HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RALTEGRAVIR TABLETS safely and effectively. See full prescribing information for RALTEGRAVIR TABLETS

RALTEGRAVIR film-coated tablets, for oral use
Initial U.S. Approval: 2007

----------INDICATIONS AND USAGE ----------
Adult Patients:
Raltegravir tablets are human immunodeficiency virus integrase strand transfer inhibitors (HIV-1 INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients (1).

Pediatric Patients:
Raltegravir tablets are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients weighing at least 40 kg (1).

---------- DOSAGE AND ADMINISTRATION ----------
Raltegravir tablets can be administered with or without food (2.1).

Do not substitute ISENTRESS chewable tablets or ISENTRESS for oral suspension for the raltegravir 400 mg or 600 mg film-coated tablet.

Adults

- Treatment-naive patients or patients who are virologically suppressed on an initial regimen of raltegravir tablets, 400 mg twice daily:
  - 1200 mg (2 x 600 mg) film-coated tablet orally, once daily or
  - 400 mg film-coated tablet orally, twice daily (2.2).

Pediatric

- If weighing at least 40 kg, and either
  - treatment-naïve patients or
  - patients who are virologically suppressed on an initial regimen of raltegravir tablets 400 mg twice daily:
    - 1200 mg (2 x 600 mg) film-coated tablet orally, once daily or
    - 400 mg film-coated tablet orally, twice daily

---------- DOSAGE FORMS AND STRENGTHS ----------
- Film-Coated Tablets: 600 mg (3).

----------CONTRAINDICATIONS----------
None (4).

----------WARNINGS AND PRECAUTIONS ----------
- Severe, potentially life-threatening and fatal skin reactions have been reported. This includes cases of Stevens-Johnson syndrome, hypersensitivity reaction and toxic epidermal necrolysis. Immediately discontinue treatment with raltegravir tablets and other suspect agents if severe hypersensitivity, severe rash, or rash with systemic symptoms or liver aminotransferase elevations develops and monitor clinical status, including liver aminotransferases closely (5.1).
- Monitor for Immune Reconstitution Syndrome (5.2).

---------- ADVERSE REACTIONS ----------
- The most common adverse reactions of moderate to severe intensity (≥2 %) are insomnia, headache, dizziness, nausea and fatigue (6.1).
- Creatine kinase elevations were observed in subjects who received raltegravir tablets 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 and patients with a history of rhabdomyolysis, myopathy or increased serum creatine kinase (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals, Inc. at 1-800-399-2561 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS ----------
- Coadministration of raltegravir tablets and other drugs may alter the plasma concentration of raltegravir. The potential for drug-drug interactions must be considered prior to and during therapy (7).
- Coadministration of raltegravir tablets with drugs that are strong inducers of UGT1A1, such as rifampin, may result in reduced plasma concentrations of raltegravir (2.1, 7.1).

---------- USE IN SPECIFIC POPULATIONS ----------
Lactation: Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission (8.2).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2026

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Adult Patients

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

Pediatric Patients

Raltegravir tablets are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients weighing at least 40 kg.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Recommendations

- Because the formulations have different pharmacokinetic profiles, do not substitute ISENTRESS chewable tablets or ISENTRESS for oral suspension for the raltegravir 400 mg film-coated tablet or the raltegravir 600 mg film-coated tablet.
- Because the extent to which raltegravir tablets may be dialyzable is unknown, dosing before a dialysis session should be avoided *[see Clinical Pharmacology (12.3)]*.
- Raltegravir film-coated tablets must be swallowed whole.

2.2 Adults

The recommended adult dosage of Raltegravir film-coated tablets are displayed in Table 1. Raltegravir tablets should be taken by mouth and may be taken with or without food *[see Clinical Pharmacology (12.3)]*.

Table 1: Dosing Recommendations for Raltegravir Tablets in Adult Patients

Population	Recommended Dose
Treatment-naïve patients or patients who are virologically suppressed on an initial regimen of raltegravir tablets, 400 mg twice daily	1,200 mg (2 x 600 mg) once daily or 400 mg twice daily

2.3 Pediatrics

The recommended pediatric dosage of raltegravir tablets is displayed in Table 2. Raltegravir film-coated tablets should be taken by mouth and may be taken with or without food *[see Clinical Pharmacology (12.3)]*.

Table 2: Dosing Recommendations for Raltegravir Tablets in Pediatric Patients

	Recommended Pediatric Dosage and Formulation	
Population/Weight	**Film-Coated Tablets, 400 mg**	**Film-Coated Tablets, 600 mg**
If at least 40 kg and either: • treatment-naïve or • virologically suppressed on an initial regimen of raltegravir tablets 400 mg twice daily	400 mg twice daily	1,200 mg (2 x 600 mg) once daily

- No data are available in pre-term neonates. The use of raltegravir tablets is not recommended in preterm neonates.

3 DOSAGE FORMS AND STRENGTHS

- Film-coated Tablets
  - 600 mg yellow, modified capsule shaped, biconvex, film-coated tablets debossed with "LU" on one side and "J04" on the other side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Severe Skin and Hypersensitivity Reactions

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

5.2 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including raltegravir tablets. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, tuberculosis), which may necessitate further evaluation and treatment.

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

6 ADVERSE REACTIONS

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.

6.1 Clinical Trials Experience

Treatment-Naive Adults

The safety of raltegravir tablets was evaluated in HIV-infected treatment-naive subjects in 2 Phase III studies: STARTMRK evaluated raltegravir tablets, 400 mg twice daily versus efavirenz, both

in combination with emtricitabine (+) tenofovir disoproxil fumarate (TDF), and ONCEMRK evaluated raltegravir tablets, 1200 mg (2 x 600 mg) once daily versus raltegravir tablets, 400 mg twice daily, both in combination with emtricitabine (+) tenofovir disoproxil fumarate. Safety data from these two studies are presented side-by-side in Tables 6 and 7 to simplify presentation; direct comparisons across trials should not be made due to differing duration of follow-up and study design.

STARTMRK (Raltegravir Tablets 400 mg Twice Daily):
In STARTMRK, subjects received raltegravir tablets, 400 mg twice daily (N=281) or efavirenz (EFV) 600 mg at bedtime (N=282) both in combination with emtricitabine (+) tenofovir disoproxil fumarate, (N=282). During double-blind treatment, the total follow-up for subjects receiving raltegravir tablets, 400 mg twice daily +emtricitabine (+) tenofovir disoproxil fumarate was 1104 patient-years and 1036 patient-years for subjects receiving efavirenz 600 mg at bedtime + emtricitabine (+) tenofovir disoproxil fumarate.

In STARTMRK, the rate of discontinuation of therapy due to adverse events through Week 240 was 5 % in subjects receiving raltegravir tablets + emtricitabine (+) tenofovir disoproxil fumarate and 10 % in subjects receiving efavirenz + emtricitabine (+) tenofovir disoproxil fumarate.

ONCEMRK (Raltegravir Tablets, 1200 mg [2 x 600 mg] Once Daily):
In ONCEMRK, subjects received raltegravir tablets, 1200 mg once daily (n=531) or raltegravir tablets, 400 mg twice daily (n=266) both in combination with emtricitabine (+) tenofovir disoproxil fumarate. During double-blind treatment, the total follow-up for subjects with raltegravir tablets, 1200 mg once daily was 913 patient-years and for raltegravir tablets, 400 mg twice daily was 450 patient-years.

In ONCEMRK, the rate of discontinuation of therapy due to adverse events through Week 96 was 1 % in subjects receiving raltegravir tablets, 1200 mg (2 x 600 mg) once daily and 2 % in subjects receiving raltegravir tablets, 400 mg twice daily.

Clinical adverse reactions of moderate to severe intensity occurring in ≥2 % of treatment-naïve subjects treated with raltegravir tablets, 400 mg twice daily or efavirenz in STARTMRK through Week 240 or raltegravir tablets, 1200 mg once daily or raltegravir tablets, 400 mg twice daily in ONCEMRK through Week 96 are presented in Table 6.

In STARTMRK, clinical adverse reactions of all intensities (mild, moderate and severe) occurring in ≥2 % of subjects on raltegravir tablets, 400 mg twice daily through Week 240 also include diarrhea, flatulence, asthenia, decreased appetite, abnormal dreams, depression and nightmare. In ONCEMRK, clinical adverse reactions of all intensities (mild, moderate and severe) occurring in ≥2% of subjects on raltegravir tablets, 400 mg twice daily through Week 96 also include abdominal pain, diarrhea, vomiting, and decreased appetite.

Table 6: Adverse Reactions[*] of Moderate to Severe Intensity[†] Occurring in ≥2 % of Treatment-Naive Adult Subjects Receiving Raltegravir Tablets

System Organ Class, Preferred Term	STARTMRK Week 240		ONCEMRK Week 96	
	Raltegravir Tablets, 400 mg Twice Daily (N=281)	Efavirenz 600 mg At Bedtime (N= 282)	Raltegravir Tablets, 1200 mg Once Daily (N=531)	Raltegravir Tablets, 400 mg Twice Daily (N=266)
Headache	4 %	5 %	1 %	<1 %
Insomnia	4 %	4 %	<1 %	<1 %
Nausea	3 %	4 %	1 %	0 %
Dizziness	2 %	6 %	<1 %	0 %
Fatigue	2 %	3 %	0 %	0 %

Note: Raltegravir BID, Raltegravir tablets and efavirenz were administered with emtricitabine (+) tenofovir disoproxil fumarate

[*] Includes adverse experiences considered by investigators to be at least possibly, probably, or definitely related to the drug.

