SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the finished pharmaceutical product

INN Name: Raltegravir Potassium (Amorphous)

Trade Name: Not Applicable

Strength: 400 mg

Pharmaceutical form: Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains 434.4 mg Raltegravir Potassium equivalent to 400 mg Raltegravir.

3. Pharmaceutical form

Dosage form: Film coated tablet

Description: Pink, oval, biconvex film coated tablets debossed with 'I' on one side and '46' on the other side.

4. Clinical particulars

4.1 Therapeutic indications

RALTEGRAVIR is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in patients 4 weeks of age and older.

• The use of other active agents with RALTEGRAVIR is associated with a greater likelihood of treatment response.

4.2 Posology and method of administration

General Dosing Recommendations

• RALTEGRAVIR Film-Coated Tablets, Chewable Tablets and For Oral Suspension can be administered with or without food.

• Because the formulations are not bioequivalent, do not substitute RALTEGRAVIR chewable tablets or RALTEGRAVIR for oral suspension for the RALTEGRAVIR 400 mg film-coated tablet. See specific dosing guidance for chewable tablets and the formulation for oral suspension.

• During coadministration of RALTEGRAVIR 400 mg film-coated tablets with rifampin, the recommended dosage of RALTEGRAVIR is 800 mg twice daily in adults. There are no data to guide co-administration of RALTEGRAVIR with rifampin in patients below 18 years of age.

• Maximum dose of chewable tablets is 300 mg twice daily.

• Maximum dose of oral suspension is 100 mg twice daily.

• Each single-use packet for oral suspension contains 100 mg of raltegravir which is suspended in 5 mL of water giving a final concentration of 20 mg/mL.

Adults

For the treatment of adult patients with HIV-1 infection, the dosage of RALTEGRAVIR is one 400 mg film-coated tablet administered orally, twice daily.

Pediatrics

• If at least 25 kg: One 400 mg film-coated tablet orally, twice daily.

• If unable to swallow a tablet, consider the chewable tablet, as specified in Table 1.

Table 1: Alternative Dose* with RALTEGRAVIR Chewable Tablets for Pediatric Patients Weighing at Least 25 kg

Body Weight (kg)	Dose	Number of Chewable Tablets
25 to less than 28	150 mg twice daily	1.5 x 100 mg† twice daily
28 to less than 40	200 mg twice daily	2 x 100 mg twice daily
At least 40	300 mg twice daily	3 x 100 mg twice daily

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.

• If at least 4 weeks of age and weighing at least 3 kg to less than 25 kg: Weight based dosing, as specified in Table 2.

• For patients weighing between 11 and 20 kg, either the chewable tablet or oral suspension can be used, as specified in Table 2. Patients can remain on the oral suspension as long as their weight is below 20 kg. Refer to Table 2 for appropriate dosing.

Table 2: Recommended Dose* for RALTEGRAVIR For Oral Suspension and Chewable Tablets in Pediatric Patients Weighing Less than 25 kg

Body Weight (kg)	Volume (Dose) of Suspension to be Administered	Number of Chewable Tablets
3 to less than 4	1 mL (20 mg) twice daily	1.5 x 100 mg† twice daily
4 to less than 6	1.5 mL (30 mg) twice daily	2 x 100 mg twice daily
6 to less than 8	2 mL (40 mg) twice daily	3 x 100 mg twice daily
8 to less than 11	3 mL (60 mg) twice daily	
11 to less than 14†	4 mL (80 mg) twice daily	3 x 25 mg twice daily
14 to less than 20†	5 mL (100 mg) twice daily	1 x 100 mg twice daily
20 to less than 25		1.5 x 100 mg‡ twice daily

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

†For weight between 11 and 20 kg either formulation can be used.

Note: The chewable tablets are available as 25 mg and 100 mg tablets.

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

Method of Administration

RALTEGRAVIR Film-Coated Tablets

• Film-Coated Tablets must be swallowed whole

RALTEGRAVIR Chewable Tablets

• Chewable Tablets may be chewed or swallowed whole

RALTEGRAVIR For Oral Suspension

Each single-use RALTEGRAVIR packet for oral suspension contains 100 mg of raltegravir which is to be suspended in 5 mL of water giving a final concentration of 20 mg/mL.

