1.12, 2.33)	1.27* (0.94, 1.71)	0.47* (0.36, 0.61)
ritonavir	100 mg twice daily	400 mg single dose	10	0.76 (0.55, 1.04)	0.84 (0.70, 1.01)	0.99 (0.70,1.40)
tenofovir	300 mg daily	400 mg twice daily	9	1.64 (1.16, 2.32)	1.49 (1.15, 1.94)	1.03 (0.73, 1.45)
tipranavir/ritonavir	500 mg/200 mg twice daily	400 mg twice daily	15 (14 for C_{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.						

ADVERSE 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 randomized clinical studies, BENCHMRK 1 and BENCHMRK 2 reported using the recommended dose of ISENTRESS 400 mg twice

daily in combination with optimized background therapy (OBT) in 462 patients, in comparison to 237 patients taking placebo in combination with OBT. During double-blind treatment, the total follow-up was 1051 patient-years in the group receiving ISENTRESS 400 mg b.i.d. and 322 patient-years in the group receiving placebo.

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 9.

Table 9: 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, %	**Randomized 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		

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System Organ Class, Preferred Term, %	Randomized 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 %**
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 gastroesophageal 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

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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 hospitalization 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.

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CLINICAL TRIALS EXPERIENCE

TREATMENT- NAIVE

The following safety assessment of ISENTRESS in treatment-naïve patients is based on the randomized double-blind active controlled study of treatment-naïve patients, protocol 021 (STARTMRK) with ISENTRESS 400 mg twice daily in combination with a fixed dose of emtricitabine 200 mg (+) tenofovir 245 mg, (N=281) versus efavirenz (EFV) 600 mg at bedtime in combination with emtricitabine (+) tenofovir (N=282). During double-blind treatment, the total follow-up for patients with ISENTRESS 400 mg twice daily + emtricitabine (+) tenofovir was 830 patient-years and 788 patient-years for patients with efavirenz 600 mg at bedtime + emtricitabine (+) tenofovir.

Numbers (%) of patients with clinical adverse experiences and with drug-related adverse experiences in the group receiving ISENTRESS, were less frequent than in the group receiving efavirenz. In this study, the rates of discontinuation of therapy due to adverse experiences (clinical and laboratory) were 4.6% in patients receiving ISENTRESS + emtricitabine (+) tenofovir and 8.5% in patients receiving efavirenz + emtricitabine (+) tenofovir.

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

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

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Nervous System Disorders		
Dizziness	8.9	37.6
Headache	23.5	27.0
Psychiatric Disorders		
Abnormal dreams	7.1	13.1
Insomnia	13.9	12.4
Respiratory, Thoracic and Medastinal Disorders		
Cough	14.9	10.3
Skin and Subcutaneous Tissue Disorder		
Rash	7.5	13.1

*Intensities are defined as follows: Mild (awareness of sign or symptom, but easily tolerated); Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).

†n=total number of 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 as compared with the group receiving efavirenz + emtricitabine (+) tenofovir, 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.

Drug-related clinical adverse reactions of moderate to severe intensity occurring in ≥2% of treatment-naïve adult patients are presented in Table 11.

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Table 11: 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	Randomized Study STARTMRK	
	ISENTRESS 400 mg b.i.d. + Emtricitabine (+) Tenofovir N = 281 %	Efavirenz 600 mg at bedtime + Emtricitabine (+) Tenofovir N = 282 %
Gastrointestinal Disorders		
Diarrhoea	1.1	2.8
Nausea	2.8	3.5
General Disorders and Administration Site Conditions		
Fatigue	1.8	2.8
Nervous System Disorders		
Dizziness	1.4	6.4
Headache	3.9	5.0
Psychiatric Disorders		
Insomnia	3.6	3.9
Skin and Subcutaneous Tissue Disorders		
Rash	0.0	2.8
Rash Maculo-Papular	0.0	2.5
* Includes adverse experiences at least possibly, probably, or very likely related to the drug **N=total number of patients per treatment group		

Less Common Adverse Reactions

Drug related clinical adverse experiences, occurring in less than 2% of treatment-naïve patients (n=281) receiving ISENTRESS + emtricitabine (+) tenofovir and of moderate to severe intensity are listed below by System Organ Class.

