ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 400 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect
Each tablet contains 26.06 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink, oval tablet, marked with "227" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ISENTRESS is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection (see sections 4.2, 4.4, 5.1 and 5.2).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

ISENTRESS should be used in combination with other active anti-retroviral therapies (ARTs) (see sections 4.4 and 5.1).

Adults
The recommended dosage is 400 mg (one tablet) twice daily.

Paediatric population
The recommended dosage for paediatric patients of at least 25 kg body weight is 400 mg (one tablet) twice daily. If unable to swallow a tablet, consider the chewable tablet.

Additional formulations and strengths available:
ISENTRESS is also available in a chewable tablet formulation and in granules for oral suspension formulation Refer to the chewable tablet and granules for oral suspension SmPCs for additional dosing information.
The safety and efficacy of raltegravir in preterm (<37 weeks of gestation) and low birth weight (<2,000 g) newborns have not been established. No data are available in this population and no dosing recommendations can be made.

The maximum dose of the chewable tablet is 300 mg twice daily. Because the formulations have different pharmacokinetic profiles neither the chewable tablets nor the granules for oral suspension should be substituted for the 400 mg tablet or 600 mg tablet (see section 5.2). The chewable tablets

and the granules for oral suspension have not been studied in HIV-infected adolescents (12 to 18 years) or adults.

ISENTRESS is also available for adults and paediatric patients (weighing at least 40 kg), as a 600 mg tablet to be administered as 1,200 mg once daily (two 600 mg tablets) for treatment-naïve patients or patients who are virologically suppressed on an initial regimen of ISENTRESS 400 mg twice daily. The 400 mg tablet should not be used to administer the 1,200 mg once daily regimen. Refer to the 600 mg Summary of Product Characteristics for additional dosing information.

Elderly
There is limited information regarding the use of raltegravir in the elderly (see section 5.2). Therefore, ISENTRESS should be used with caution in this population.

Renal impairment
No dosage adjustment is required for patients with renal impairment (see section 5.2).

Hepatic impairment
No dosage adjustment is required for patients with mild to moderate hepatic impairment. The safety and efficacy of raltegravir have not been established in patients with severe underlying liver disorders. Therefore, ISENTRESS should be used with caution in patients with severe hepatic impairment (see sections 4.4 and 5.2).

Method of administration

Oral use.
ISENTRESS 400 mg tablets can be administered with or without food.
The tablets should not be chewed, crushed or split due to anticipated changes in the pharmacokinetic profile.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General

Patients should be advised that current anti-retroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV to others through blood contact.

Raltegravir has a relatively low genetic barrier to resistance. Therefore, whenever possible, raltegravir should be administered with two other active ARTs to minimise the potential for virological failure and the development of resistance (see section 5.1).

In treatment-naïve patients, the clinical study data on use of raltegravir are limited to use in combination with two nucleotide reverse transcriptase inhibitors (NRTIs) (emtricitabine and tenofovir disoproxil fumarate).

Depression

Depression, including suicidal ideation and behaviours, has been reported, particularly in patients with a pre-existing history of depression or psychiatric illness. Caution should be used in patients with a pre-existing history of depression or psychiatric illness.

Hepatic impairment

The safety and efficacy of raltegravir have not been established in patients with severe underlying liver disorders. Therefore, raltegravir should be used with caution in patients with severe hepatic impairment (see sections 4.2 and 5.2).

Patients with pre-existing liver dysfunction including chronic hepatitis have an increased frequency of liver function abnormalities during combination anti-retroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment should be considered.

Patients with chronic hepatitis B or C and treated with combination anti-retroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Osteonecrosis

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

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination anti-retroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and pneumonia caused by *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*). Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation: however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Antacids

Co-administration of raltegravir with aluminium and magnesium antacids resulted in reduced raltegravir plasma levels. Co-administration of raltegravir with aluminium and/or magnesium antacids is not recommended (see section 4.5).