[†] Intensities are defined as follows: 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

Laboratory Abnormalities:

The percentages of adult subjects with selected Grade 2 to 4 laboratory abnormalities (that represent a worsening Grade from baseline) who were treated with raltegravir tablets, 400 mg twice daily or efavirenz in STARTMRK or raltegravir tablets, 1200 mg once daily or raltegravir tablets, 400 mg twice daily in ONCEMRK are presented in Table 7.

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

		STARTMRK Week 240		ONCEMRK Week 96	
Laboratory Parameter Preferred Term (Unit)	**Limit**	**Raltegravir Tablets, 400 mg Twice Daily (N=281)**	**Efavirenz 600 mg At Bedtime (N=282)**	**Raltegravir Tablets, 1200 mg Once Daily (N=531)**	**Raltegravir Tablets, 400 mg Twice Daily (N=266)**
Hematology					
Absolute neutrophil count (10^3/mcL)					
Grade 2	0.75 to 0.999	3 %	5 %	2 %	1 %
Grade 3	0.50 to 0.749	3 %	1 %	1 %	1 %
Grade 4	<0.50	1 %	1 %	<1 %	0 %
Hemoglobin(gm/dL)					
Grade 2	7.5 to 8.4	1 %	1 %	0 %	0 %
Grade 3	6.5 to 7.4	1 %	1 %	0 %	0 %
Grade 4	<6.5	<1 %	0 %	0%	0 %
Platelet count (10^3/mcL)					
Grade 2	50 to 99.999	1 %	0 %	1 %	<1 %
Grade 3	25 to 49.999	<1 %	<1 %	0 %	0 %
Grade 4	<25	0 %	0 %	0%	<1 %
Blood chemistry					
Fasting (non-random) serum glucose test (mg/dL)[†]					
Grade 2	126 to 250	7 %	6 %	-	-
Grade 3	251 to 500	2 %	1 %	-	-
Grade 4	>500	0 %	0 %	-	-
Total serum bilirubin					
Grade 2	1.6 to 2.5 x ULN	5 %	<1 %	3 %	2 %
Grade 3	2.6 to 5 x ULN	1 %	0 %	1 %	<1 %
Grade 4	>5 x ULN	<1 %	0 %	<1 %	0 %
Creatinine					
Grade 2	1.4 to 1.8 x ULN	1 %	1 %	0 %	<1 %
Grade 3	1.9 to 3.4 x ULN	0 %	<1 %	0 %	0 %
Grade 4	≥3.5 x ULN	0 %	0 %	0%	0 %
Serum aspartate aminotransferase					
Grade 2	2.6 to 5 x ULN	8 %	10 %	5 %	3 %
Grade 3	5.1 to 10 x ULN	5 %	3 %	2 %	<1 %
Grade 4	>10 x ULN	1 %	<1 %	1 %	<1 %
Serum alanine aminotransferase					
Grade 2	2.6 to 5 x ULN	11 %	12 %	4 %	2 %
Grade 3	5.1 to 10 x ULN	2 %	2 %	1 %	<1 %
Grade 4	>10 x ULN	2 %	1 %	1 %	<1 %

		STARTMRK Week 240		ONCEMRK Week 96	
Laboratory Parameter Preferred Term (Unit)	**Limit**	**Raltegravir Tablets, 400 mg Twice Daily (N=281)**	**Efavirenz 600 mg At Bedtime (N=282)**	**Raltegravir Tablets, 1200 mg Once Daily (N=531)**	**Raltegravir Tablets, 400 mg Twice Daily (N=266)**
Serum alkaline phosphatase					
Grade 2	2.6 to 5 x ULN	1 %	3 %	1 %	0 %
Grade 3	5.1 to 10 x ULN	0 %	1 %	<1 %	0 %
Grade 4	>10 x ULN	<1 %	<1 %	0 %	0 %
Lipase*					
Grade 2	1.6 to 3 x ULN	-	-	7 %	5 %
Grade 3	3.1 to 5 x ULN	-	-	2 %	1 %
Grade 4	>5 x ULN	-	-	2 %	1 %
Creatine kinase*					
Grade 2	6 to 9.9 x ULN	-	-	4 %	5 %
Grade 3	10 to 19.9 x ULN	-	-	3 %	3 %
Grade 4	≥20 x ULN	-	-	3 %	2 %
ULN = Upper limit of normal range					
Note: Raltegravir BID, Raltegravir tablets and Efavirenz were administered with emtricitabine (+) tenofovir disoproxil fumarate * Test not done in STARTMRK † Test not done in ONCEMRK					

Lipids, Change from Baseline:

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

Table 8: Lipid Values, Mean Change from Baseline, STARTMRK Study

Laboratory Parameter Preferred Term	Raltegravir Tablets, 400 mg Twice Daily + Emtricitabine (+) Tenofovir Disoproxil Fumarate N = 207			Efavirenz 600 mg At Bedtime + Emtricitabine (+) Tenofovir Disoproxil Fumarate N = 187		
			Change from Baseline at Week 240			Change from Baseline at Week
	Baseline Mean (mg/dL)	Week 240 Mean (mg/dL)	Mean Change	Baseline Mean (mg/dL)	Week 240 Mean (mg/dL)	Mean Change (mg/dL)
LDL-Cholesterol*	96	106	10	93	118	25
HDL-Cholesterol*	38	44	6	38	51	13
Total Cholesterol*	159	175	16	157	201	44
Triglyceride*	128	130	2	141	178	37

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

Notes:

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

If subjects initiated or increased serum lipid-reducing agents, the last available lipid values prior to the change in therapy were used in the analysis. If the missing data was due to other reasons, subjects were censored thereafter for the analysis. At baseline, serum lipid-reducing agents were used in 5 % of subjects in the group receiving raltegravir tablets and 3 % in the efavirenz group. Through Week 240, serum lipid-reducing agents were used in 9 % of subjects in the group receiving raltegravir tablets and 15 % in the efavirenz group.

Treatment-Experienced Adults

The safety assessment of raltegravir tablets in treatment-experienced subjects is based on the pooled safety data from the randomized, double-blind, placebo-controlled trials, BENCHMRK 1 and BENCHMRK 2 in antiretroviral treatment-experienced HIV-1 infected adult subjects. A total of 462 subjects received the recommended dose of raltegravir tablets, 400 mg twice daily in combination with optimized background therapy (OBT) compared to 237 subjects taking placebo in combination with OBT. The median duration of therapy in these trials was 96 weeks for subjects receiving raltegravir tablets and 38 weeks for subjects receiving placebo. The total exposure to raltegravir tablets was 708 patient-years versus 244 patient-years on placebo. The rates of discontinuation due to adverse events were 4 % in subjects receiving raltegravir tablets and 5 % in subjects receiving placebo.

Clinical ADRs were considered by investigators to be causally related to raltegravir tablets + OBT or placebo + OBT. Clinical ADRs of moderate to severe intensity occurring in ≥2 % of subjects

treated with raltegravir tablets and occurring at a higher rate compared to placebo are presented in Table 9.

Table 9: Adverse Drug Reactions* of Moderate to Severe Intensity† Occurring in ≥2 % of Treatment-Experienced Adult Subjects Receiving Raltegravir Tablets and at a Higher Rate Compared to Placebo (96 Week Analysis)

System Organ Class, Adverse Reactions	Randomized Studies BENCHMRK 1 and BENCHMRK 2	
	Raltegravir Tablets, 400 mg Twice Daily +OBT (n=462)	Placebo + OBT (n = 237)
Nervous System Disorders		
Headache	2 %	<1 %

* Includes adverse reactions at least possibly, probably, or definitely related to the drug.

† Intensities are defined as follows: 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.

Laboratory Abnormalities

The percentages of adult subjects treated with raltegravir tablets, 400 mg twice daily or placebo in Studies BENCHMRK 1 and BENCHMRK 2 with selected Grade 2 to 4 laboratory abnormalities representing a worsening Grade from baseline are presented in Table 10.