• Pour packet contents of RALTEGRAVIR for oral suspension into 5 mL of water and mix

• Once mixed, measure the recommended volume (dose) of suspension with a syringe and administer the dose orally

• The volume (dose) of suspension should be administered orally within 30 minutes of mixing

• Discard any remaining suspension

• For more details on preparation and administration of the suspension, see Instructions for Use.

4.3 Contraindications

None

4.4 Special warnings and precautions for use

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 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.

Immune Reconstitution Syndrome

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

Phenylketonurics

Raltegravir Chewable Tablets contain phenylalanine, a component of aspartame. Each 25 mg Raltegravir Chewable Tablet contains approximately 0.05 mg phenylalanine. Each 100 mg Raltegravir Chewable Tablet contains approximately 0.10 mg phenylalanine. Phenylalanine can be harmful to patients with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category C

RALTEGRAVIR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no adequate and well-controlled studies in pregnant women. In addition, there have been no pharmacokinetic studies conducted in pregnant patients.

Developmental toxicity studies were performed in rabbits (at oral doses up to 1000 mg/kg/day) and rats (at oral doses up to 600 mg/kg/day). The reproductive toxicity study in rats was performed with pre-, peri-, and postnatal evaluation. The highest doses in these studies produced systemic exposures in these species approximately 3-to 4-fold 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 addition, no treatment-related external, visceral, or skeletal changes were observed in rabbits. However, treatment-related increases over controls in the incidence of supernumerary ribs were seen in rats at 600 mg/kg/day (exposures 3-fold the exposure at the recommended human dose).

Placenta transfer of drug was demonstrated in both rats and rabbits. At a maternal dose of 600 mg/kg/day in rats, 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. Mean drug concentrations in fetal plasma were approximately 2% of the mean maternal concentration at both 1 and 24 hours postdose at a maternal dose of 1000 mg/kg/day in rabbits. Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant patients exposed to RALTEGRAVIR, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1800-258-4263

Nursing Mothers

Breastfeeding is not recommended while taking RALTEGRAVIR. In addition, it is recommended that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1.

It is not known whether raltegravir is secreted in human milk. However, raltegravir is secreted in the milk of lactating rats. Mean drug concentrations in milk were approximately 3-fold greater than those in maternal plasma at a maternal dose of 600 mg/kg/day in rats. There were no effects in rat offspring attributable to exposure of RALTEGRAVIR through the milk.

Pediatric Use

The safety, tolerability, pharmacokinetic profile, and efficacy of RALTEGRAVIR 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. The safety profile was comparable to that observed in adults. for dosing recommendations for children 4 weeks of age and older. The safety and dosing information for RALTEGRAVIR have not been established in infants less than 4 weeks of age.

Geriatric Use

Clinical studies of RALTEGRAVIR 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.

Use in Patients with Hepatic Impairment

No clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and healthy subjects were observed. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of raltegravir has not been studied.

Use in Patients with Renal Impairment

No clinically important pharmacokinetic differences between subjects with severe renal impairment and healthy subjects were observed. No dosage adjustment is necessary.

4.7 Effects on ability to drive and use machines

Not Applicable

4.8 Undesirable effects

Effect of Raltegravir on the Pharmacokinetics of Other Agents

Raltegravir does not inhibit (IC50>100 μM) CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A in vitro. Moreover, in vitro, raltegravir did not induce CYP1A2, CYP2B6 or 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 effect of raltegravir on the pharmacokinetics of midazolam, a sensitive CYP3A4 substrate. Similarly, raltegravir is not an inhibitor (IC50>50 μM) of UGT1A1 or 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, opioid analgesics, statins, azole antifungals, proton pump inhibitors and anti-erectile dysfunction agents).

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 with drugs that inhibit UGT1A1 may increase plasma levels of raltegravir and coadministration of RALTEGRAVIR with drugs that induce UGT1A1, such as rifampin, may reduce plasma levels of raltegravir.

The impact of other inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown.

Selected drug interactions are presented in Table 8.