Rifampicin

Caution should be used when co-administering raltegravir with strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 (e.g., rifampicin). Rifampicin reduces plasma levels of raltegravir; the impact on the efficacy of raltegravir is unknown. However, if co-administration with rifampicin is unavoidable, a doubling of the dose of raltegravir can be considered in adults. There are no data to guide co-administration of raltegravir with rifampicin in patients below 18 years of age (see section 4.5).

Myopathy and rhabdomyolysis

Myopathy and rhabdomyolysis have been reported. Use with caution in patients who have had myopathy or rhabdomyolysis in the past or have any predisposing issues including other medicinal products associated with these conditions (see section 4.8).

Severe skin and hypersensitivity reactions

Severe, potentially life-threatening, and fatal skin reactions have been reported in patients taking raltegravir, in most cases concomitantly with other medicinal products associated with these reactions. These include cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. Hypersensitivity reactions have also been reported and were characterised by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure. Discontinue 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 oedema, 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.

Rash

Rash occurred more commonly in treatment-experienced patients receiving regimens containing raltegravir and darunavir compared to patients receiving raltegravir without darunavir or darunavir without raltegravir (see section 4.8).

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies indicate that raltegravir is not a substrate of cytochrome P450 (CYP) enzymes, does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A, does not inhibit UDP glucuronosyltransferases (UGTs) 1A1 and 2B7, does not induce CYP3A4 and does not inhibit P-glycoprotein-mediated transport. Based on these data, raltegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of these enzymes or P-glycoprotein.

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

Considerable inter- and intra-individual variability was observed in the pharmacokinetics of raltegravir.

Effect of raltegravir on the pharmacokinetics of other medicinal products

In interaction studies, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of etravirine, maraviroc, tenofovir disoproxil fumarate, hormonal contraceptives, methadone, midazolam or boceprevir.

In some studies, co-administration of raltegravir with darunavir resulted in a modest decrease in darunavir plasma concentrations; the mechanism for this effect is unknown. However, the effect of raltegravir on darunavir plasma concentrations does not appear to be clinically meaningful.

Effect of other medicinal products on the pharmacokinetics of raltegravir

Given that raltegravir is metabolised primarily via UGT1A1, caution should be used when co-administering raltegravir with strong inducers of UGT1A1 (e.g., rifampicin). Rifampicin reduces plasma levels of raltegravir; the impact on the efficacy of raltegravir is unknown. However, if co-administration with rifampicin is unavoidable, a doubling of the dose of raltegravir can be considered in adults. There are no data to guide co-administration of raltegravir with rifampicin in patients below 18 years of age (see section 4.4). The impact of other strong inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown. Less potent inducers (e.g., efavirenz, nevirapine, etravirine, rifabutin, glucocorticoids, St. John's wort, pioglitazone) may be used with the recommended dose of raltegravir.

Co-administration of raltegravir with medicinal products that are known to be potent UGT1A1 inhibitors (e.g., atazanavir) may increase plasma levels of raltegravir. Less potent UGT1A1 inhibitors (e.g., indinavir, saquinavir) may also increase plasma levels of raltegravir, but to a lesser extent compared with atazanavir. In addition, tenofovir disoproxil fumarate may increase plasma levels of raltegravir, however, the mechanism for this effect is unknown (see Table 1). From the clinical trials, a large proportion of patients used atazanavir and / or tenofovir disoproxil fumarate, both agents that result in increases in raltegravir plasma levels, in the optimised background regimens. The safety profile observed in patients who used atazanavir and / or tenofovir disoproxil fumarate was generally similar to the safety profile of patients who did not use these agents. Therefore, no dose adjustment is required.

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

Co-administration of raltegravir with other agents that increase gastric pH (e.g., omeprazole and famotidine) may increase the rate of raltegravir absorption and result in increased plasma levels of raltegravir (see Table 1). Safety profiles in the subgroup of patients in Phase III trials taking proton pump inhibitors or H2 antagonists were comparable with those who were not taking these antacids. Therefore, no dose adjustment is required with use of proton pump inhibitors or H2 antagonists.