Table 10: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Experienced Subjects (96 Week Analysis)

Laboratory Parameter Preferred Term (Unit)	Limit	Randomized Studies BENCHMRK 1 and BENCHMRK 2	
		Raltegravir Tablets, 400 mg Twice Daily + OBT (N = 462))	Placebo + OBT (N =237)
Hematology			
Absolute neutrophil count (10^3/mcL)			
Grade 2	0.75 to 0.999	4 %	5 %
Grade 3	0.50 to 0.749	3 %	3 %
Grade 4	<0.50	1 %	<1 %
Hemoglobin (gm/dL)			
Grade 2	7.5 to 8.4	1 %	3 %
Grade 3	6.5 to 7.4	1%	1 %
Grade 4	<6.5	<1 %	0 %
Platelet count (10^3/mcL)			
Grade 2	50 to 99.999	3 %	5 %
Grade 3	25 to 49.999	1 %	<1 %
Grade 4	<25	1 %	<1 %

Laboratory Parameter Preferred Term (Unit)	Limit	Randomized Studies BENCHMRK 1 and BENCHMRK 2	
		Raltegravir Tablets, 400 mg Twice Daily + OBT (N = 462))	Placebo + OBT (N =237)
Blood chemistry			
Fasting (non-random) serum glucose test (mg/dL)			
Grade 2	126 to 250	10 %	7 %
Grade 3	251 to 500	3 %	1 %
Grade 4	>500	0 %	0 %
Total serum bilirubin			
Grade 2	1.6 to 2.5 x ULN	6 %	3 %
Grade 3	2.6 to 5 x ULN	3 %	3 %
Grade 4	>5 x ULN	1 %	0 %
Serum aspartate aminotransferase			
Grade 2	2.6 to 5 x ULN	9 %	7 %
Grade 3	5.1 to 10 x ULN	4 %	3 %
Grade 4	>10 x ULN	1 %	1 %
Serum alanine aminotransferase			
Grade 2	2.6 to 5 x ULN	9 %	9 %
Grade 3	5.1 to 10 x ULN	4 %	2 %
Grade 4	>10 x ULN	1 %	2 %
Serum alkaline phosphatase			
Grade 2	2.6 to 5 x ULN	2 %	<1 %
Grade 3	5.1 to 10 x ULN	<1 %	1 %
Grade 4	>10 x ULN	1 %	<1 %
Serum pancreatic amylase test			
Grade 2	1.6 to 2 x ULN	2 %	1 %
Grade 3	2.1 to 5 x ULN	4 %	3 %
Grade 4	>5 x ULN	<1 %	<1 %
Serum lipase test			
Grade 2	1.6 to 3 x ULN	5 %	4 %
Grade 3	3.1 to 5 x ULN	2 %	1 %
Grade 4	>5 x ULN	0 %	0 %
Serum creatine kinase			
Grade 2	6 to 9.9 x ULN	2 %	2 %
Grade 3	10 to 19.9 x ULN	4 %	3 %
Grade 4	≥20 x ULN	3 %	1 %

ULN= Upper limit of normal range

Less Common Adverse Reactions Observed in Treatment-Naive and Treatment-Experienced Studies

The following ADRs occurred in <2 % of treatment-naive or treatment-experienced subjects receiving raltegravir tablets in a combination regimen. These events have been included because of their seriousness, increased frequency compared with efavirenz or placebo, or investigator's assessment of potential causal relationship.

Gastrointestinal Disorders: abdominal pain, gastritis, dyspepsia, vomiting

General Disorders and Administration Site Conditions: asthenia

Hepatobiliary Disorders: hepatitis

Immune System Disorders: hypersensitivity

Infections and Infestations: genital herpes, herpes zoster

Psychiatric Disorders: depression (particularly in subjects with a pre-existing history of psychiatric illness), including suicidal ideation and behaviors

Renal and Urinary Disorders: nephrolithiasis, renal failure

Selected Adverse Events – Adults

In studies of raltegravir tablets, 400 mg twice daily, cancers were reported in treatment-experienced subjects who initiated raltegravir tablets or placebo, both with OBT, and in treatment-naïve subjects who initiated raltegravir tablets 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 tablets and the group receiving the comparator.

Grade 2 to 4 creatine kinase laboratory abnormalities were observed in subjects treated with raltegravir tablets (see Tables 6 and 8). Myopathy and rhabdomyolysis have been reported with raltegravir tablets. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions and patients with a history of rhabdomyolysis, myopathy or increased serum creatine kinase.

Rash occurred more commonly in treatment-experienced subjects receiving regimens containing raltegravir tablets + darunavir/ritonavir compared to subjects receiving raltegravir tablets without darunavir/ritonavir or darunavir/ritonavir without raltegravir tablets. 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 - Adults

Patients Co-infected with Hepatitis B and/or Hepatitis C Virus:

In Phase III studies of raltegravir tablets, patients with chronic (but not acute) active hepatitis B

and/or hepatitis C virus co-infection were permitted to enroll provided that baseline liver function tests did not exceed 5 times the upper limit of normal (ULN). In the treatment-experienced studies, BENCHMRK 1 and BENCHMRK 2, 16 % of all patients (114/699) were co-infected; in the treatment-naïve studies, STARTMRK and ONCEMRK, 6 % (34/563) and 3 % (23/797), respectively, were co-infected. In general, the safety profile of raltegravir tablets in subjects with hepatitis B and/or hepatitis C virus co-infection was similar to that in subjects without hepatitis B and/or hepatitis C virus co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or hepatitis C virus co-infection for all treatment groups.

At 96 weeks, in treatment-experienced subjects receiving raltegravir tablets, 400 mg twice daily, Grade 2 or higher laboratory abnormalities that represent a worsening Grade from baseline of AST, ALT or total bilirubin occurred in 29 %, 34 % and 13 %, respectively, of co-infected subjects treated with raltegravir tablets as compared to 11 %, 10 % and 9 % of all other subjects treated with raltegravir tablets. At 240 weeks, in treatment- naïve subjects receiving raltegravir tablets, 400 mg twice daily, Grade 2 or higher laboratory abnormalities that represent a worsening Grade from baseline of AST, ALT or total bilirubin occurred in 22 %, 44 % and 17 %, respectively, of co-infected subjects treated with raltegravir tablets as compared to 13 %, 13 % and 5 % of all other subjects treated with raltegravir tablets.

At 96 weeks, in treatment-naive subjects receiving raltegravir tablets, 1200 mg (2 x 600 mg) once daily, Grade 2 or higher laboratory abnormalities that represent a worsening Grade from baseline of AST, ALT or total bilirubin occurred in 27 %, 40 % and 13 %, respectively, of co-infected subjects treated with raltegravir tablets, 1200 mg once daily as compared to 7 %, 5 % and 3 % of all other subjects treated with raltegravir tablets, 1200 mg once daily.

Pediatrics

2 to 18 Years of Age:

Raltegravir tablets have 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 Use in Specific Populations (8.4) and Clinical Studies (14.4)]*. Of the 126 patients, 96 received the recommended dose of raltegravir tablets.

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.

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.

4 Weeks to Less than 2 Years of Age:

Raltegravir tablets have also been studied in 26 HIV-1 infected infants and toddlers 4 weeks to less than 2 years of age, in combination with other antiretroviral agents in IMPAACT P1066 *[see Use in Specific Populations (8.4) and Clinical Studies (14.4)]*.

In these 26 infants and toddlers, the frequency, type and severity of drug-related adverse reactions through Week 48 were comparable to those observed in adults.

One patient experienced a Grade 3 serious drug-related allergic rash that resulted in treatment discontinuation.

HIV-1 Exposed Neonates:
Forty-two neonates were treated with raltegravir tablets for up to 6 weeks from birth, and followed for a total of 24 weeks in IMPAACT P1110 *[see Use in Specific Populations (8.4)]*. There were no drug related clinical adverse reactions and three drug-related laboratory adverse reactions (one case of transient Grade 4 neutropenia in a subject receiving zidovudine-containing regimen for prevention of mother to child transmission (PMTCT), and two bilirubin elevations (one each, Grade 1 and Grade 2) considered non- serious and not requiring specific therapy). The safety profile in neonates was generally similar to that observed in older patients treated with raltegravir tablets. No clinically meaningful differences in the adverse event profile of neonates were observed when compared to adults.

6.2 Postmarketing Experience
The following adverse reactions have been identified during postapproval use of raltegravir tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: thrombocytopenia

Gastrointestinal Disorders: diarrhea

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: anxiety, paranoia

7 DRUG INTERACTIONS
7.1 Effect of Other Agents on the Pharmacokinetics of Raltegravir
Raltegravir is not a substrate of cytochrome P450 (CYP) enzymes. Based on *in vivo* and *in vitro* studies, raltegravir is eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway. Coadministration of raltegravir tablets with drugs that inhibit UGT1A1 may increase plasma levels of raltegravir and coadministration of raltegravir tablets with drugs that induce UGT1A1, such as rifampin, may reduce plasma levels of raltegravir (see Table 11).

Selected drug interactions are presented in Table 11 *[see Clinical Pharmacology (12.3)]*. In some

cases, recommendations differ for raltegravir tablets, 400 mg versus raltegravir tablets, 600 mg.

