PRODUCT CIRCULAR

SG-MK0518-T-112020

ISENTRESS®-G Tablets
(raltegravir 400 mg)
ISENTRESS® Chewable Tablets
(raltegravir 25 mg and 100 mg)

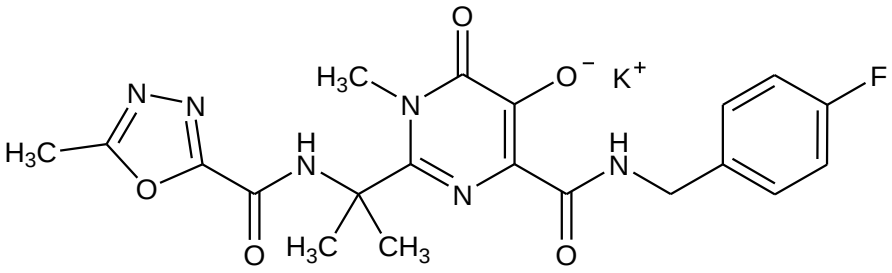
I. THERAPEUTIC CLASS

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

II. CHEMISTRY

The chemical name for raltegravir potassium is *N*-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt.

The empirical formula is $C_{20}H_{20}FKN_6O_5$ and the molecular weight is 482.51. The structural formula is:



Raltegravir potassium is a white to off-white powder. It is soluble in water, slightly soluble in methanol, very slightly soluble in ethanol and acetonitrile and insoluble in isopropanol.

III. COMPOSITION

IIIa. Active Ingredients

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

Each 100 mg chewable tablet of ISENTRESS contains 108.6 mg of raltegravir (as potassium salt), equivalent to 100 mg of raltegravir free phenol.

Each 25 mg chewable tablet of ISENTRESS contains 27.16 mg of raltegravir (as potassium salt), equivalent to 25 mg of raltegravir free phenol.

IIIb. Inactive Ingredients – 400 mg Tablet

Each film-coated tablet of ISENTRESS-G 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, and black iron oxide.

IIIc. Inactive Ingredients – Chewable Tablets

Each 100 mg chewable tablet of ISENTRESS contains the following inactive ingredients: hydroxypropyl cellulose, sucralose, saccharin sodium, sodium citrate dihydrate, mannitol, red ferric oxide, yellow ferric oxide, monoammonium glycyrrhizinate, sorbitol, fructose, natural and artificial flavors (orange, banana, and masking that contains aspartame), crospovidone, magnesium stearate, sodium stearyl fumarate, ethylcellulose 20 cP, ammonium hydroxide, medium chain triglycerides, oleic acid, hypromellose 2910/6cP, macrogol/PEG 400.

Each 25 mg chewable tablet of ISENTRESS contains the following inactive ingredients: hydroxypropyl cellulose, sucralose, saccharin sodium, sodium citrate dihydrate, mannitol, yellow ferric oxide, monoammonium glycyrrhizinate, sorbitol, fructose, natural and artificial flavors (orange, banana, and masking that contains aspartame), crospovidone, magnesium stearate, sodium stearyl fumarate, ethylcellulose 20 cP, ammonium hydroxide, medium chain triglycerides, oleic acid, hypromellose 2910/6cP, macrogol/PEG 400.

IV. PHARMACEUTICAL FORM

400 mg Tablet

Film-coated tablet.

Grey, oval, biconvex tablet, debossed with "227" and Merck logo on one side and plain on the other.

100 mg Chewable Tablet

Pale orange, oval shaped scored tablet, debossed with the Merck logo on one side of the score and 477 on the other, and scored on the other side of the tablet.

25 mg Chewable Tablet

Pale yellow, round, flat faced, beveled edge tablet debossed with the Merck logo on one side and 473 on the other.

V. INDICATIONS

Adults

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

This indication is based on analyses of plasma HIV-1 RNA levels in three double-blind controlled studies of raltegravir. Two of these studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, NRTI, PI) treatment-experienced adults through 96 weeks and one was conducted in treatment-naïve adults through 240 weeks.

The use of other active agents with raltegravir is associated with a greater likelihood of treatment response (see VIId. Clinical Studies).

Pediatrics

Raltegravir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in children and adolescents 2 years of age and older.

This indication is based on the evaluation of safety, tolerability, pharmacokinetic parameters and efficacy of raltegravir through at least 24-weeks in a multi-center, open-label, noncomparative study in HIV-1 infected, treatment-experienced children and adolescents 2 to 18 years of age (see VIId. Clinical Studies).

The safety and efficacy of raltegravir 400 mg tablets have not been established in children less than 6 years of age. The safety and efficacy of raltegravir chewable tablets have not been established in children less than 2 years of age.

VI. DOSAGE AND ADMINISTRATION

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

The maximum dose of the chewable tablet is 300 mg twice daily. Because the formulations are not bioequivalent, do not substitute chewable tablets for the 400 mg tablet.

Raltegravir can be administered with or without food (see VII. Clinical Pharmacology).