Table 8: Selected Drug Interactions in Adults

Concomitant Drug Class: Drug Name	Effect on Concentration of Raltegravir	Clinical Comment
Metal-Containing Antacids		
aluminum and/or magnesium-containing antacids	↓	Coadministration or staggered administration of aluminum and/or magnesium hydroxide-containing antacids and RALTEGRAVIR is not recommended.
Other Agents		
rifampin	↓	The recommended dosage of RALTEGRAVIR is 800 mg twice daily during

		coadministration with rifampin. There are no data to guide co-administration of RALTEGRAVIR with rifampin in patients below 18 years of age

Drugs without Clinically Significant Interactions with RALTEGRAVIR

In drug interaction studies, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of the following: hormonal contraceptives, methadone, lamivudine, tenofovir, etravirine, darunavir/ritonavir, or boceprevir. Moreover, atazanavir, atazanavir/ritonavir, boceprevir, calcium carbonate antacids, darunavir/ritonavir, efavirenz, etravirine, omeprazole, or tipranavir/ritonavir did not have a clinically meaningful effect on the pharmacokinetics of raltegravir. No dose adjustment is required when RALTEGRAVIR is coadministered with these drugs.

4.9 Overdose

No specific information is available on the treatment of over dosage with Raltegravir. Doses as high as 1600-mg single dose and 800-mg twice-daily multiple doses were studied in healthy volunteers without evidence of toxicity. Occasional doses of up to 1800 mg per day were taken in the clinical studies of HIV- 1 infected subjects without evidence of toxicity.

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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Pharmacotherapeutic group: Antiretroviral drug

ATC code: J05AX08

Mechanism of action

Raltegravir is an HIV-1 antiviral drug.

In a monotherapy study raltegravir (400 mg twice daily) demonstrated rapid antiviral activity with mean viral load reduction of 1.66 log10 copies/mL by Day 10.

In the randomized, double-blind, placebo-controlled, dose-ranging trial, Protocol 005, and Protocols 018 and 019, antiviral responses were similar among subjects regardless of dose.

Effects on Electrocardiogram

In a randomized, placebo-controlled, crossover study, 31 healthy subjects were administered a single oral supratherapeutic dose of raltegravir 1600 mg and placebo. Peak raltegravir plasma concentrations were approximately 4-fold higher than the peak concentrations following a 400 mg dose. Raltegravir did not appear to prolong the QTc interval for 12 hours post dose. After baseline and placebo adjustment, the maximum mean QTc change was -0.4 msec (1-sided 95% upper Cl: 3.1 msec).

5.2 Pharmacokinetics properties

Adults

Absorption

Raltegravir (film-coated tablet) is absorbed with a Tmax of approximately 3 hours postdose in the fasted state. Raltegravir AUC and Cmax increase dose proportionally over the dose range 100 mg to 1600 mg. Raltegravir C12hr 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 within approximately the first 2 days of dosing. There is little to no accumulation in AUC and Cmax. The average accumulation ratio for C12hr ranged from approximately 1.2 to 1.6.

The absolute bioavailability of raltegravir has not been established. Based on a formulation comparison study in healthy adult volunteers, the chewable tablet and oral suspension have higher oral bioavailability compared to the 400 mg film-coated tablet.

In subjects who received 400 mg twice daily alone, raltegravir drug exposures were characterized by a geometric mean AUC0-12hr of 14.3 μM●hr and C12hr of 142 nM.

Considerable variability was observed in the pharmacokinetics of raltegravir. For observed C12hr in Protocols 018 and 019, the coefficient of variation (CV) for inter-subject variability = 212% and the CV for intra-subject variability = 122%.

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-1-infected patients. The effect of consumption of low-, moderate- and high-fat meals on steady-state raltegravir pharmacokinetics was assessed in healthy volunteers administered the 400 mg film-coated tablet. Administration of multiple doses of raltegravir following a moderate-fat meal (600 Kcal, 21 g fat) did not affect raltegravir AUC to a clinically meaningful degree with an increase of 13% relative to fasting. Raltegravir C12hr was 66% higher and Cmax was 5% higher following a moderate-fat meal compared to fasting. Administration of raltegravir following a high-fat meal (825 Kcal, 52 g fat) increased AUC and Cmax by approximately 2-fold and increased C12hr by 4.1- fold. Administration of raltegravir following a low-fat meal (300 Kcal, 2.5 g fat) decreased AUC and Cmax by 46% and 52%, respectively; C12hr was essentially unchanged. Food appears to increase pharmacokinetic variability relative to fasting.