All interaction studies were performed in adults.

Table 1
Pharmacokinetic Interaction Data

Medicinal products by therapeutic area	**Interaction** (mechanism, if known)	**Recommendations concerning co-administration**
ANTI-RETROVIRAL		
Protease inhibitors (PI)		
atazanavir /ritonavir (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 41 % raltegravir C_{12hr} ↑ 77 % raltegravir C_{max} ↑ 24 % (UGT1A1 inhibition)	No dose adjustment required for raltegravir.

Medicinal products by therapeutic area	**Interaction** (mechanism, if known)	**Recommendations concerning co-administration**
tipranavir /ritonavir (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 24 % raltegravir C_{12hr} ↓ 55 % raltegravir C_{max} ↓ 18 % (UGT1A1 induction)	No dose adjustment required for raltegravir.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
efavirenz (raltegravir 400 mg Single Dose)	raltegravir AUC ↓ 36 % raltegravir C_{12hr} ↓ 21 % raltegravir C_{max} ↓ 36 % (UGT1A1 induction)	No dose adjustment required for raltegravir.
etravirine (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 10 % raltegravir C_{12hr} ↓ 34 % raltegravir C_{max} ↓ 11 % (UGT1A1 induction) etravirine AUC ↑ 10 % etravirine C_{12hr} ↑ 17 % etravirine C_{max} ↑ 4 %	No dose adjustment required for raltegravir or etravirine.
Nucleoside/tide reverse transcriptase inhibitors		
tenofovir disoproxil fumarate (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 49 % raltegravir C_{12hr} ↑ 3 % raltegravir C_{max} ↑ 64 % (mechanism of interaction unknown) tenofovir AUC ↓ 10 % tenofovir C_{24hr} ↓ 13 % tenofovir C_{max} ↓ 23 %	No dose adjustment required for raltegravir or tenofovir disoproxil fumarate.
CCR5 inhibitors		
maraviroc (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 37 % raltegravir C_{12hr} ↓ 28 % raltegravir C_{max} ↓ 33 % (mechanism of interaction unknown) maraviroc AUC ↓ 14 % maraviroc C_{12hr} ↓ 10 % maraviroc C_{max} ↓ 21 %	No dose adjustment required for raltegravir or maraviroc.
HCV ANTIVIRALS		
NS3/4A protease inhibitors (PI)		
boceprevir (raltegravir 400 mg Single Dose)	raltegravir AUC ↑ 4 % raltegravir C_{12hr} ↓ 25 % raltegravir C_{max} ↑ 11 % (mechanism of interaction unknown)	No dose adjustment required for raltegravir or boceprevir.