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

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

Adults: One 400 mg tablet administered orally twice daily

Children and adolescents:

- If at least 25 kg: One 400 mg tablet administered orally twice daily
- If unable to swallow a tablet, consider the chewable tablet, as specified in Table 1

Table 1: Recommended[+] Dose for ISENTRESS Chewable Tablets for Pediatric Patients Weighing at Least 10 kg

Body Weight		Dose	Number of Chewable Tablets per dose
(kg)	(lbs)		
10 to <14	22 to <31	75 mg twice daily	3 x 25 mg
14 to <20	31 to <44	100 mg twice daily	1 x 100 mg
20 to <28	44 to <62	150 mg twice daily	1.5 x 100 mg*
28 to <40	62 to <88	200 mg twice daily	2 x 100 mg

At least 40	at least 88	300 mg twice daily	3 x 100 mg

+The weight-based dosing recommendation for the chewable tablet is based on approximately 6 mg/kg/dose twice daily.

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

VII. CLINICAL PHARMACOLOGY

VIIa. 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 .

VIIb. Pharmacokinetics

VIIb-1. Absorption - 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 may be administered with or without food. Raltegravir was administered without regard to food in the pivotal safety and efficacy studies in HIV-infected patients. The effect of consumption of low-, moderate- and high-fat meals on steady-state raltegravir pharmacokinetics was assessed in

healthy volunteers. Administration of multiple doses of raltegravir following a moderate-fat meal did not affect raltegravir AUC to a clinically meaningful degree with an increase of 13% relative to fasting. Raltegravir C_{12hr} was 66% higher and C_{max} was 5% higher following a moderate-fat meal compared to fasting. Administration of raltegravir following a high-fat meal increased AUC and C_{max} by approximately 2-fold and increased C_{12hr} by 4.1-fold. Administration of raltegravir following a low-fat meal decreased AUC and C_{max} by 46% and 52%, respectively; C_{12hr} was essentially unchanged. Food appears to increase pharmacokinetic variability relative to fasting.

VIIb-2. Distribution - Adults

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

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

In two studies of HIV-1 infected subjects 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.

VIIb-3. 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 preclinical species. Two components, namely raltegravir and raltegravir-glucuronide, were detected in urine and accounted for approximately 9 and 23% of the dose, respectively. The major circulating entity was raltegravir and represented approximately 70% of the total radioactivity; the remaining radioactivity in plasma was accounted for by raltegravir-glucuronide. Studies using isoform-selective chemical inhibitors and cDNA-expressed UDP-glucuronosyltransferases (UGT) show that UGT1A1 is the main enzyme responsible for the formation of raltegravir-glucuronide. Thus the data indicate that the major mechanism of clearance of raltegravir in humans is UGT1A1-mediated glucuronidation.

VIIb-4. 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 subjects and 28 HIV patients receiving raltegravir monotherapy with fasted administration. The effect of gender was also evaluated in a population pharmacokinetic (PK) analysis of concentration data from 80 healthy subjects and HIV patients receiving raltegravir alone or in combination with other drugs and in fasted and fed conditions. There were no clinically important pharmacokinetic differences due to gender. No dosage adjustment is necessary.

Age

The effect of age (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.

Pediatric

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 VI. DOSAGE AND ADMINISTRATION) resulted in a pharmacokinetic profile of raltegravir similar to that observed in adults receiving 400 mg twice daily. Table 2 displays pharmacokinetic parameters in the 400 mg tablet (6 to 18 years of age) and the chewable tablet (2 to less than 12 years of age), by body weight.

Table 2: Raltegravir Pharmacokinetic Parameters IMPAACT P1066 Following Administration of Doses in DOSAGE AND ADMINISTRATION

Body Weight	Formulation	Dose	N*	Geometric Mean (%CV†) AUC_{0-12hr} (µ M• hr)	Geometric Mean (%CV†) C_{12hr} (nM)

≥ 25 kg	Film-coated tablet	400 mg twice daily	18	14.1 *(121%)*	233 (*157%*)
≥ 25 kg	Chewable tablet	Weight based dosing, see Table 1	9	22.1 (*36%*)	113 (*80%*)
11 to less than 25 kg	Chewable tablet	Weight based dosing, see Table 1	13	18.6 (*68%*)	82 (*123%)*
*Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose. † Geometric coefficient of variation.					

The pharmacokinetics of raltegravir as 400 mg tablets in children less than 6 years of age has not been established. The pharmacokinetics of raltegravir chewable tablets 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 subjects. No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency. The effect of severe hepatic insufficiency on the pharmacokinetics of raltegravir has not been studied. Therefore raltegravir should be used with caution in patients with severe hepatic impairment.

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 subjects. No dosage adjustment is necessary. Because the extent to which raltegravir 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 subjects with *28/*28 genotype (associated with reduced activity of UGT1A1) to 27 adult subjects with wild-type genotype, the geometric mean ratio (90% CI) of AUC was 1.41 (0.96, 2.09).