Table 11: Selected Drug Interactions in Adults

Concomitant Drug Class: Drug Name	Effect on Concentration of Raltegravir	Clinical Comment for Raltegravir Tablets, 400 mg	Clinical Comment for Raltegravir Tablets, 600 mg
Metal-Containing Antacids			
Aluminum and/or magnesium-containing antacids	↓	Coadministration or staggered administration is not recommended.	
Calcium carbonate antacid	↓	No dose adjustment	Co-administration is not recommended
Other Agents			
Rifampin	↓	The recommended dosage is 800 mg twice daily during coadministration with rifampin. There are no data to guide co-administration of raltegravir tablets with rifampin in patients below 18 years of age *[see Dosage and Administration (2.1)]*.	Coadministration is not recommended.
Tipranavir/ritonavir		No dose adjustment	Coadministration is not recommended
Etravirine	↓	No dose adjustment	Coadministration is not recommended.
Strong inducers of drug metabolizing enzymes not mentioned above e.g., Carbamazepine Phenobarbital Phenytoin	↓↔	The impact of other strong inducers of drug metabolizing enzymes on raltegravir is unknown. Coadministration is not recommended.	

7.2 Drugs without Clinically Significant Interactions with Raltegravir

In drug interaction studies, efavirenz did not have a clinically meaningful effect on the pharmacokinetics of raltegravir tablets, 1200 mg (2 x 600 mg) once daily. No dose adjustment is recommended when raltegravir tablets, 1200 mg once daily is coadministered with atazanavir, atazanavir/ritonavir, hormonal contraceptives, methadone, lamivudine, tenofovir disoproxil

fumarate, darunavir/ritonavir, boceprevir, efavirenz and omeprazole.

There is no predicted pharmacokinetic drug interaction between raltegravir tablets, 600 mg and tenofovir alafenamide.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Available data from the APR show no difference in the rate of overall birth defects for raltegravir compared to the background rate for major birth defects of 2.7 % in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data)*. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15 to 20 %. The background risk for major birth defects and miscarriage for the indicated population is unknown. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation *(see Data)*.

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

Data

Human Data:

Based on prospective reports from the APR of over 850 exposures to raltegravir during pregnancy resulting in live births (including over 450 exposures in the first trimester), there was no difference between the overall risk of birth defects for raltegravir compared with the background birth defect rate of 2.7 % in the U.S. reference population of the MACDP. The prevalence of defects in live births was 3.1 % (95 % CI: 1.7 % to 5.1 %) following first trimester exposure to raltegravir-containing regimens and 3.7 % (95 % CI: 2.1 % to 6 %) following second and third trimester exposure to raltegravir-containing regimens.

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

Animal Data:

In a combined embryo/fetal and pre/postnatal development study, raltegravir was administered orally to rats at doses of 100, 300, 600 mg/kg/day on gestation day 6 to 20 or from gestation day 6 to lactation day 20. No effects on pre/postnatal development were observed up to the highest dose tested. Embryo-fetal findings were limited to an increase in the incidence of supernumerary

ribs in the 600 mg/kg/day group. Systemic exposure (AUC) at 600 mg/kg/day was approximately 3 times higher than exposure at the MRHD of 1200 mg.

In pregnant rabbits, raltegravir was administered orally at doses of 100, 500, or 1000 mg/kg/day during the gestation days 7 to 20. No embryo/fetal effects were noted up to the highest dose of 1000 mg/kg/day. Systemic exposure (AUC) at 1000 mg/kg/day was approximately 4 times higher than exposures at the MRHD of 1200 mg. In both species, raltegravir has been shown to cross the placenta, with fetal plasma concentrations observed in rats approximately 1.5 to 2.5 times greater than in maternal plasma and fetal plasma concentrations in rabbits approximately 2 % that of maternal concentrations on gestation day 20.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. There are no data on the presence of raltegravir in human milk, the effects on the breastfed infant, or the effects on milk production. When administered to lactating rats, raltegravir was present in milk *[see Data]*. Because of the potential for: 1) HIV transmission (in HIV-negative infants), 2) developing viral resistance (in HIV-positive infants), and 3) adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving raltegravir tablets.

Data

Raltegravir was excreted into the milk of lactating rats following oral administration (600 mg/kg/day) from gestation day 6 to lactation day 14, with milk concentrations approximately 3 times that of maternal plasma concentrations observed 2 hours postdose on lactation day 14.

8.4 Pediatric Use

Raltegravir tablets, 600 mg once daily have not been studied in pediatric patients. However, population PK modeling and simulation support the use of 1,200 mg (2 x 600 mg) once daily in pediatric patients weighing at least 40 kg *[see Clinical Pharmacology (12.3)]*.

8.5 Geriatric Use

Clinical studies of raltegravir tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects. 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.

8.6 Use in Patients with Hepatic Impairment

No dosage adjustment of raltegravir tablets 400 mg is necessary for patients with mild to moderate (Child-Pugh A and B) hepatic impairment. No hepatic impairment study has been conducted with raltegravir tablets 600 mg and therefore administration in subjects with hepatic impairment is not recommended. The effect of severe hepatic impairment on the pharmacokinetics of raltegravir has not been studied *[see Clinical Pharmacology (12.3)]*.

8.7 Use in Patients with Renal Impairment

No dosage adjustment of raltegravir tablets is necessary in patients with any degree of renal impairment *[see Clinical Pharmacology (12.3)]*. The extent to which raltegravir tablets may be dialyzable is unknown; therefore, dosing before a dialysis session should be avoided.

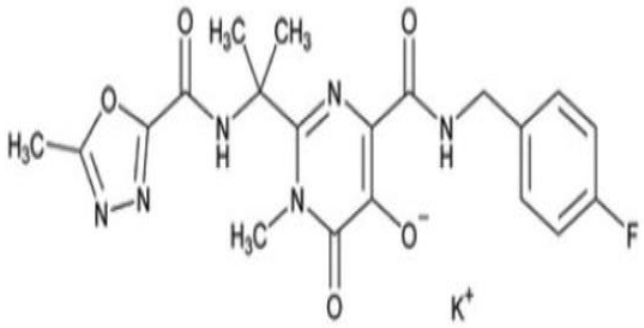
10 OVERDOSAGE

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 tablets may be dialyzable is unknown.

11 DESCRIPTION

Raltegravir tablets contain raltegravir potassium, a human immunodeficiency virus integrase strand transfer inhibitor. The chemical name for raltegravir potassium is N-(4-fluorobenzyl)-5-hydroxy-1-methyl-2-(1-methyl-1-{[(5-methyl-1, 3, 4-oxadiazol-2-yl) carbonyl] amino} ethyl)-6-oxo-1,6- dihydro pyrimidine-4-carboxamide potassium.

The empirical formula is $C_{20}H_{20}N_6O_5FK$ and the molecular weight is 482.51. The structural formula is:



Raltegravir potassium is a white to cream color powder. It is slightly soluble in water and methanol.

Each film coated tablet for oral administration contains 651.6 mg raltegravir potassium USP, equivalent to raltegravir 600 mg and the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone K30 and tartaric acid. The film coating contains the following inactive ingredients: iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

FDA approved dissolution test specifications differ from USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Raltegravir is an HIV-1 antiviral drug *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

In a monotherapy study raltegravir (400 mg twice daily) demonstrated rapid antiviral activity with mean viral load reduction of 1.66 $\log_{10}$ copies/mL by Day 10**.**

Cardiac Electrophysiology

At a dose 1.33 times the maximum approved recommended dose (and peak concentrations 1.25-fold higher than the maximum approved dose), raltegravir does not prolong the QT interval or PR interval to any clinically relevant extent.

12.3 Pharmacokinetics

Adults

Absorption:

Raltegravir, given 400 mg twice daily, is absorbed with a T_{max} of approximately 3 hours postdose in the fasted state in healthy subjects Raltegravir 1200 mg once daily is rapidly absorbed with median T_{max} of ~1.5 to 2 hours in the fasted state.

Raltegravir increases dose proportionally (AUC and $C_{max)}$ or slightly less than dose proportionally (C_{12hr}) over the dose range 100 mg to 1600 mg.

The absolute bioavailability of raltegravir has not been established. The chewable tablet and oral suspension have higher oral bioavailability compared to the 400 mg film-coated tablet.

Relative to the raltegravir 400 mg formulation, the raltegravir 600 mg formulation has higher relative bioavailability.

Steady-state is generally reached in 2 days, with little to no accumulation with multiple dose administration for the 400 mg twice daily and 1200 once daily formulation.

Effect of Food on Oral Absorption:

The food effect of various formulations are presented in Table 12

Table 12: Effect of Food on the Pharmacokinetics of Raltegravir Formulations

		PK Parameter Ratio (Fed/Fasted)		
Formulation	**Meal Type**	**AUC Ratio (90 % CI)**	**C_{max} Ratio (90 % CI)**	**C_{min} Ratio (90 % CI)**
400 mg twice daily	Low Fat	0.54 (0.41 to 0.71)	0.48 (0.35 to 0.67)	0.86 (0.54 to 1.36)
	Moderate Fat	1.13 (0.85 to 1.49)	1.05 (0.75 to 1.46)	1.66 (1.04 to 2.64)
	High Fat	2.11 (1.60 to 2.80)	1.96 (1.41 to 2.73)	4.13 (2.60 to 6.57)
1200 mg once daily	Low Fat	0.58 (0.46 to 0.74)	0.48 (0.37 to 0.62)	0.84 (0.63 to 1.10)
	High Fat	1.02 (0.86 to 1.21)	0.72 (0.58 to 0.90)	0.88 (0.66 to 1.18)
Chewable tablet	High Fat	0.94 (0.78 to 1.14)	0.38 (0.28 to 0.52)	2.88 (2.21 to 3.75)
Oral suspension	The effect of food on oral suspension was not studied.			
Low-fat meal: 300 Kcal, 2.5 g fat Moderate-fat meal: 600 Kcal, 21 g fat High-fat meal: 825 Kcal, 52 g fat				

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

In one study of HIV-1 infected subjects who received raltegravir 400 mg twice daily, raltegravir was measured in the cerebrospinal fluid. In the study (n=18), the median cerebrospinal fluid concentration was 5.8 % (range 1 to 53.5 %) of the corresponding plasma concentration. This median proportion was approximately 3-fold lower than the free fraction of raltegravir in plasma. The clinical relevance of this finding is unknown.