Medicinal products by therapeutic area	**Interaction** (mechanism, if known)	**Recommendations concerning co-administration**
ANTIMICROBIALS		
Antimycobacterial		
rifampicin (raltegravir 400 mg Single Dose)	raltegravir AUC ↓ 40 % raltegravir C_{12hr} ↓ 61 % raltegravir C_{max} ↓ 38 % (UGT1A1 induction)	Rifampicin reduces plasma levels of raltegravir. If co-administration with rifampicin is unavoidable, a doubling of the dose of raltegravir can be considered (see section 4.4).
SEDATIVE		
midazolam (raltegravir 400 mg Twice Daily)	midazolam AUC ↓ 8 % midazolam C_{max} ↑ 3 %	No dosage adjustment required for raltegravir or midazolam. These results indicate that raltegravir is not an inducer or inhibitor of CYP3A4, and raltegravir is thus not anticipated to affect the pharmacokinetics of medicinal products which are CYP3A4 substrates.
METAL CATION ANTACIDS		
aluminium and magnesium hydroxide antacid (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 49 % raltegravir $C_{12\ hr}$ ↓ 63 % raltegravir C_{max} ↓ 44 % <u>2 hours before raltegravir</u> raltegravir AUC ↓ 51 % raltegravir $C_{12\ hr}$ ↓ 56 % raltegravir C_{max} ↓ 51 % <u>2 hours after raltegravir</u> raltegravir AUC ↓ 30 % raltegravir $C_{12\ hr}$ ↓ 57 % raltegravir C_{max} ↓ 24 % <u>6 hours before raltegravir</u> raltegravir AUC ↓ 13 % raltegravir $C_{12\ hr}$ ↓ 50 % raltegravir C_{max} ↓ 10 % <u>6 hours after raltegravir</u> raltegravir AUC ↓ 11 % raltegravir $C_{12\ hr}$ ↓ 49 % raltegravir C_{max} ↓ 10 % (chelation of metal cations)	Aluminium and magnesium containing antacids reduce raltegravir plasma levels. Co-administration of raltegravir with aluminium and/or magnesium containing antacids is not recommended.
calcium carbonate antacid (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 55 % raltegravir $C_{12\ hr}$ ↓ 32 % raltegravir C_{max} ↓ 52 % (chelation of metal cations)	No dose adjustment required for raltegravir.

Medicinal products by therapeutic area	Interaction (mechanism, if known)	Recommendations concerning co-administration
Other METAL CATION		
Iron salts	Expected: Raltegravir AUC ↓ (chelation of metal cations)	Given simultaneously iron salts are expected to reduce raltegravir plasma levels; taking iron salts at least two hours from the administration of raltegravir may allow to limit this effect.
H2 BLOCKERS AND PROTON PUMP INHIBITORS		
omeprazole (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 37 % raltegravir $C_{12\ hr}$ ↑ 24 % raltegravir C_{max} ↑ 51 % (increased solubility)	No dose adjustment required for raltegravir.
famotidine (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 44 % raltegravir $C_{12\ hr}$ ↑ 6 % raltegravir C_{max} ↑ 60 % (increased solubility)	No dose adjustment required for raltegravir.
HORMONAL CONTRACEPTIVES		
Ethinyl Estradiol **Norelgestromin** (raltegravir 400 mg Twice Daily)	Ethinyl Estradiol AUC ↓ 2 % Ethinyl Estradiol C_{max} ↑ 6 % Norelgestromin AUC ↑ 14 % Norelgestromin C_{max} ↑ 29 %	No dosage adjustment required for raltegravir or hormonal contraceptives (estrogen- and/or progesterone-based).
OPIOID ANALGESICS		
methadone (raltegravir 400 mg Twice Daily)	methadone AUC ↔ methadone C_{max} ↔	No dose adjustment required for raltegravir or methadone.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women with exposure to raltegravir 400 mg twice daily during the first trimester (more than 1,000 prospective pregnancy outcomes) indicates no malformative toxicity. Animal studies have shown reproductive toxicity (see section 5.3).
A moderate amount of data on pregnant women with exposure to raltegravir 400 mg twice daily during the second and/or third trimester (between 300-1,000 prospective pregnancy outcomes) indicates no increased risk of feto/neonatal toxicity.
Raltegravir 400 mg twice daily can be used during pregnancy if clinically needed.

Anti-retroviral Pregnancy Registry
To monitor maternal-foetal outcomes in patients inadvertently administered raltegravir while pregnant, an Anti-retroviral Pregnancy Registry has been established. Physicians are encouraged to register patients in this registry.

As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account in order to characterise the safety for the foetus.

Breast-feeding

Raltegravir/metabolites are excreted in human milk to such an extent that effects on the breastfed newborns/infants are likely. Available pharmacodynamics/toxicological data in animals have shown excretion of raltegravir/metabolites in milk (for details see section 5.3).

A risk to the newborns/infants cannot be excluded.