VIIc. Pharmacodynamics

Microbiology

Raltegravir at concentrations of 31 ± 20 nM resulted in 95% inhibition (IC_{95}) of viral spread (relative to an untreated virus-infected culture) in human T-lymphoid cell cultures infected with the cell-line adapted HIV-1 variant H9IIIB. In addition, raltegravir at concentrations of 6 to 50 nM resulted in 95% inhibition of viral spread in cultures of mitogen-activated human peripheral blood mononuclear cells infected with diverse, primary clinical isolates of HIV-1, including isolates from 5 non-B subtypes, and isolates resistant to reverse transcriptase inhibitors and protease inhibitors. In a single-cycle infection assay, raltegravir inhibited infection of 23 HIV isolates representing 5 non-B subtypes and 5 circulating recombinant forms with IC_{50} values ranging from 5 to 12 nM. Raltegravir also inhibited replication of an HIV-2 isolate when tested in CEMx174 cells (IC_{95} = 6 nM). Additive to synergistic antiretroviral activity was observed when human T-lymphoid cells infected with the H9IIIB variant of HIV-1 were incubated with raltegravir in combination with nucleoside analog reverse transcriptase inhibitors (zidovudine, zalcitabine, stavudine, abacavir, tenofovir disoproxil fumarate, 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, Q95K/R, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230R, and D232N). E92Q and F121C are occasionally seen in the absence of substitutions at Y143, Q148, or N155 in raltegravir-treatment failure subjects.

Recombinant viruses containing a single primary mutation (Q148H, K or R, or N155H) displayed decreased replication capacity and reduced susceptibility to raltegravir *in vitro*. Secondary mutations

further decreased susceptibility to raltegravir and sometimes acted as compensatory mutations for viral replication capacity.

Treatment-Naïve Adult Subjects: By Week 240 in the STARTMRK trial, the primary raltegravir resistance-associated substitutions were observed in 4 (2 with Y143H/R and 2 with Q148H/R) of the 23 virologic failure subjects with evaluable genotypic data from paired baseline and raltegravir treatment-failure isolates.

Treatment-Experienced Adult Subjects: By Week 96 in the BENCHMRK trials, at least one of the primary raltegravir resistance-associated substitutions, Y143C/H/R, Q148H/K/R, and N155H, was observed in 76 of the 112 virologic failure subjects with evaluable genotypic data from paired baseline and raltegravir treatment-failure isolates. The emergence of the primary raltegravir resistance-associated substitutions was observed cumulatively in 70 subjects by Week 48 and 78 subjects by Week 96, 15.2% and 17% of the raltegravir recipients, respectively. Some (n=58) of those HIV-1 isolates harboring one or more of the primary raltegravir resistance-associated substitutions were evaluated for raltegravir susceptibility yielding a median decrease of 26.3-fold (mean 48.9 ± 44.8-fold decrease, ranging from 0.8- to 159-fold) compared to the wild-type reference.

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

Cardiac Electrophysiology

In a randomized, placebo-controlled, crossover study, 31 healthy subjects 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.

VIId. Clinical Studies

Description of Clinical Studies

Adults

The evidence of durable efficacy of raltegravir 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 240-week data from an ongoing, randomized, double-blind, active-control trial, STARTMRK (P021).

Treatment-Experienced Patients

BENCHMRK 1 and BENCHMRK 2 are Phase III studies to evaluate the safety and antiretroviral activity of raltegravir 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 3 shows the demographic characteristics between patients in the group receiving raltegravir 400 mg b.i.d. and patients in the group receiving placebo.

Table 3: Baseline Characteristics

BENCHMRK 1 and 2 Pooled	Raltegravir 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 4 compares the characteristics of optimized background therapy at baseline in the group receiving raltegravir 400 mg b.i.d. and patients in the control group.

Table 4: Characteristics of Optimized Background Therapy at Baseline

BENCHMRK 1 and 2 Pooled	Raltegravir 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 raltegravir 400 mg b.i.d. or comparator in the pooled BENCHMRK 1 and 2 studies are shown in Table 5.

Table 5: Outcomes by Treatment Group through Week 48 and 96*

Randomized Studies Protocol 018 and 019	Outcome at Week 48		Outcome at Week 96	
	Raltegravir 400 mg b.i.d. (N=462) n (%)	Placebo (N=237) n (%)	Raltegravir 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)	134 (56.5)	150 (32.5)	148 (62.4)
Non responder	12 (2.6)	72 (30.4)	12 (2.6)	72 (30.4)
Rebound	93 (20.1)	62 (26.2)	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.