Blood and Lymphatic System Disorders

lymph node pain, neutropenia, anaemia, lympadenopathy

Ear and Labyrinth Disorders

tinnitus, *vertigo*

Gastrointestinal Disorders

diarrhoea, *abdominal pain, vomiting, abdominal pain upper, dyspepsia, erosive duodenitis, gastoesophageal reflux disease, abdominal distension*

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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, hypercholesterolemia

Musculoskeletal and Connective Tissue Disorders

arthritis, neck pain

Nervous System Disorders

dizziness, hypersomnia, somnolence, *memory impairment*

Psychiatric Disorders

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

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: anaemia, immune reconstitution syndrome, mental disorder, suicide attempt.

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SELECTED ADVERSE EXPERIENCES – Treatment experienced and naive:

CANCERS:

Cancers were observed in treatment-experienced patients who initiated ISENTRESS or placebo, both with OBT, and in treatment-naïve patients who initiated ISENTRESS or efavirenz, both with emtricitabine (+) tenofovir; several were recurrent. The types and rates of specific cancers were those expected in a highly immunodeficient population (many had CD4+ counts below 50 cells/mm^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 12). 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.

PATIENTS WITH CO-EXISTING CONDITIONS

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

In Phase III studies, treatment-experienced patients (N=114/699 or 16%) and treatment-naïve patients (N = 34/563 or 6%)with chronic (but not acute) active hepatitis B and/or hepatitis C coinfection were permitted to enroll provided that baseline liver function tests did not exceed 5 times the upper limit of normal. In general, the safety profile of ISENTRESS in patients with hepatitis B and/or hepatitis C co-infection was similar to that in patients without hepatitis B and/or hepatitis C coinfection, although the rates of AST and ALT abnormalities were somewhat higher in the subgroup with hepatitis B and/or hepatitis C coinfection 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 CLINICAL TRIALS]. Of the 126 patients, 96 received the recommended dose of ISENTRESS.

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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

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 12.

Table 12: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Experienced Adult Patients

		Randomized Studies, BENCHMRK 1 and BENCHMRK 2	
Laboratory Parameter Preferred Term (Unit)	**Limit**	**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			

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Laboratory Parameter Preferred Term (Unit)	Limit	Randomized Studies, BENCHMRK 1 and BENCHMRK 2 ISENTRESS 400 mg b.i.d. + OBT (N = 462)	Placebo + OBT (N = 237)
Grade 2	2.6 - 5.0 x ULN	2.2%	0.4%
Grade 3	5.1 - 10.0 x ULN	0.4%	1.3%
Grade 4	>10.0 x ULN	0.7%	0.4%
Serum creatine kinase			
Grade 2	6.0 - 9.9 x ULN	2.6%	2.1%
Grade 3	10.0 - 19.9 x ULN	4.1%	2.5%
Grade 4	≥20.0 x ULN	3.0%	1.3%
ULN = Upper limit of normal range			

The percentages of treatment-naïve adult patients receiving either ISENTRESS 400 mg twice daily or efavirenz (both with emtricitabine (+) tenofovir) in P021 with selected Grade 2 to 4 laboratory abnormalities that represent a worsening Grade from baseline are presented in Table 13.

Table 13: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Naïve Adult Patients

Laboratory Parameter Preferred Term (Unit)	Limit	Randomized Study STARTMRK ISENTRESS 400 mg b.i.d. + Emtricitabine (+) Tenofovir (N = 281) % (n/m)	Efavirenz 600 mg at bedtime + Emtricitabine (+) Tenofovir (N = 282) % (n/m)
Blood chemistry			
Fasting (non-random) serum glucose test (mg/dL)			
Grade 2	126 – 250	4.4% (12/274)	5.3% (14/266)
Grade 3	251 – 500	1.5% (4/274)	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)	0.0% (0/279)
Grade 3	2.6 - 5.0 x ULN	0.7% (2/281)	0.0% (0/279)

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		Randomized Study STARTMRK	
		ISENTRESS	**Efavirenz**
		400 mg	**600 mg**
		b.i.d. + Emtricitabine (+) Tenofovir	**at bedtime + Emtricitabine (+) Tenofovir**
Laboratory Parameter Preferred Term (Unit)	**Limit**	**(N = 281)**	**(N = 282)**
		% (n/m)	**% (n/m)**
Blood chemistry			
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	5.3% (15/281)	7.2% (20/279)
Grade 3	5.1 - 10.0 x ULN	3.2% (9/281)	2.5 % (7/279)
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	10.3% (29/281)	9.7% (27/279)
Grade 3	5.1 - 10.0 x ULN	1.1% (3/281)	1.8% (5/279)
Grade 4	>10.0 x ULN	1.1% (3/281)	0.7% (2/279)
Serum alkaline phosphatase			
Grade 2	2.6 - 5.0 x ULN	1.1% (3/281)	2.9% (8/279)
Grade 3	5.1 - 10.0 x ULN	0.4% (1/281)	0.4% (1/279)
Grade 4	>10.0 x ULN	0.0% (0/281)	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 144 weeks of therapy, ISENTRESS demonstrated minimal effects on serum lipids with small increases in total and LDL cholesterol and a decrease in serum triglycerides. The group treated with efavirenz had a significantly higher mean change from baseline in total cholesterol, triglycerides, non-HDL-C, and LDL-C. Modest increases in HDL were observed in both groups, significantly higher for efavirenz (see Table 14 Lipids, Change from Baseline).