It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

Fertility

No effect on fertility was seen in male and female rats at doses up to 600 mg/kg/day which resulted in 3-fold exposure above the exposure at the recommended human dose.

4.7 Effects on ability to drive and use machines

Dizziness has been reported in some patients during treatment with regimens containing raltegravir. Dizziness may influence some patients' ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

In randomised clinical trials raltegravir 400 mg twice daily was administered in combination with fixed or optimised background treatment regimens to treatment-naïve (N=547) and treatment-experienced (N=462) adults for up to 96 weeks. A further 531 treatment-naïve adults have received raltegravir 1,200 mg once daily with emtricitabine and tenofovir disoproxil fumarate for up to 96 weeks. See section 5.1.

The most frequently reported adverse reactions during treatment were headache, nausea and abdominal pain. The most frequently reported serious adverse reaction was immune reconstitution syndrome and rash. The rates of discontinuation of raltegravir due to adverse reactions were 5% or less in clinical trials.

Rhabdomyolysis was an uncommonly reported serious adverse reaction in post-marketing use of raltegravir 400 mg twice daily.

Tabulated summary of adverse reactions

Adverse reactions considered by investigators to be causally related to raltegravir (alone or in combination with other ART), as well as adverse reactions established in post-marketing experience, are listed below by System Organ Class. Frequencies are defined as common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reactions Raltegravir (alone or in combination with other ART)
Infections and infestations	Uncommon	genital herpes, folliculitis, gastroenteritis, herpes simplex, herpes virus infection, herpes zoster, influenza, lymph node abscess, molluscum contagiosum, nasopharyngitis, upper respiratory tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Uncommon	skin papilloma

System Organ Class	Frequency	Adverse reactions Raltegravir (alone or in combination with other ART)
Blood and lymphatic system disorders	Uncommon	anaemia, iron deficiency anaemia, lymph node pain, lymphadenopathy, neutropenia, thrombocytopenia
Immune system disorders	Uncommon	immune reconstitution syndrome, drug hypersensitivity, hypersensitivity
Metabolism and nutrition disorders	Common Uncommon	decreased appetite cachexia, diabetes mellitus, dyslipidaemia, hypercholesterolaemia, hyperglycaemia, hyperlipidaemia, hyperphagia, increased appetite, polydipsia, body fat disorder
Psychiatric disorders	Common Uncommon	abnormal dreams, insomnia, nightmare, abnormal behaviour, depression mental disorder, suicide attempt, anxiety, confusional state, depressed mood, major depression, middle insomnia, mood altered, panic attack, sleep disorder, suicidal ideation, suicidal behaviour (particularly in patients with a pre-existing history of psychiatric illness)
Nervous system disorders	Common Uncommon	dizziness, headache, psychomotor hyperactivity amnesia, carpal tunnel syndrome, cognitive disorder, disturbance in attention, dizziness postural, dysgeusia, hypersomnia, hypoaesthesia, lethargy, memory impairment, migraine, neuropathy peripheral, paraesthesia, somnolence, tension headache, tremor, poor quality sleep
Eye disorders	Uncommon	visual impairment
Ear and labyrinth disorders	Common Uncommon	vertigo tinnitus
Cardiac disorders	Uncommon	palpitations, sinus bradycardia, ventricular extrasystoles
Vascular disorders	Uncommon	hot flush, hypertension
Respiratory, thoracic and mediastinal disorders	Uncommon	dysphonia, epistaxis, nasal congestion
Gastrointestinal disorders	Common Uncommon	abdominal distention, abdominal pain, diarrhoea, flatulence, nausea, vomiting, dyspepsia gastritis, abdominal discomfort, abdominal pain upper, abdominal tenderness, anorectal discomfort, constipation, dry mouth, epigastric discomfort, erosive duodenitis, eructation, gastroesophageal reflux disease, gingivitis, glossitis, odynophagia, pancreatitis acute, peptic ulcer, rectal haemorrhage