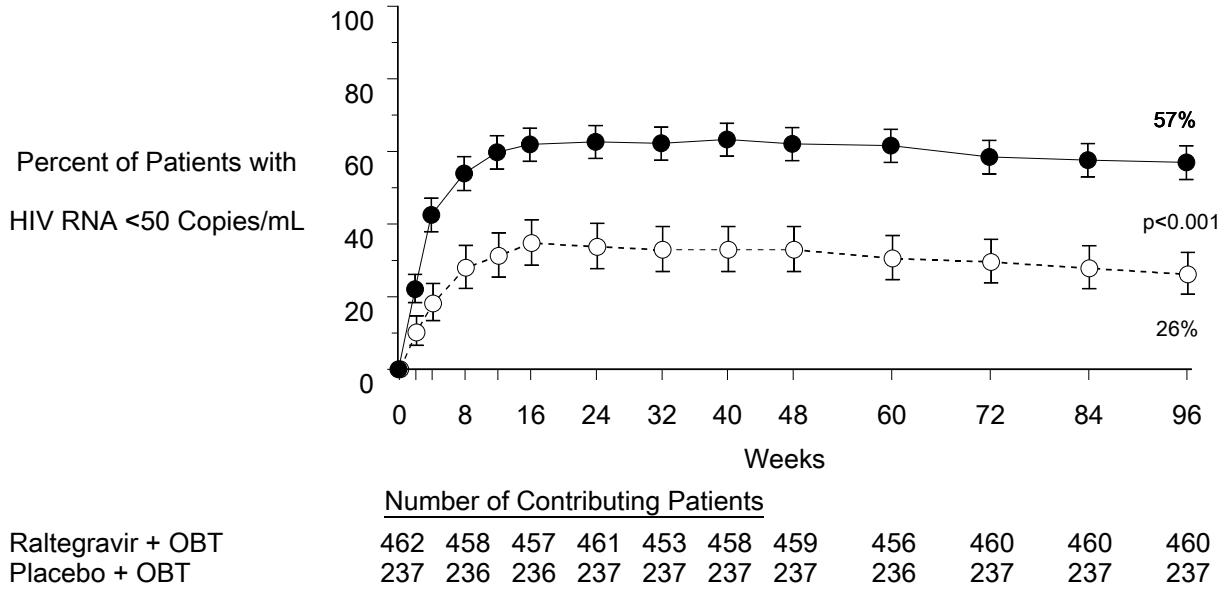
Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).

N = Number of patients in each treatment group.

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)



Virologic responses at Week 96 by baseline genotypic and phenotypic sensitivity score are shown in Table 6.

Table 6: Virologic Response at Week 96 by Baseline Genotypic/Phenotypic Sensitivity Score†

BENCHMRK 1 and 2 Pooled	Raltegravir 400 mg b.i.d. + OBT (N = 462)			Placebo + OBT (N = 237)		
	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 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 is a Phase III study to evaluate the safety and antiretroviral activity of raltegravir 400 mg b.i.d. + emtricitabine (+) tenofovir disoproxil fumarate versus efavirenz + emtricitabine (+) tenofovir disoproxil fumarate in treatment-naïve HIV-infected patients with HIV RNA >5000 copies/mL. Randomization was stratified by screening HIV RNA level (≤ 50,000 copies/mL; and >50,000 copies/mL) and by hepatitis status.

Table 7 shows the demographic characteristics between patients in the group receiving raltegravir 400 mg b.i.d and patients in the group receiving efavirenz.

Table 7: Patient Baseline Characteristics

	Raltegravir 400 mg b.i.d. (N = 281)	Efavirenz 600 mg q.h.s. (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	103205	106215	104702
Median (min, max)	114000 (400 to 750000)	104000 (4410 to 750000)	110000 (400 to 750000)
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:

Raltegravir 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.

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 raltegravir and 230/281 (81.9%) in the group receiving efavirenz. The treatment difference (raltegravir-efavirenz) was 4.2% with an associated 95% CI of (-1.9, 10.3) establishing that raltegravir is non-inferior to efavirenz (p-value for non-inferiority <0.001). At Week 240, the treatment difference (raltegravir-efavirenz) was 9.5% with an associated 95% CI of (1.7, 17.3). Week 48 and 240 outcomes in STARTMRK are shown in Table 8.

Table 8: Outcomes by Treatment Group through Week 48 and 240

Randomized Study Protocol 021	Outcome at Week 48			Outcome at Week 240		
	Raltegravir 400 mg b.i.d. (N=281) n (%)	Efavirenz 600 mg q.h.s. (N=282) n (%)	Difference (Raltegravir – Efavirenz) (CI†)	Raltegravir 400 mg b.i.d. (N=281) n (%)	Efavirenz 600 mg q.h.s. (N=282) n (%)	Difference (Raltegravir – Efavirenz) (CI†)
			4.2%			9.5%

Patients with HIV RNA less than 50 copies/mL*†	241 (86.1)	230 (81.9)	(-1.9, 10.3)	198 (71.0)	171 (61.3)	(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)	

*Raltegravir 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 raltegravir 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.

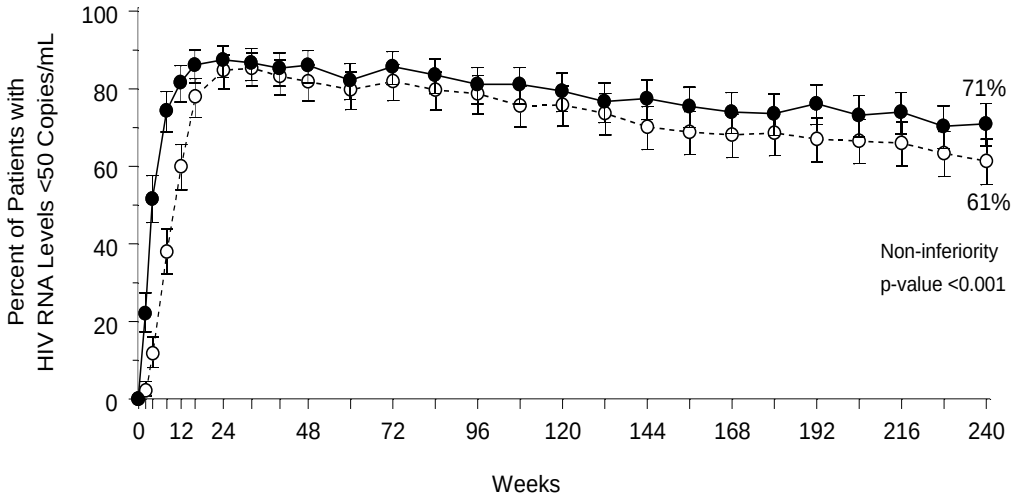
Note: Raltegravir and Efavirenz were administered with TRUVADA™.