Metabolism and Excretion:
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. The major mechanism of clearance of raltegravir in humans is UGT1A1-mediated glucuronidation.

Table 13: Multiple-Dose Pharmacokinetic Parameters of Raltegravir Following the Administration of 400 mg Twice Daily and 1200 mg Once Daily in HIV-infected Subjects

Parameter	**400 mg BID Geometric Mean (%CV) N=6**	**1200 mg QD Geometric Mean (%CV) N=524**
AUC (mcM●hr)	$AUC_{0 \text{ to } 12}$ = 14.3 (88.6)	$AUC_{0 \text{ to } 24}$ = 55.3 (41.5)
C_{max} (mcM)	4.5 (128)	15.7 (45.8)
C_{min} (nM)	C_{12} = 142 (63.8)	C_{24} = 107 (97.5)

Special Populations
Pediatric:
Raltegravir tablets, 1200 mg (2 x 600 mg) were not evaluated in a pediatric clinical study. Exposures for pediatric subjects weighing at least 40 kg administered raltegravir tablets are predicted to be comparable to adult exposures observed from Phase III ONCEMRK.

Age/Race/Gender:
There is no clinically meaningful effect of age (18 years and older), race, or gender on the pharmacokinetics of raltegravir.

Hepatic Impairment:
Raltegravir is eliminated primarily by glucuronidation in the liver. The pharmacokinetics of a

single 400-mg dose of raltegravir were not altered in patients with moderate (Child-Pugh Score 7 to 9) hepatic impairment.

No hepatic impairment study has been conducted with raltegravir tablets, 1200 mg (2 x 600 mg) once daily. The effect of severe hepatic impairment on the pharmacokinetics of raltegravir has not been studied.

Renal Impairment:
Renal clearance of unchanged drug is a minor pathway of elimination. The pharmacokinetics of a single 400-mg dose of raltegravir were not altered in patients with severe (24-hour creatinine clearance of <30 mL/min/1.73 m^2) renal impairment.

No renal impairment study was conducted with raltegravir tablets, 1200 mg (2 x 600 mg) once daily.

The extent to which raltegravir tablets may be dialyzable is unknown.

Drug Interactions
In vitro, raltegravir does not inhibit (IC50>100 mcM) CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A. *In vivo*, raltegravir does not inhibit CYP3A4. Moreover, *in vitro*, raltegravir did not induce CYP1A2, CYP2B6 or CYP3A4. Similarly, raltegravir is not an inhibitor (IC50>50 mcM) of UGT1A1 or UGT2B7, and raltegravir does not inhibit P-glycoprotein-mediated transport.

Raltegravir drug interaction study results are shown in Tables 16 and 17. For information regarding clinical recommendations *[see Drug Interactions (7)]*.

Table 16: 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 raltegravir		23	0.49 (0.33, 0.71)	0.49 (0.35, 0.67)	0.44 (0.34, 0.55)
	20 mL single dose given 2 hours after raltegravir		23	0.78 (0.53, 1.13)	0.70 (0.50, 0.96)	0.43 (0.34, 0.55)

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}
	20 mL single dose given 4 hours before raltegravir		17	0.78 (0.55, 1.10)	0.81 (0.63, 1.05)	0.40 (0.31, 0.52)
	20 mL single dose given 4 hours after raltegravir		18	0.70 (0.48, 1.04)	0.68 (0.50, 0.92)	0.38 (0.30, 0.49)
	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)
aluminum and magnesium hydroxide antacid*	20 mL single dose given 12 hours after raltegravir	200 mg single dose	19	0.86 (0.65, 1.15)	0.86 (0.73, 1.03)	0.42 (0.34, 0.52)
atazanavir	400 mg daily	100 mg single dose	10	1.53 (1.11, 2.12)	1.72 (1.47, 2.02)	1.95 (1.30, 2.92)
atazanavir	400 mg daily	1200 mg single dose	14	1.16 (1.01, 1.33)	1.67 (1.34, 2.10)	1.26 (1.08, 1.46)
atazanavir/ritonavir	300 mg/100 mg daily	400 mg twice daily	10	1.24 (0.87, 1.77)	1.41 (1.12, 1.78)	1.77 (1.39, 2.25)
boceprevir	800 mg three times daily	400 mg single dose	22	1.11 (0.91, 1.36)	1.04 (0.88, 1.22)	0.75 (0.45, 1.23)
calcium carbonate antacid*	3000 mg single dose given with raltegravir	400 mg twice daily	24	0.48 (0.36, 0.63)	0.45 (0.35, 0.57)	0.68 (0.53, 0.87)
calcium carbonate antacid*	3000 mg single dose given with raltegravir	1200 mg single dose	19	0.26 (0.21, 0.32)	0.28 (0.24, 0.32)	0.52 (0.45, 0.61)
	3000 mg single dose given 12 hours after raltegravir			0.98 (0.81, 1.17)	0.90 (0.80, 1.03)	0.43 (0.36, 0.51)
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}
efavirenz	600 mg daily	1200 mg single dose	21	0.91 (0.70, 1.17)	0.86 (0.73, 1.01)	0.94 (0.76, 1.17)
etravirine	200 mg twice daily	400 mg twice daily	19	0.89 (0.68, 1.15)	0.90 (0.68, 1.18)	0.66 (0.34, 1.26)
omeprazole*	20 mg daily	400 mg twice daily	18	1.51 (0.98, 2.35)	1.37 (0.99, 1.89)	1.24 (0.95, 1.62)
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	400 mg twice daily when administered alone; 800 mg twice daily when administered with rifampin	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)

*Study conducted in HIV-infected subjects.

Table 17: Effect of Raltegravir on the Pharmacokinetics of Other Agents in Adult

Substrate Drug	Raltegravir Dose/Schedule	Ratio (90 % Confidence Interval) of Substrate Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00			
		n	C_{max}	AUC	C_{min}
Tenofovir disoproxil fumarate 300 mg	400 mg	9	0.77 (0.69, 0.85)	0.90 (0.82, 0.99)	C_{24hr} 0.87 (0.74, 1.02)
Etravirine 200 mg	400 mg	19	1.04 (0.97, 1.12)	1.10 (1.03, 1.16)	1.17 (1.10, 1.26)

In drug interaction studies, there was no effect of raltegravir on the PK of ethinyl estradiol, methadone, midazolam or boceprevir.

12.4 Microbiology

Mechanism of Action

Raltegravir inhibits the catalytic activity of HIV-1 integrase, an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the covalent insertion, or integration, of unintegrated linear HIV-1 DNA into the host cell genome preventing the formation of the HIV-1 provirus. The provirus is required to direct the production of progeny virus, so inhibiting integration prevents propagation of the viral infection. Raltegravir did not significantly inhibit human phosphoryl transferases including DNA polymerases α, β, and γ.

Antiviral Activity in Cell Culture

Raltegravir at concentrations of 31 ± 20 nM resulted in 95 % inhibition (EC_{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, 5 clinical isolates of HIV-1 subtype B had EC_{95} values ranging from 9 to 19 nM in cultures of mitogen-activated human peripheral blood mononuclear cells. In a single-cycle infection assay, raltegravir inhibited infection of 23 HIV-1 isolates representing 5 non-B subtypes (A, C, D, F, and G) and 5 circulating recombinant forms (AE, AG, BF, BG, and cpx) with EC_{50} values ranging from 5 to 12 nM. Raltegravir also inhibited replication of an HIV-2 isolate when tested in CEMx174 cells (EC_{95} value = 6 nM). No antagonism was observed when human T-lymphoid cells infected with the H9IIIB variant of HIV-1 were incubated with raltegravir in combination with non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, or nevirapine); nucleoside analog reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, tenofovir, or zidovudine); protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir); or the entry inhibitor enfuvirtide.

Resistance

The mutations observed in the HIV-1 integrase coding sequence that contributed to raltegravir resistance (evolved either in cell culture or in subjects treated with raltegravir) generally included an amino acid 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 substitutions (i.e., L74M, E92Q, Q95K/R,

T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230R, and D232N). E92Q, T97A, and F121C are occasionally seen in the absence of substitutions at Y143, Q148, or N155 in raltegravir-treatment failure subjects.