System Organ Class	Frequency	Adverse reactions Raltegravir (alone or in combination with other ART)
Hepato-biliary disorders	Uncommon	hepatitis, hepatic steatosis, hepatitis alcoholic, hepatic failure
Skin and subcutaneous tissue disorders	Common Uncommon	rash acne, alopecia, dermatitis acneiforme, dry skin, erythema, facial wasting, hyperhidrosis, lipoatrophy, lipodystrophy acquired, lipohypertrophy, night sweats, prurigo, pruritus, pruritus generalised, rash macular, rash maculo-papular, rash pruritic, skin lesion, urticaria, xeroderma, Stevens Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Uncommon	arthralgia, arthritis, back pain, flank pain, musculoskeletal pain, myalgia, neck pain, osteopenia, pain in extremity, tendonitis, rhabdomyolysis
Renal and urinary disorders	Uncommon	renal failure, nephritis, nephrolithiasis, nocturia, renal cyst, renal impairment, tubulointerstitial nephritis
Reproductive system and breast disorders	Uncommon	erectile dysfunction, gynaecomastia, menopausal symptoms
General disorders and administration site conditions	Common Uncommon	asthenia, fatigue, pyrexia chest discomfort, chills, face oedema, fat tissue increased, feeling jittery, malaise, submandibular mass, oedema peripheral, pain
Investigations	Common Uncommon	alanine aminotransferase increased, atypical lymphocytes, aspartate aminotransferase increased, blood triglycerides increased, lipase increased, blood pancreatic amylase increased absolute neutrophil count decreased, alkaline phosphatase increased, blood albumin decreased, blood amylase increased, blood bilirubin increased, blood cholesterol increased, blood creatinine increased, blood glucose increased, blood urea nitrogen increased, creatine phosphokinase increased, fasting blood glucose increased, glucose urine present, high density lipoprotein increased, international normalised ratio increased, low density lipoprotein increased, platelet count decreased, red blood cells urine positive, waist circumference increased, weight increased, white blood cell count decreased
Injury, poisoning and procedural complications	Uncommon	accidental overdose

Description of selected adverse reactions

Cancers were reported in treatment-experienced and treatment-naïve patients who initiated raltegravir in conjunction with other antiretroviral agents. The types and rates of specific cancers were those expected in a highly immunodeficient population. The risk of developing cancer in these studies was similar in the groups receiving raltegravir and in the groups receiving comparators.

Grade 2-4 creatine kinase laboratory abnormalities were observed in patients treated with raltegravir. Myopathy and rhabdomyolysis have been reported. Use with caution in patients who have had myopathy or rhabdomyolysis in the past or have any predisposing issues including other medicinal products associated with these conditions (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

For each of the following clinical adverse reactions there was at least one serious occurrence: genital herpes, anaemia, immune reconstitution syndrome, depression, mental disorder, suicide attempt, gastritis, hepatitis, renal failure, accidental overdose.

In clinical studies of treatment-experienced patients, rash, irrespective of causality, was more commonly observed with regimens containing raltegravir and darunavir compared to those containing raltegravir without darunavir or darunavir without raltegravir. Rash considered by the investigator to be drug-related occurred at similar rates. The exposure-adjusted rates of rash (all causality) were 10.9, 4.2, and 3.8 per 100 patient-years (PYR), respectively; and for drug-related rash were 2.4, 1.1, and 2.3 per 100 PYR, respectively. The rashes observed in clinical studies were mild to moderate in severity and did not result in discontinuation of therapy (see section 4.4).

Patients co-infected with hepatitis B and/or hepatitis C virus
In clinical trials, there were 79 patients co-infected with hepatitis B, 84 co-infected with hepatitis C, and 8 patients co-infected with hepatitis B and C who were treated with raltegravir in combination with other agents for HIV-1. In general, the safety profile of raltegravir in patients with hepatitis B and/or hepatitis C virus co-infection was similar to that in patients without hepatitis B and/or hepatitis C virus co-infection, although the rates of AST and ALT abnormalities were somewhat higher in the subgroup co-infected with hepatitis B and/or hepatitis C virus.