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

Figure 2 presents the proportion of patients with plasma HIV RNA <50 copies/mL over time by treatment group. Patients on raltegravir achieved viral suppression (HIV RNA <50 copies/mL) earlier than those receiving EFV. Through 240 weeks of treatment 71% in the group receiving raltegravir 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

● ISENTRESS 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

In the STARTMRK trial of combination antiretroviral therapy in treatment-naive patients, raltegravir 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/mm^3, 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 raltegravir 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).

Pediatric Patients

IMPAACT P1066 is a Phase I/II open label multicenter trial to evaluate the pharmacokinetic profile, safety, tolerability, and efficacy of raltegravir in HIV infected children. This study enrolled 126 treatment experienced children and adolescents 2 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 to 18 years of age) or the chewable tablet formulation (2 to less than 12 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 plasma 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 raltegravir (see VI. 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, 72% achieved ≥ 1 $\log_{10}$ HIV RNA drop from baseline or <400 copies/mL; 54% achieved HIV RNA <50 copies/mL. 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, 77% achieved ≥ 1 $\log_{10}$ HIV RNA drop from baseline or <400 copies/mL; 56% achieved HIV RNA <50 copies/mL. The mean CD4 count (percent) increase from baseline to Week 48 was 155 cells/mm^3 (4.7%).

VIII. CONTRAINDICATIONS

ISENTRESS-G Film-Coated Tablets and ISENTRESS Chewable Tablets are contraindicated in patients who are hypersensitive to any component of this medicine.

IX. PRECAUTIONS

Severe Skin and Hypersensitivity Reactions

Severe, potentially life-threatening, and fatal skin reactions have been reported in patients taking raltegravir, in most cases 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 characterized by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure. Discontinue raltegravir 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 edema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping raltegravir treatment or other suspect agents after the onset of severe rash may result in a life-threatening reaction.

Drug Interactions

Coadministration of raltegravir with aluminum and magnesium antacids resulted in reduced raltegravir plasma levels. Coadministration of raltegravir with aluminum and/or magnesium antacids is not recommended (see XIV. DRUG INTERACTIONS).

Caution should be used when coadministering raltegravir with strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 (e.g., rifampin) due to reduced plasma concentrations of raltegravir. There are no data to guide co-administration of raltegravir with rifampin in patients below 18 years of age (see XIV. DRUG INTERACTIONS).

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.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including raltegravir. 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.

Hepatic impairment

The safety and efficacy of raltegravir have not been established in patients with severe underlying liver disorders. Therefore raltegravir should be used with caution in patients with severe hepatic impairment. Patients with pre-existing liver dysfunction including chronic hepatitis have an increased frequency of liver function abnormalities during combination anti-retroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment should be considered. Patients with chronic hepatitis B or C and treated with combination anti-retroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events.

Osteonecrosis

Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to combination anti-retroviral therapy. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Excipients

Lactose

ISENTRESS-G tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Fructose

ISENTRESS chewable tablets contain fructose and sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Phenylketonurics

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

X. PREGNANCY

There are no adequate and well-controlled studies in pregnant women. Existing post-marketing data suggest that tolerability and safety of ISENTRESS 400 mg twice daily in pregnant women is consistent with that observed in other populations.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant patients exposed to ISENTRESS, an International Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients via email at SM_APR@INCResearch.com or via facsimile at +1-910-256-0637 (in the U.S. and in Canada, call 1-800-258-4263).

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 1200 mg (2 x 600 mg) once daily in pregnant women.

Animal Data

Developmental toxicity studies were performed in rabbits (at doses up to 1000 mg/kg/day) and rats (at doses up to 600 mg/kg/day). The highest doses in these studies produced systemic exposures in these species approximately 3- to 4-fold above the exposure at the recommended human dose. No treatment-related external, visceral, or skeletal changes were observed in rabbits. Treatment-related increases over controls in the incidence of supernumerary ribs were seen in rats at 600 mg/kg/day (exposures 4.4-fold above the exposure at the recommended human dose). In both rabbits and rats, no treatment-related effects on embryonic/fetal survival or fetal weights were observed.

In rats, at a maternal dose of 600 mg/kg/day, mean drug concentrations in fetal plasma were approximately 1.5- to 2.5-fold greater than in maternal plasma at 1 hour and 24 hours postdose, respectively. In rabbits, at a maternal dose of 1000 mg/kg/day, mean drug concentrations in fetal plasma were approximately 2% of the mean maternal concentration at both 1 and 24 hours postdose. Toxicokinetic studies demonstrated placental transfer of drug in both species.

XI. NURSING MOTHERS

It is not known whether raltegravir is secreted in human milk. However, raltegravir is secreted in the milk of lactating rats. In rats, at a maternal dose of 600 mg/kg/day, mean drug concentrations in milk were approximately 3-fold greater than in maternal plasma. Breastfeeding is not recommended while taking raltegravir. In addition, it is recommended that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.