Treatment-Naive 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 12 virologic failure subjects with evaluable genotypic data from paired baseline and raltegravir treatment-failure isolates. By Week 96 in the ONCEMRK trial, primary raltegravir resistance substitutions were observed in on treatment isolates obtained from 4 (3 with N155H and 1 with E92Q) of 14 virologic failure subjects with evaluable genotypic data in the 1,200 mg QD arm and 2 (1 with N155H and 1 with T97A) of 6 virologic failure subjects in the 400 mg BID arm. Additional integrase substitutions observed included L74M, Q95K, V151I, E170A, I203M and D232N. These resistant isolates exhibited 6.2 to 19-fold reductions in susceptibility to raltegravir. Overall, at Week 96, detection of raltegravir resistance was not different between the QD and BID arms in subjects who were failing treatment and had resistance data evaluable (28.6 % versus 33.3 %, respectively).

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.

Cross Resistance
Cross resistance has been observed among HIV-1 integrase strand transfer inhibitors (INSTIs). Amino acid substitutions in HIV-1 integrase conferring resistance to raltegravir generally also confer resistance to elvitegravir. Substitutions at amino acid Y143 confer greater reductions in susceptibility to raltegravir than to elvitegravir, and the E92Q substitution confers greater reductions in susceptibility to elvitegravir than to raltegravir. Viruses harboring a substitution at amino acid Q148, along with one or more other raltegravir resistance substitutions, may also have clinically significant resistance to dolutegravir.

12.5 Pharmacogenomics

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).

In the neonatal study IMPAACT P1110, there was no association between apparent clearance (CL/F) of raltegravir and UGT1A1 genotype polymorphisms.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 1.8-fold (females) or 1.2-fold (males) greater than the AUC (54 mcM●hr) at the 400-mg twice daily human dose. Treatment-related squamous cell carcinoma of nose/nasopharynx was observed in female rats dosed with 600 mg/kg/day raltegravir for 104 weeks. These tumors were possibly the result of local irritation and inflammation due to local deposition and/or aspiration of drug in the mucosa of the nose/nasopharynx during dosing. No tumors of the nose/nasopharynx were observed in rats dosed with 150 mg/kg/day (males) and 50 mg/kg/day (females) and the systemic exposure in rats was 1.7-fold (males) to 1.4-fold (females) greater than the AUC (54 mcM●hr) at the 400-mg twice daily human dose.

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

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 exposure above the exposure at the recommended human dose.

14 CLINICAL STUDIES

14.1 Description of Clinical Studies

The evidence of durable efficacy of raltegravir tablets, 400 mg twice daily is based on the analyses of 240-week data from a randomized, double-blind, active-controlled trial, STARTMRK evaluating raltegravir tablets, 400 mg twice daily in antiretroviral treatment-naïve HIV-1 infected adult subjects, the analysis of 96-week data from a randomized, double-blind, active-control trial, ONCEMRK evaluating raltegravir tablets, 1200 mg (2 x 600 mg) once daily in treatment-naïve adult subjects, and 96-week data from 2 randomized, double-blind, placebo-controlled studies, BENCHMRK 1 and BENCHMRK 2, evaluating raltegravir tablets, 400 mg twice daily in antiretroviral treatment-experienced HIV-1 infected adult subjects. See Table 18.

Table 18: Trials Conducted with Raltegravir Tablets, 400 mg and Raltegravir Tablets, 600 mg in Subjects with HIV-1 Infection

Trial	Study Type	Population	Study Arms (N)	Dose/ Formulation	Timepoint
STARTMRK	Randomized, double-blind, active-controlled	Treatment-Naïve Adults	Raltegravir Tablets 400 mg Twice Daily (281) Efavirenz 600 mg At Bedtime (282) Both in combination with emtricitabine (+) tenofovir disoproxil fumarate	400 mg film-coated tablet	Week 240
ONCEMRK	Randomized, double- blind, active-controlled	Treatment-Naive Adults	Raltegravir Tablets 1200 mg Once Daily (531) Raltegravir Tablets 400 mg Twice Daily (266) In combination with emtricitabine (+) tenofovir disoproxil fumarate	600 mg film-coated tablet 400 mg film-coated tablet	Week 96
BENCHMRK 1	Randomized, double- blind, placebo-controlled	Treatment-Experienced Adults	Raltegravir Tablets 400 mg Twice Daily (232) Placebo (118) Both in combination with optimized background therapy	400 mg film-coated tablet	Week 240 (Week 156 on double-blind plus Week 84 on open-label)
BENCHMRK 2	Randomized, double- blind, placebo-controlled	Treatment-Experienced Adults	Raltegravir Tablets 400 mg Twice Daily (230) Placebo (119) Both in combination with optimized background therapy	400 mg film-coated tablet	Week 240 (Week 156 on double-blind plus Week 84 on open-label)

Trial	Study Type	Population	Study Arms (N)	Dose/ Formulation	Timepoint
IMPAACT P1066	Open-label, non-comparative	Pediatric Patients – 4 weeks to 18 years of age (Treatment-Experienced or Failed Prior PMTCT)	Raltegravir 400 mg tablet Twice Daily – 12 to 18 years or 6 to <12 years and ≥25 kg (87) In combination with optimized background therapy	400 mg film-coated tablet	Week 240

14.2 Treatment-Naive Adult Subjects

STARTMRK (Raltegravir Tablets 400 mg Twice Daily)

STARTMRK is a Phase 3 randomized, international, double-blind, active-controlled trial to evaluate the safety and efficacy of raltegravir tablets, 400 mg twice daily versus efavirenz 600 mg at bedtime both with emtricitabine (+) tenofovir disoproxil fumarate in treatment-naïve HIV-1-infected subjects with HIV-1 RNA >5000 copies/mL. Randomization was stratified by screening HIV-1 RNA level (≤50,000 copies/mL; or>50,000 copies/mL) and by hepatitis status. In STARTMRK, 563 subjects were randomized andreceived at least 1 dose of either raltegravir 400 mg twice daily or efavirenz 600 mg at bedtime, both in combination with emtricitabine (+) tenofovir disoproxil fumarate. There were 563 subjects included in the efficacy and safety analyses. At baseline, the median age of subjects was 37 years (range 19 to 71), 19 % female, 58 % non-white, 6 % had hepatitis B and/or C virus co-infection, 20 % were CDC Class C (AIDS), 53 % had HIV-1 RNA greater than 100,000 copies per mL, and 47 % had CD4+ cell count less than 200 cells per mm3; the frequencies of these baseline characteristics were similar between treatment groups.

ONCEMRK (Raltegravir Tablets 1200 mg [2 x 600 mg] Once Daily)

ONCEMRK is a Phase 3 randomized, international, double-blind, active-controlled trial to evaluate the safety and efficacy of raltegravir tablets, 1200 mg (2 x 600 mg) once daily versus raltegravir tablets, 400 mg twice daily, both in combination with emtricitabine (+) tenofovir disoproxil fumarate, in treatment-naïve HIV-1-infected subjects with HIV-1 RNA ≥1000 copies/mL. Randomization was stratified by screening HIV-1 RNA level (≤100,000 or >100,000 copies/mL) and by hepatitis B and C infection status.

In ONCEMRK, 797 subjects were randomized and received at least 1 dose of either raltegravir 1200 mg once daily or raltegravir 400 mg twice daily, both in combination with emtricitabine (+) tenofovir disoproxil fumarate. There were 797 subjects included in the efficacy and safety analyses. At baseline, the median age of subjects was 34 years (range 18 to 84), 15 % female, 41 % non-white, 3 % had hepatitis B and/or C virus co-infection, 13 % were CDC Class C (AIDS), 28 % had HIV-1 RNA greater than 100,000 copies per mL, and 13 % had CD4+ cell count less than 200 cells per mm^3; the frequencies of these baseline characteristics were similar between treatment groups.

Table 19 shows the virologic outcomes in both studies. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing duration of

follow-up.

Table 19: Virologic Outcomes of Randomized Treatment in STARTMRK and ONCEMRK (Snapshot Algorithm) in HIV Treatment-Naive Adults

	STARTMRK Week 240		**ONCEMRK Week 96**	
	Raltegravir Tablets, 400 mg Twice Daily (N=281)	**Efavirenz 600 mg At Bedtime (N=282)**	**Raltegravir Tablets, 1200 mg Once Daily (N=531)**	**Raltegravir Tablets, 400 mg Twice Daily (N=266)**
HIV RNA < Lower Limit of Quantitation*	66 %	60 %	82 %	80 %
Treatment Difference	6.6 % (95 % CI: -1.4 %, 14.5 %)		1.4% (95% CI: -4.4%, 7.3%)	
HIV RNA ≥ Lower Limit of Quantitation	8 %	15 %	9 %	8 %
No Virologic Data at Analysis Timepoint	26 %	26 %	9 %	12 %
Reasons				
Discontinued trial due to AE or Death†	5 %	10 %	1 %	3 %
Discontinued trial for Other Reasons‡	15 %	14 %	7 %	8 %
On trial but missing data at timepoint	6 %	2 %	1 %	2 %

Note: Raltegravir BID, Raltegravir tablets and Efavirenz were administered with emtricitabine (+) tenofovir disoproxil fumarate

* Lower Limit of Quantitation: STARTMRK <50 copies/mL; ONCEMRK < 40 copies/mL.