At 96-weeks, in treatment-experienced patients, 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 patients treated with raltegravir as compared to 11 %, 10 % and 9 % of all other patients treated with raltegravir. At 240-weeks, in treatment-naïve patients, 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 patients treated with raltegravir as compared to 13 %, 13 % and 5 % of all other patients treated with raltegravir.

Paediatric population

Children and adolescents 2 to 18 years of age
Raltegravir has been studied in 126 antiretroviral treatment-experienced HIV-1 infected children and adolescents 2 to 18 years of age, in combination with other antiretroviral agents in IMPAACT P1066 (see sections 5.1 and 5.2). Of the 126 patients, 96 received the recommended dose of raltegravir.

In these 96 children and adolescents, frequency, type and severity of drug related adverse reactions through Week 48 were comparable to those observed in adults.

One patient experienced drug related clinical adverse reactions of Grade 3 psychomotor hyperactivity, abnormal behaviour and insomnia; one patient experienced a Grade 2 serious drug related allergic rash.

One patient experienced drug related laboratory abnormalities, Grade 4 AST and Grade 3 ALT, which were considered serious.

Infants and toddlers 4 weeks to less than 2 years of age
Raltegravir has 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 sections 5.1 and 5.2).

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
In IMPAACT P1110 (see section 5.2) eligible infants were at least 37 weeks gestation and at least 2 kg in weight. Sixteen (16) neonates received 2 doses of ISENTRESS in first 2 weeks of life, and 26 neonates received 6 weeks of daily dosing; all were followed for 24 weeks. There were no drug related clinical adverse experiences and three drug-related laboratory adverse experiences (one a transient Grade 4 neutropenia in a subject receiving zidovudine containing 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).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No specific information is available on the treatment of overdose with raltegravir.

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. It should be taken into account that raltegravir is presented for clinical use as the potassium salt. The extent to which raltegravir may be dialysable is unknown.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, integrase inhibitors, ATC code: J05AJ01.

Mechanism of action

Raltegravir is an integrase strand transfer inhibitor active against the Human Immunodeficiency Virus (HIV-1). Raltegravir inhibits the catalytic activity of integrase, an HIV-encoded enzyme that is

required for viral replication. Inhibition of integrase prevents the covalent insertion, or integration, of the HIV genome into the host cell genome. HIV genomes that fail to integrate cannot direct the production of new infectious viral particles, so inhibiting integration prevents propagation of the viral infection.

Antiviral activity *in vitro*

Raltegravir at concentrations of 31 ± 20 nM resulted in 95 % inhibition (IC_{95}) of HIV-1 replication (relative to an untreated virus-infected culture) in human T-lymphoid cell cultures infected with the cell-line adapted HIV-1 variant H9IIIB. In addition, raltegravir inhibited viral replication in cultures of mitogen-activated human peripheral blood mononuclear cells infected with diverse, primary clinical isolates of HIV-1, including isolates from 5 non-B subtypes, and isolates resistant to reverse transcriptase inhibitors and protease inhibitors. In a single-cycle infection assay, raltegravir inhibited infection of 23 HIV isolates representing 5 non-B subtypes and 5 circulating recombinant forms with IC_{50} values ranging from 5 to 12 nM.