XII. PEDIATRIC USE

The safety, tolerability, pharmacokinetic profile, and efficacy of raltegravir (as 400 mg tablets, chewable tablets and another formulation) were evaluated in HIV-1 infected infants, children and adolescents 4 weeks to 18 years of age in an open-label, multicenter clinical trial, IMPAACT P1066 (see VII. CLINICAL PHARMACOLOGY, VIIb-4. Characteristics in Patients and VIId. Clinical Studies). The safety profile was comparable to that observed in adults (see XV. SIDE EFFECTS). See VI. DOSAGE AND ADMINISTRATION for dosing recommendations for children 2 years of age and older. Safety and effectiveness of raltegravir in infants less than 4 weeks of age have not been established.

XIII. USE IN ELDERLY

Clinical studies of raltegravir 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.

XIV. DRUG INTERACTIONS

Raltegravir is not a substrate of cytochrome P450 (CYP) enzymes and does not inhibit (IC_{50}>100 μM) CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A *in vitro*. Moreover, *in vitro*, raltegravir did not induce CYP3A4. A midazolam drug interaction study confirmed the low propensity of raltegravir to alter the pharmacokinetics of agents 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, raltegravir 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 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 raltegravir with drugs that are potent inducers of UGT1A1, such as rifampin (an inducer of numerous drug metabolizing enzymes), reduces plasma concentrations of raltegravir. Caution should be used when coadministering raltegravir with rifampin or other strong inducers of UGT1A1. There are no data to guide co-administration of raltegravir with rifampin in patients below 18 years of age (see IX. PRECAUTIONS). The impact of other potent inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown. Other less potent inducers (e.g., efavirenz, nevirapine, rifabutin, glucocorticoids, St. John's wort, pioglitazone) may be used with the recommended dose of raltegravir.

Coadministration of raltegravir 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.

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

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

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.

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 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 disoproxil fumarate 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.

Effect of Other Agents on the Pharmacokinetics of Raltegravir

In drug interaction studies, atazanavir, efavirenz, ritonavir, tenofovir disoproxil fumarate, 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.

As aluminum and magnesium antacid significantly decreased raltegravir plasma levels, coadministration of raltegravir with aluminum and/or magnesium containing antacids is not recommended.

All interaction studies were performed in adults. Drug interactions are further described below in Table 9.

Table 9: 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}
aluminum 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		23	0.49 (0.33, 0.71)	0.49 (0.35, 0.67)	0.44 (0.34, 0.55)

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}
	raltegravir					
	20 mL single dose given 2 hours after raltegravir		23	0.78 (0.53, 1.13)	0.70 (0.50, 0.96)	0.43 (0.34, 0.55)
	20 mL single dose given 6 hours before raltegravir		16	0.90 (0.58, 1.40)	0.87 (0.64, 1.18)	0.50 (0.39, 0.65)
	20 mL single dose given 6 hours after raltegravir		16	0.90 (0.58, 1.41)	0.89 (0.64, 1.22)	0.51 (0.40, 0.64)
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)
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)

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}
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.						

XV. SIDE EFFECTS

ADULTS

Treatment-Experienced Adverse Experiences

The safety assessment of raltegravir in treatment-experienced patients is based on the pooled safety data from the randomized clinical studies, P018 and P019 reported using the recommended dose of raltegravir 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 raltegravir 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 raltegravir 400 mg twice daily + OBT (mean follow-up 118.7 weeks) and the comparator group receiving placebo + OBT (mean follow-up 71.0 weeks) in the pooled analysis for studies P018 and P019, the most commonly reported clinical adverse experiences (>10% in either group), of all intensities and regardless of causality were: diarrhea in 26.6% and 24.9%, nausea in 13.6% and 16.0%, headache in 12.1% and 13.5%, nasopharyngitis in 14.3% and 8.9%, fatigue in 12.1% and 5.9%, upper respiratory tract infection in 15.8% and 10.1%, bronchitis in 12.1% and 6.8%, pyrexia in 9.7% and 13.9%, vomiting in 8.9% and 11.0% of patients, respectively. In this pooled analysis, the rates of discontinuation of therapy due to adverse experiences (clinical and laboratory) were 4.5% in patients receiving raltegravir + OBT and 5.5% in patients receiving placebo + OBT.

Drug Related Adverse Experiences

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

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 10.

Table 10: 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 P018 and P019	
	Raltegravir 400 mg b.i.d. + OBT N = 462	Placebo + OBT N = 237
	Mean Follow-up (weeks)	Mean Follow-up (weeks)

	118.7 %	71.0 %
Gastrointestinal Disorders		
Diarrhea	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		