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

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

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

Consistent efficacy in subjects receiving raltegravir tablets, 1200 mg (2 x 600 mg) once daily was observed across HIV subtypes with 80.6 % (270/335) and 83.5 % (162/194) of subjects with B and non-B subtypes respectively, achieving HIV RNA <40 copies/mL at week 96 (Snapshot approach).

14.3 Treatment-Experienced Adult Subjects

BENCHMRK 1 and BENCHMRK 2 are Phase 3 studies to evaluate the safety and antiretroviral activity of raltegravir tablets, 400 mg twice daily in combination with an optimized background therapy (OBT), versus OBT alone, in HIV-1-infected subjects, 16 years or older, with documented resistance to at least 1 drug in each of 3 classes (NNRTIs, NRTIs, 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 20 shows the demographic characteristics of subjects in the group receiving raltegravir tablets, 400 mg twice daily and subjects in the placebo group.

Table 20: Trials BENCHMRK 1 and BENCHMRK 2 Baseline Characteristics

Randomized Studies BENCHMRK 1 and BENCHMRK 2	**Raltegravir Tablets, 400 mg Twice Daily + OBT (N = 462)**	**Placebo + OBT (N = 237)**
Gender		
Male	88 %	89 %
Female	12 %	11 %
Race		
White	65 %	73 %
Black	14 %	11 %
Asian	3 %	3 %
Hispanic	11 %	8 %
Others	6 %	5 %
Age (years)		
Median (min, max)	45 (16 to 74)	45 (17 to 70)
CD4+ Cell Count		
Median (min, max), cells/mm^3	119 (1 to 792)	123 (0 to 759)

Randomized Studies BENCHMRK 1 and BENCHMRK 2	Raltegravir Tablets, 400 mg Twice Daily + OBT (N = 462)	Placebo + OBT (N = 237)
≤50 cells/mm^3	32 %	33 %
>50 and ≤200 cells/mm^3	37 %	36 %
Plasma HIV-1 RNA		
Median (min, max), log_{10} copies/mL	4.8 (2 to 6)	4.7 (2 to 6)
>100,000 copies/mL	36 %	33 %
History of AIDS		
Yes	92 %	91 %
Prior Use of ART, Median (1st Quartile, 3rd Quartile)		
Years of ART Use Number of ART	10 (7 to 12) 12 (9 to 15)	10 (8 to 12) 12 (9 to 14)
Hepatitis Co-infection*		
No Hepatitis B or C virus Hepatitis B virus only Hepatitis C virus only Co-infection of Hepatitis B and C virus	83 % 8 % 8 % 1 %	84 % 3 % 12 % 1 %
Stratum		
Enfuvirtide in OBT Resistant to ≥2 PI	38 % 97 %	38 % 95 %

* Hepatitis B virus surface antigen positive or hepatitis C virus antibody positive.

Table 21 compares the characteristics of optimized background therapy at baseline in the group receiving raltegravir tablets, 400 mg twice daily and subjects in the control group.

Table 21: Trials BENCHMRK 1 and BENCHMRK 2 Characteristics of Optimized Background Therapy at Baseline

Randomized Studies BENCHMRK 1 and BENCHMRK 2	Raltegravir Tablets, 400 mg Twice Daily + OBT (N = 462)	Placebo + OBT (N = 237)
Number of ARTs in OBT		
Median (min, max)	4 (1 to 7)	4 (2 to 7)
Number of Active PI in OBT by Phenotypic Resistance Test*		
0	36 %	41 %
1 or more	60 %	58 %
Phenotypic Sensitivity Score (PSS)†		
0	15 %	18 %
1	31 %	30 %
2	31 %	28 %
3 or more	18 %	20 %
Genotypic Sensitivity Score (GSS)†		
0	25 %	27 %
1	38 %	40 %
2	24 %	21 %
3 or more	11 %	10 %

* Darunavir use in OBT in darunavir-naïve subjects 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 subject's viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide-naïve subjects was counted as one active drug in OBT in the GSS and PSS. Similarly, darunavir use in OBT in darunavir-naïve subjects was counted as one active drug in OBT.

Week 96 outcomes for the 699 subjects randomized and treated with the recommended dose of raltegravir tablets, 400 mg twice daily or placebo in the pooled BENCHMRK 1 and 2 studies are shown in Table 22.

Table 22: Virologic Outcomes of Randomized Treatment of BENCHMRK 1 and BENCHMRK 2 Trials at 96 Weeks (Pooled Analysis)

	Raltegravir Tablets, 400 mg Twice Daily + OBT (N = 462)	**Placebo + OBT (N = 237)**
Subjects with HIV-1 RNA less than 50 copies/mL	55 %	27 %
Virologic Failure*	35 %	66 %
No virologic data at Week 96 Window		
Reasons		
Discontinued study due to AE or death†	3 %	3 %
Discontinued study for other reasons‡	4 %	4 %
Missing data during window but on study	4 %	<1 %

* Includes subjects who switched to open-label raltegravir after Week 16 due to the protocol-defined virologic failure, subjects who discontinued prior to Week 96 for lack of efficacy, subjects changed OBT due to lack of efficacy prior to Week 96, or subjects who were ≥50 copies in the 96 week window.

† Includes subjects who discontinued due to AE or death at any time point from Day 1 through the Week 96 window if this resulted in no virologic data on treatment during the Week 96 window.

‡ Other includes: withdrew consent, loss to follow-up, moved etc., if the viral load at the time of discontinuation was <50 copies/mL.

The mean changes in CD4 count from baseline were 118 cells/mm^3 in the group receiving raltegravir tablets, 400 mg twice daily and 47 cells/mm^3 for the control group.

Treatment-emergent CDC Category C events occurred in 4 % of the group receiving raltegravir tablets, 400 mg twice daily and 5 % of the control group.

Virologic responses at Week 96 by baseline genotypic and phenotypic sensitivity score are shown in Table 23.

Table 23: Virologic Response at 96 Week Window by Baseline Genotypic/Phenotypic Sensitivity Score

	Percent with HIV-1 RNA <50 copies/mL At Week 96			
	n	**Raltegravir Tablets, 400 mg Twice Daily + OBT (N = 462)**	**n**	**Placebo + OBT (N = 237)**
Phenotypic Sensitivity Score (PSS)*				
0	67	43	43	5
1	144	58	71	23
2	142	61	66	32
3 or more	85	48	48	42
Genotypic Sensitivity Score (GSS)*				
0	116	39	65	5
1	177	62	95	26
2	111	61	49	53
3 or more	51	49	23	35

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

Switch of Suppressed Subjects from Lopinavir (+) Ritonavir to Raltegravir

The SWITCHMRK 1 and 2 Phase 3 studies evaluated HIV-1 infected subjects receiving suppressive therapy (HIV-1 RNA <50 copies/mL on a stable regimen of lopinavir 200 mg (+) ritonavir 50 mg 2 tablets twice daily plus at least 2 nucleoside reverse transcriptase inhibitors for >3 months) and randomized them 1:1 to either continue lopinavir (+) ritonavir (n=174 and n=178, SWITCHMRK 1 and 2, respectively) or replace lopinavir (+) ritonavir with raltegravir tablets, 400 mg twice daily (n=174 and n=176, respectively). The primary virology endpoint was the proportion of subjects with HIV-1 RNA less than 50 copies/mL at Week 24 with a prespecified non-inferiority margin of -12 % for each study; and the frequency of adverse events up to 24 weeks.

Subjects 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 each failed to demonstrate non-inferiority of switching to raltegravir tablets versus continuing on lopinavir (+) ritonavir. In the combined analysis of these studies at Week 24, suppression of HIV-1 RNA to less than 50 copies/mL was maintained in 82.3 % of the raltegravir tablets group

versus 90.3 % of the lopinavir (+) ritonavir group. Clinical and laboratory adverse events occurred at similar frequencies in the treatment groups.

14.4 Pediatric Subjects

2 to 18 Years of Age

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. Subjects were stratified by age, enrolling adolescents first and then successively younger children. Subjects were enrolled into cohorts according to age and received the following formulations: Cohort I (12 to less than 18 years old), 400 mg film-coated tablet; Cohort IIa (6 to less than 12 years old), 400 mg film-coated tablet; Cohort IIb (6 to less than 12 years old), chewable tablet; Cohort III (2 to less than 6 years), chewable tablet. 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 subjects were enrolled for evaluation of long term safety, tolerability and efficacy. Of the 126 subjects, 96 received the recommended dose of raltegravir tablets *[see Dosage and Administration (2.3)]*.

These 96 subjects 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 to 2361) and median CD4 % was 23.3 % (range: 0 to 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 subjects had previously used at least one NNRTI (78 %) or one PI (83 %).

Ninety-three (97 %) subjects 2 to 18 years of age completed 24 weeks of treatment (3 discontinued due to non-compliance). At Week 24, 54 % achieved HIV RNA <50 copies/mL; 66 % achieved HIV RNA <400 copies/mL. The mean CD4 count (percent) increase from baseline to Week 24 was 119 cells/mm^3 (3.8 %).