Administration of the chewable tablet with a high fat meal led to an average 6% decrease in AUC, 62% decrease in Cmax, and 188% increase in C12hr 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 effect of food on the formulation for oral suspension was not studied.

Distribution

Raltegravir is approximately 83% bound to human plasma protein over the concentration

range of 2 to 10 µM.

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. Studies using isoform-selective chemical inhibitors and cDNA-expressed UDP-glucuronosyl transferases (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

Special Populations

Pediatric

Two pediatric formulations were evaluated in healthy adult volunteers, where the chewable tablet and oral suspension were compared to the 400 mg tablet. The chewable tablet and oral suspension demonstrated higher oral bioavailability, thus higher AUC, compared to the 400 mg tablet. In the same study, the oral suspension resulted in higher oral bioavailability compared to the chewable tablet. These observations resulted in proposed pediatric doses

targeting 6 mg/kg/dose for the chewable tablets and oral suspension. As displayed in Table 9, the doses recommended for HIV-infected infants, children and adolescents 4 weeks to 18 years of age [see Dosage and Administration (2.3)] resulted in a pharmacokinetic profile of raltegravir similar to that observed in adults receiving 400 mg twice daily.

Overall, dosing in pediatric patients achieved exposures (Ctrough) above 45 nM in the majority of subjects, but some differences in exposures between formulations were observed. Pediatric patients above 25 kg administered the chewable tablets had lower trough concentrations (113 nM) compared to pediatric patients above 25 kg administered the 400 mg tablet formulation (233 nM).

As a result, the 400 mg film-coated tablet is the recommended dose in patients weighing at least 25 kg; however, the chewable tablet offers an alternative regimen in patients weighing at least 25 kg who are unable to swallow the film-coated tablet [see Dosage and Administration (2.3)]. In addition, pediatric patients weighing 11 to 25 kg who were administered the chewable tablets had the lowest trough concentrations (82 nM) compared to all other pediatric subgroups.

Table 9: Raltegravir Steady State Pharmacokinetic Parameters in Pediatric Patients Following Administration of Recommended Doses

Body Weight	**Formulation**	**Dose**	**N***	**Geometric Mean (%CV†) AUC0-12hr (µM●hr)**	**Geometric Mean (%CV†) C12hr (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 2	13	18.6 (68%)	82 (123%)
3 to less than 20 kg	Oral suspension	Weight based dosing, see Table 2	19	24.5 (43%)	113 (69%)
*Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose. †Geometric coefficient of variation.					

The pharmacokinetics of raltegravir in infants under 4 weeks of age has not been established.

Age

The effect of age (18 years and older) on the pharmacokinetics of raltegravir was evaluated in the composite analysis. No dosage adjustment is necessary.

Race

The effect of race on the pharmacokinetics of raltegravir in adults was evaluated in the composite analysis. No dosage adjustment is necessary.

Gender

A study of the pharmacokinetics of raltegravir was performed in healthy adult males and females. Additionally, the effect of gender was evaluated in a composite analysis of pharmacokinetic data from 103 healthy subjects and 28 HIV-1 infected subjects receiving raltegravir monotherapy with fasted administration. No dosage adjustment is necessary.

Hepatic Impairment

Raltegravir is eliminated primarily by glucuronidation in the liver. A study of the pharmacokinetics of raltegravir was performed in adult subjects with moderate hepatic impairment. Additionally, hepatic impairment was evaluated in the composite pharmacokinetic analysis. There were no clinically important pharmacokinetic differences

between subjects with moderate hepatic impairment and healthy subjects. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. 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. A study of the pharmacokinetics of raltegravir was performed in adult subjects with severe renal impairment. Additionally, renal impairment was evaluated in the composite pharmacokinetic analysis. There were no clinically important pharmacokinetic differences between subjects with severe renal impairment 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).