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

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

Cardiac Disorders

Uncommon: ventricular extrasystoles

Ear and Labyrinth Disorders

Uncommon: vertigo

Eye Disorders

Uncommon: visual impairment

Gastrointestinal Disorders

Common: diarrhea, nausea

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

General Disorders and Administration Site Conditions

Common: asthenia, fatigue

Uncommon: pyrexia, chills, face edema, peripheral edema

Hepatobiliary Disorders

Uncommon: hepatitis

Immune System Disorders

Uncommon: drug hypersensitivity

Infections and Infestations

Uncommon: herpes simplex, genital herpes, gastroenteritis

Investigations

Uncommon: weight increased, weight decreased

Metabolism and Nutrition Disorders

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

Musculoskeletal and Connective Tissue Disorders

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

Nervous System Disorders

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

Psychiatric Disorders

Uncommon: depression, insomnia, anxiety

Renal and Urinary Disorders

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

Reproductive System and Breast Disorders

Uncommon: gynaecomastia

Respiratory, Thoracic and Mediastinal Disorders

Uncommon: epistaxis

Skin and Subcutaneous Tissue Disorders

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

Serious Events

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

Treatment Naïve Adverse Experiences

The following safety assessment of raltegravir in treatment-naïve patients is based on the randomized double-blind active controlled study of treatment-naïve patients, protocol 021 (STARTMRK) with raltegravir 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 raltegravir 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 raltegravir, were less frequent than in the group receiving efavirenz based on the nominal p-values (0.325 and <0.001, respectively). In this study, the rates of discontinuation of therapy due to adverse experiences (clinical and laboratory) were 5.0% in patients receiving raltegravir + emtricitabine (+) tenofovir disoproxil fumarate and 10.0% in patients receiving efavirenz + emtricitabine (+) tenofovir disoproxil fumarate.

For patients in the group receiving raltegravir 400 mg twice daily + emtricitabine (+) tenofovir disoproxil fumarate and the group receiving the comparator, efavirenz 600 mg at bedtime + emtricitabine (+) tenofovir disoproxil fumarate, the most commonly reported clinical adverse experiences (>10% in either group), of all intensities and regardless of causality are shown in Table 11.

Table 11: 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 P021	
	Raltegravir 400 mg	Efavirenz 600 mg

	b.i.d. + Emtricitabine (+) Tenofovir disoproxil fumarate (n = 281)† %	q.h.s. + Emtricitabine (+) Tenofovir disoproxil fumarate (n = 282)† %
Gastrointestinal Disorders		
Diarrhea	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		
Arthralgia	8.5	11.7
Back pain	12.1	9.9
Nervous System Disorders		
Dizziness	16.4	38.3
Headache	26.0	28.4
Psychiatric Disorders		
Abnormal dreams	8.2	13.1
Anxiety	8.9	11.0
Depression	10.3	11.7
Insomnia	15.7	14.9
Respiratory, Thoracic and Mediastinal Disorders		
Cough	16.7	12.1
Skin and Subcutaneous Tissue Disorder		
Rash	7.8	13.8

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

† n=total number of subjects per treatment group.

CNS Events

In treatment naïve patients (P021) central nervous system (CNS) adverse experiences, as measured by proportion of patients with 1 or more CNS symptoms (described below), were reported significantly less frequently in the group receiving raltegravir + emtricitabine (+) tenofovir disoproxil fumarate as compared with the group receiving efavirenz + emtricitabine (+) tenofovir disoproxil fumarate, p <0.001, p<0.001 and <0.001 for cumulative events through Weeks 8, 48 and 96, respectively. In the group receiving raltegravir, the percentage of patients with 1 or more CNS symptoms was 20.3% compared to 52.1% in the group receiving efavirenz by Week 8, 26.3% compared to 58.5% by Week 48 and 28.8% compared to 60.6% by Week 96. CNS adverse experiences for this analysis were dizziness, insomnia, concentration impaired, somnolence, depression, nightmare, confusional state, suicidal ideation, nervous system disorder, psychotic disorder, abnormal dreams, suicide attempt, acute psychosis, delirium, depressed level of consciousness, hallucination, auditory hallucination, completed suicide and major depression.

Drug Related Adverse Experiences

The clinical adverse reactions listed below were considered by investigators to be of moderate to severe intensity and causally related to raltegravir 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 in either treatment group are presented in Table 12.

Table 12: 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 P021	
	Raltegravir 400 mg b.i.d. + Emtricitabine (+) Tenofovir disoproxil fumarate N = 281 %	Efavirenz 600 mg q.h.s. + Emtricitabine (+) Tenofovir disoproxil fumarate N = 282 %
Gastrointestinal Disorders		
Diarrhea	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	4.6
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		

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

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

Blood and Lymphatic System Disorders

Uncommon: lymph node pain, neutropenia, anemia, lymphadenopathy

Ear and Labyrinth Disorders

Uncommon: tinnitus, *vertigo*

Gastrointestinal Disorders

Common: diarrhea, abdominal pain

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

General Disorders and Administration Site Conditions

Common: fatigue, asthenia

Uncommon: submandibular mass

Hepatobiliary Disorders

Uncommon: hepatitis alcoholic

Immune System Disorders

Uncommon: immune reconstitution syndrome

Infections and Infestations

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

Metabolism and Nutrition Disorders

Uncommon: decreased appetite, hypercholesterolemia, body fat disorder

Musculoskeletal and Connective Tissue Disorders

Uncommon: arthritis, neck pain

Nervous System Disorders

Common: dizziness

Uncommon: hypersomnia, somnolence, memory impairment

Psychiatric Disorders

Common: abnormal dreams, nightmare, depression

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

Renal and Urinary Disorders

Common: nephrolithiasis

Reproductive System and Breast Disorders

Uncommon: erectile dysfunction

Skin and Subcutaneous Tissue Disorders

Uncommon: acne, alopecia, skin lesion, lipoatrophy

Serious Events

The following serious drug-related adverse experiences were reported in the clinical study, P021 in treatment-naïve patients receiving raltegravir + emtricitabine (+) tenofovir disoproxil fumarate: anemia, immune reconstitution syndrome, mental disorder, suicide attempt, depression.