4 Weeks to Less Than 2 Years of Age

IMPAACT P1066 also enrolled HIV-infected, infants and toddlers 4 weeks to less than 2 years of age (Cohorts IV and V) who had received prior antiretroviral therapy either as prophylaxis for prevention of mother-to-child transmission (PMTCT) and/or as combination antiretroviral therapy for treatment of HIV infection. Raltegravir was administered as an oral suspension without regard to food in combination with an optimized background regimen.

The 26 subjects had a median age of 28 weeks (range: 4 to 100), were 35 % female, 85 % Black and 8 % Caucasian. At baseline, mean plasma HIV-1 RNA was 5.7 $\log_{10}$ copies/mL (range: 3.1 to 7), median CD4 cell count was 1400 cells/mm^3 (range: 131 to 3648) and median CD4 % was 18.6 % (range: 3.3 to 39.3). Overall, 69 % had baseline plasma HIV-1 RNA exceeding 100,000 copies/mL and 23 % had a CDC HIV clinical classification of category B or C. None of the 26 subjects were completely treatment naïve. All infants under 6 months of age had received

nevirapine or zidovudine for prevention of mother-to-infant transmission, and 43 % of subjects greater than 6 months of age had received two or more antiretrovirals.

Of the 26 treated subjects, 23 subjects were included in the Week 24 and 48 efficacy analyses, respectively. All 26 treated subjects were included for safety analyses.

At Week 24, 39 % achieved HIV RNA <50 copies/mL and 61 % achieved HIV RNA <400 copies/mL. The mean CD4 count (percent) increase from baseline to Week 24 was 500 cells/mm^3 (7.5 %).

At Week 48, 44% achieved HIV RNA <50 copies/mL and 61 % achieved HIV RNA <400 copies/mL. The mean CD4 count (percent) increase from baseline to Week 48 was 492 cells/mm^3 (7.8 %).

16 HOW SUPPLIED/STORAGE AND HANDLING

Raltegravir tablets USP, 600 mg are Yellow, modified capsule shaped, biconvex, film-coated tablets debossed with "LU" on one side and "J04" on the other side.

They are supplied as follows:
NDC 70748-327-07 unit-of-use bottles of 60.

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). see USP Controlled Room Temperature. Store in the original package with the bottle tightly closed.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

Severe and Potentially Life-threatening Rash

Inform patients that severe and potentially life-threatening rash has been reported. Advise patients to immediately contact their healthcare provider if they develop rash. Instruct patients to immediately stop taking raltegravir tablets, 600 mg and other suspect agents, and seek medical attention if they develop a rash associated with any of the following symptoms as it may be a sign of a more serious reaction such as Stevens-Johnson syndrome, toxic epidermal necrolysis or severe hypersensitivity: fever, generally ill feeling, extreme tiredness, muscle or joint aches, blisters, oral lesions, eye inflammation, facial swelling, swelling of the eyes, lips, mouth, breathing difficulty, and/or signs and symptoms of liver problems (e.g., yellowing of the skin or whites of the eyes, dark or tea colored urine, pale colored stools/bowel movements, nausea, vomiting, loss of appetite, or pain, aching or sensitivity on the right side below the ribs). Inform patients that if severe rash occurs, their physician will closely monitor them, order laboratory tests and initiate appropriate therapy.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any symptoms of infection, as in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from

previous infections may occur soon after anti-HIV treatment is started *[see Warnings and Precautions (5.2)]*.

Rhabdomyolysis
Before patients begin raltegravir tablets, 600 mg; ask them if they have a history of rhabdomyolysis, myopathy or increased creatine kinase or if they are taking medications known to cause these conditions such as statins, fenofibrate, gemfibrozil or zidovudine *[see Adverse Reactions (6.1)]*.
Instruct patients to immediately report to their healthcare provider any unexplained muscle pain, tenderness, or weakness while taking raltegravir tablets.

Drug Interactions
Inform patients that raltegravir tablets, 600 mg may interact with some drugs and ask them to identify all their current medications including over-the-counter agents *[see Drug Interactions (7.2)]*.

Missed Dosage
Inform patients that it is important to take raltegravir tablets, 600 mg on a regular dosing schedule as instructed by their healthcare provider and to avoid missing doses as it can result in development of resistance *[see Dosage and Administration (2)]*.

Important Administration Instructions
Film-Coated Tablets
Inform patients that the film-coated tablets must be swallowed whole.

Pregnancy Registry
Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to raltegravir tablets, 600 mg during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation
Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk *[see Use in Specific Populations (8.2)]*.

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PATIENT INFORMATION
Raltegravir (ral teg' ra vir) film-coated tablets

What are raltegravir tablets?

Raltegravir tablets are a prescription medicine used with other HIV-1 medicines to treat HIV-1 infection in adults, and in children weighing at least 88 pounds (40 kg).

Before you take raltegravir tablets, tell your doctor about all of your medical conditions, including if you:

- have liver problems
- have a history of a muscle disorder called rhabdomyolysis or myopathy
- have increased levels of creatine kinase in your blood
- receive kidney dialysis treatment
- are pregnant or plan to become pregnant. It is not known if raltegravir tablets can harm your unborn baby.

  Pregnancy Registry: There is a pregnancy registry for women who take raltegravir tablets during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your doctor about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. Do not breastfeed if you take raltegravir.
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - It is not known if raltegravir can pass into your breast milk.
  - Talk with your doctor about the best way to feed your baby.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines interact with raltegravir tablets.

- **Keep a list of your medicines to show your doctor and pharmacist.**
- You can ask your doctor or pharmacist for a list of medicines that interact with raltegravir tablets.
- **Do not start taking a new medicine without telling your doctor**. Your doctor can tell you if it is safe to take raltegravir tablets with other medicines.

How should I take raltegravir tablets?

- Take raltegravir tablets exactly as prescribed by your doctor.
- **Do not** change your dose of raltegravir 400 mg film-coated tablets or raltegravir 600 mg film-coated tablets or stop your treatment without talking with your doctor first.
- Stay under the care of your doctor during treatment with raltegravir tablets.
- Raltegravir 600 mg film-coated tablets **must be swallowed whole**.
- **Do not switch between the film-coated tablet, the chewable tablet, or the oral suspension without talking with your doctor first.**
- **Do not** switch between the raltegravir 400 mg film-coated tablets and raltegravir 600 mg film-coated tablets if your prescribed dose is 1200 mg.
- **Do not** run out of raltegravir tablets. The virus in your blood may increase and the virus may become harder to treat. Get a refill of your raltegravir tablets from your doctor or pharmacy before you run out.
- Take raltegravir tablets on a regular dosing schedule as instructed by your doctor. Do not miss doses.

- If you take too much raltegravir tablets, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of raltegravir tablets?

Raltegravir tablets can cause serious side effects including:

- **Severe skin reactions and allergic reactions.** Some people who take raltegravir tablets develop severe skin reactions and allergic reactions that can be serious, and may be life-threatening or lead to death.
    - If you develop a rash, call your doctor right away.
    - If you develop a rash with any of the following symptoms, stop using raltegravir tablets and call your doctor or get medical help right away:
        - fever
        - generally ill feeling
        - extreme tiredness
        - muscle or joint aches
        - blisters or sores in mouth
        - blisters or peeling of the skin
        - redness or swelling of the eyes
        - swelling of the mouth, lips, or face
        - problems breathing

Sometimes allergic reactions can affect body organs, such as your liver. Call your doctor right away if you have any of the following signs or symptoms of liver problems:

- yellowing of your skin or whites of your eyes
- dark or tea colored urine
- pale colored stools (bowel movements)
- nausea or vomiting
- loss of appetite
- pain, aching, or tenderness on the right side of your stomach area

- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your doctor right away if you start having new symptoms after starting your HIV-1 medicine.

The most common side effects of raltegravir tablets include:

- trouble sleeping
- dizziness
- headache
- nausea
- tiredness

Less common side effects of raltegravir tablets:

- depression
- hepatitis
- genital herpes
- herpes zoster including shingles

- kidney failure
- kidney stones
- indigestion or stomach area pain
- vomiting
- suicidal thoughts and actions
- weakness

Tell your doctor right away if you get unexplained muscle pain, tenderness, or weakness during treatment with raltegravir tablets. These may be signs of a rare serious muscle problem that can lead to kidney problems.

These are not all the possible side effects of raltegravir tablets.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store raltegravir tablets?

Raltegravir 600 mg film-coated tablets:

- Store raltegravir tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Store raltegravir tablets in the original package with the bottle tightly closed.

Keep raltegravir and all medicines out of the reach of children.

General information about the safe and effective use of raltegravir tablets

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use raltegravir tablets for a condition for which it was not prescribed. Do not give raltegravir tablets to other people, even if they have the same symptoms that you have. It may harm them. You can ask your doctor or pharmacist for information about raltegravir tablets that is written for health professionals.

What are the ingredients in raltegravir tablets?

Active ingredient: Raltegravir

Inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone K30 and tartaric acid.

The film coating contains: iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

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