Changes from baseline in fasting lipids are shown in Table 14.

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Table 14: STARTMRK Lipid Values, Change from Baseline in Serum Lipids at Week 144 - Adults

Laboratory Parameter Preferred Term (Unit)	ISENTRESS 400 mg b.i.d. N = 281		Efavirenz 600 mg at bedtime. N = 282	
		Change from Baseline at Week 144		Change from Baseline at Week144
	Baseline Mean (N)	Mean Change (95% CI)[†]	Baseline Mean (N)	Mean Change (95% CI)[†]
Total Cholesterol (mg/dL)[‡]	159.5 (224)	12.5 (8.2, 16.8)	155.5 (208)	39.2 (34.2, 44.1)
HDL-Cholesterol (mg/dL)[‡]	38.4 (222)	4.5 (3.3, 5.6)	37.9 (207)	10.5 (9.0, 12.0)
LDL-Cholesterol (mg/dL)[‡]	97.0 (217)	7.5 (3.8, 11.2)	92.0 (200)	22.3 (18.2, 26.5)
Triglyceride (mg/dL)[‡]	125.9 (224)	1.3 (-9.8, 12.4)	138.8 (208)	34.8(15.6, 54.0)
Total: HDL-C ratio	4.4 (222)	-0.2 (-0.3, -0.1)	4.4 (207)	0 (-0.2, 0.2)
Non-HDL-C (mg/dL)	121.0 (222)	7.9 (3.9, 11.9)	117.8 (207)	28.7 (23.8, 33.6)

[†]Within group 95% CIs were based on t-distribution.
[‡]Fasting (non-random) laboratory tests at Week 144.
Notes:

ISENTRESS and efavirenz were administered with emtricitabine (+) tenofovir.
N = Number of patients in the treatment group. The analysis is based all available data

P≤0.001 for comparison of ISENTRESS vs. efavirenz except Total: HDL-C ratio (p-value=0.061) and Triglyceride (p-value=0.004).

The Last Obs. Carry Forward (LOCF) approach is applied for the missing data when the missing is due to increased lipids (e.g., use of rescue therapy).

POSTMARKETING EXPERIENCE

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

Blood and Lympatic 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),

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including suicidal ideation and behaviors

Skin and Subcutaneous Tissue Disorders

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

DOSAGE AND ADMINISTRATION

ISENTRESS is available as a 400 mg tablet formulation and as a chewable tablet formulation in 100 mg (scored) and 25 mg strengths.

ISENTRESS can be administered with or without food.

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

Chewable tablets are to be chewed, not swallowed whole. Because the formulations are not bioequivalent, do not substitute chewable tablets for the 400 mg tablet. Maximum dose of chewable tablets is 300 mg twice daily

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

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

Adults: One 400 mg tablet twice daily, orally.

Children and adolescents:

- 6 years of age and older (if at least 25 kg in weight): One 400 mg tablet twice daily, orally
- 2 to 11 years of age: Chewable tablets: weight based to maximum dose 300 mg, twice daily as recommended in Table 15.

Table 15: Recommended dose for ISENTRESS Chewable Tablets in Paediatric Patients 2 to11 Years of Age

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 dosage recommendation 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.

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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 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.

OVERDOSAGE

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

In the event of an overdose, it is reasonable to employ the standard supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required. The extent to which ISENTRESS may be dialyzable is unknown.

Contact the Poisons Information Centre (telephone 13 11 26) for advice regarding management of overdose.

PRESENTATION AND STORAGE CONDITIONS

FILM-COATED TABLETS

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

Available in bottles of 60.

CHEWABLE TABLETS

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

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Available in bottles of 60.

ISENTRESS film-coated and chewable tablets should be stored below 300C.

NAME AND ADDRESS OF THE SPONSOR

MERCK SHARP & DOHME (AUSTRALIA) PTY LIMITED

54-68 FERNDELL STREET

GRANVILLE

NSW 2142

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4).

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

30 January 2008

DATE OF MOST RECENT AMENDMENT

31 January 2013