SELECTED ADVERSE EXPERIENCES

Cancers were observed in treatment-experienced patients who initiated raltegravir or placebo, both with OBT, and in treatment-naïve patients who initiated raltegravir 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 raltegravir and the group receiving the comparator.

Grade 2-4 creatine kinase laboratory abnormalities were observed in subjects treated with raltegravir (see Table 13). Myopathy and rhabdomyolysis have been reported. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions.

Rash occurred more commonly in treatment-experienced patients receiving regimens containing raltegravir + darunavir compared to patients receiving raltegravir without darunavir or darunavir without raltegravir. 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.

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 raltegravir 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.

PEDIATRIC ADVERSE EXPERIENCES

Raltegravir 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 XII. PEDIATRIC USE and VII CLINICAL PHARMACOLOGY, VIId. Clinical Studies). Of the 126 patients, 96 received the recommended dose of raltegravir.

In these 96 children and adolescents, the frequency, type and severity of drug related adverse reactions through Week 24 were comparable to those observed in adults.

One patient experienced drug related clinical adverse reactions of Grade 3 psychomotor hyperactivity, abnormal behavior 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.

POSTMARKETING EXPERIENCE

The following additional adverse experiences have been reported in postmarketed 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 behaviors

Skin and Subcutaneous Tissue Disorders

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

XVI. LABORATORY TEST FINDINGS

Laboratory Abnormalities

The percentages of treatment-experienced adult patients receiving either raltegravir 400 mg twice daily or placebo (both with OBT), in P018 and P019 with selected Grades 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-Experienced Patients

		Randomized Studies P018 and P019	
Laboratory Parameter Preferred Term (Unit)	Limit	Raltegravir 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			

The percentages of treatment-naïve adult patients receiving either raltegravir 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 14.

Table 14: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Naïve Patients

Laboratory Parameter Preferred Term (Unit)	Limit	Randomized Study P021 Raltegravir 400 mg b.i.d. + Emtricitabine (+) Tenofovir disoproxil fumarate (N = 281)	Randomized Study P021 Efavirenz 600 mg q.h.s. + Emtricitabine (+) Tenofovir disoproxil fumarate (N = 282)
Blood chemistry			
Fasting (non-random) serum glucose test (mg/dL)			
Grade 2	126 – 250	6.6%	6.0%
Grade 3	251 – 500	1.8%	0.8%
Grade 4	>500	0.0%	0.0%
Total serum bilirubin			
Grade 2	1.6 - 2.5 x ULN	4.6%	0.4%
Grade 3	2.6 - 5.0 x ULN	0.7%	0.0%
Grade 4	>5.0 x ULN	0.4%	0.0%
Serum aspartate aminotransferase			
Grade 2	2.6 - 5.0 x ULN	7.5%	10.4%
Grade 3	5.1 - 10.0 x ULN	4.6%	2.9%
Grade 4	>10.0 x ULN	1.1%	0.4%
Serum alanine aminotransferase			
Grade 2	2.6 - 5.0 x ULN	11.0%	11.8%
Grade 3	5.1 - 10.0 x ULN	1.8%	2.2%
Grade 4	>10.0 x ULN	1.8%	0.7%
Serum alkaline phosphatase			
Grade 2	2.6 - 5.0 x ULN	1.1%	3.2%
Grade 3	5.1 - 10.0 x ULN	0.0%	0.7%
Grade 4	>10.0 x ULN	0.4%	0.4%
ULN = Upper limit of normal range			

Lipids, Change from Baseline

For P021, changes from baseline in fasting lipids are shown in Table 15.

Table 15: P021 Lipid Values, Change from Baseline in Serum Lipids at Week 240

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

† Within group 95% CIs were based on t-distribution.

‡ Fasting (non-random) laboratory tests at Week 240.

Notes:

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

N = Total number of subjects per treatment group with at least one lipid test result available. The analysis is based on all available data.

P≤ 0.001 for comparison of raltegravir 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).

XVII. OVERDOSAGE

No specific information is available on the treatment of overdosage with raltegravir. 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 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 raltegravir may be dialyzable is unknown.

XVIII. AVAILABILITY

ISENTRESS-G tablets each containing 434.4 mg of raltegravir (as potassium salt), equivalent to 400 mg of raltegravir (free phenol), are supplied in bottles of 60 tablets.

ISENTRESS chewable tablets each containing 108.6 mg of raltegravir (as potassium salt), equivalent to 100 mg of raltegravir (free phenol), are supplied in bottles of 60 tablets.

ISENTRESS chewable tablets each containing 27.16 mg of raltegravir (as potassium salt), equivalent to 25 mg of raltegravir (free phenol), are supplied in bottles of 60 tablets.

Not all presentations are available locally.

XIX. STORAGE

Refer to outer carton for storage condition.

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This Package Insert was last revised in January 2023.