Drug Interactions

Table 10: 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 = 1.0**			
			n	**Cmax**	**AUC**	**Cmin**
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		23	0.49 (0.33, 0.71)	0.49 (0.35, 0.67)	0.44 (0.34, 0.55)
	20 mL single dose given 2 hours after raltegravir		23	0.78 (0.53, 1.13)	0.70 (0.50, 0.96)	0.43 (0.34, 0.55)
	20 mL single dose given 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)
atazanavir	400 mg daily	100 mg single dose	10	1.53 (1.11,	1.72 (1.47,	1.95 (1.30,

				2.12)	2.02)	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 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)
efavirenz	600 mg daily	400 mg single dose	9	0.64 (0.41, 0.98)	0.64 (0.52, 0.80	0.79 (0.49, 1.28)
etravirine	200 mg twice daily	400 mg twice daily	19	0.89 (0.68, 1.15)	0.90 (0.68, 1.18)	0.66 (0.34, 1.26)
omeprazole	20 mg daily	400 mg single dose	14 (10 for AUC)	4.15 (2.82, 6.10)	3.12 (2.13, 4.56)	1.46 (1.10, 1.93)
rifampin	600 mg daily	400 mg single dose	9	0.62 (0.37, 1.04)	0.60 (0.39, 0.91)	0.39 (0.30, 0.51)
rifampin	600 mg daily	400 mg twice daily when administered	14	1.62 (1.12,	1.27 (0.94,	0.47 (0.36,

		alone; 800 mg twice daily when administered with rifampin		2.33)	1.71)	0.61)
ritonavir	100 mg twice daily	400 mg single dose	10	0.76 (0.55, 1.04)	0.84 (0.70, 1.01)	0.99 (0.70, 1.40)
tenofovir	300 mg daily	400 mg twice daily	9	1.64 (1.16, 2.32	1.49 (1.15, 1.94)	1.03 (0.73, 1.45
tipranavir/ritonavir	500 mg/200 mg twice daily	400 mg twice daily	15)14 for C_{min})	0.82 (0.46, 1.46)	0.76 (0.49, 1.19)	0.45 (0.31, 0.66)

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 phosphoryltransferases including DNA polymerases α, β, and γ.

Antiviral Activity in Cell Culture

Raltegravir at concentrations of 31 ± 20 nM resulted in 95% inhibition (EC95) 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 EC95 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 EC50 values ranging from 5 to 12 nM. Raltegravir also inhibited replication of an HIV-2 isolate when tested in CEMx174 cells (EC95 value = 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 nonnucleoside 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 and F121C are occasionally seen in the absence of substitutions at Y143, Q148, or N155 in raltegravir-treatment failure subjects. 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 12 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.

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.

5.3 Preclinical safety data

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 μM●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 μM●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.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose (Avicel PH 102), Lactose Monohydrate (Supertab 11 SD), Sodium stearyl fumarate, Magnesium stearate, Polyethylene oxide (Polyox WSR 301), Purified Water IHS/USP/Ph.Eur, Opadry II Pink 85F84416 IHS

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

<2 Years>

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Container pack: 60’s HDPE container

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorisation Holder and Manufacturing Site Addresses

7.1 Name and Address of Manufacturer

Name:	Hetero Labs Limited (Unit-III)
Address:	22-110, Industrial Development Area (IDA), Jeedimetla Hyderabad-500 055 Telangana.
Country:	INDIA
Phone:	91-40-23096171/72/73/74
Fax:	91-40-23095105, 23097756, 23140376
E-Mail	: contact@heterodrugs.com

7.2 Name and Address of Principal

Name	: Hetero Labs Limited
Business Address	: 7-2-A2, Hetero Corporate, Industrial Estates, Sanath Nagar, Hyderabad-500 018 Telangana.
Country	: INDIA
Telephone	: 0091-040-23704923/24

8. Registration Number

Not Applicable

9. Category for Distribution

Prescription only medicine – List I

10. Date of Publication of This Package Insert