Resistance

Most viruses isolated from patients failing raltegravir had high-level raltegravir resistance resulting from the appearance of two or more mutations in integrase. Most had a signature mutation at amino acid 155 (N155 changed to H), amino acid 148 (Q148 changed to H, K, or R), or amino acid 143 (Y143 changed to H, C, or R), along with one or more additional integrase mutations (e.g., L74M, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, S230R). The signature mutations decrease viral susceptibility to raltegravir and addition of other mutations results in a further decrease in raltegravir susceptibility. Factors that reduced the likelihood of developing resistance included lower baseline viral load and use of other active anti-retroviral agents. Mutations conferring resistance to raltegravir generally also confer resistance to the integrase strand transfer inhibitor elvitegravir. Mutations at amino acid 143 confer greater resistance to raltegravir than to elvitegravir, and the E92Q mutation confers greater resistance to elvitegravir than to raltegravir. Viruses harbouring a mutation at amino acid 148, along with one or more other raltegravir resistance mutations, may also have clinically significant resistance to dolutegravir.

Clinical experience

The evidence of efficacy of raltegravir was based on the analyses of 96-week data from two randomised, double-blind, placebo-controlled trials (BENCHMRK 1 and BENCHMRK 2, Protocols 018 and 019) in antiretroviral treatment-experienced HIV-1 infected adult patients and the analysis of 240-week data from randomised, double-blind, active-control trial (STARTMRK, Protocol 021) in antiretroviral treatment-naïve HIV-1 infected adult patients.

Efficacy

Treatment-experienced adult patients
BENCHMRK 1 and BENCHMRK 2 (multi-centre, randomised, double-blind, placebo-controlled trials) evaluated the safety and anti-retroviral activity of raltegravir 400 mg twice daily vs. placebo in a combination with optimised background therapy (OBT), in HIV-infected patients, 16 years or older, with documented resistance to at least 1 drug in each of 3 classes (NRTIs, NNRTIs, PIs) of anti-retroviral therapies. Prior to randomisation, OBT were selected by the investigator based on the patient's prior treatment history, as well as baseline genotypic and phenotypic viral resistance testing.

Patient demographics (gender, age and race) and baseline characteristics were comparable between the groups receiving raltegravir 400 mg twice daily and placebo. Patients had prior exposure to a median of 12 anti-retrovirals for a median of 10 years. A median of 4 ARTs was used in OBT.

Results 48 week and 96 week analyses
Durable outcomes (Week 48 and Week 96) for patients on the recommended dose raltegravir 400 mg twice daily from the pooled studies BENCHMRK 1 and BENCHMRK 2 are shown in Table 2.

Table 2
Efficacy Outcome at Weeks 48 and 96

BENCHMRK 1 and 2 Pooled	48 Weeks		96 Weeks	
Parameter	**Raltegravir 400 mg twice daily + OBT (N = 462)**	**Placebo + OBT (N = 237)**	**Raltegravir 400 mg twice daily + OBT (N = 462)**	**Placebo + OBT (N = 237)**
Percent HIV-RNA < 400 copies/mL (95% CI)				
All patients†	72 (68, 76)	37 (31, 44)	62 (57, 66)	28 (23, 34)
Baseline Characteristic‡				
HIV-RNA > 100,000 copies/mL	62 (53, 69)	17 (9, 27)	53 (45, 61)	15 (8, 25)
≤ 100,000 copies/mL	82 (77, 86)	49 (41, 58)	74 (69, 79)	39 (31, 47)
CD4-count ≤ 50 cells/mm^3	61 (53, 69)	21 (13, 32)	51 (42, 60)	14 (7, 24)
> 50 and ≤ 200 cells/mm^3	80 (73, 85)	44 (33, 55)	70 (62, 77)	36 (25, 48)
> 200 cells/mm^3	83 (76, 89)	51 (39, 63)	78 (70, 85)	42 (30, 55)
Sensitivity score (GSS) §				
0	52 (42, 61)	8 (3, 17)	46 (36, 56)	5 (1, 13)
1	81 (75, 87)	40 (30, 51)	76 (69, 83)	31 (22, 42)
2 and above	84 (77, 89)	65 (52, 76)	71 (63, 78)	56 (43, 69)
Percent HIV-RNA < 50 copies/ml :(95% CI)				
All patients†	62 (57, 67)	33 (27, 39)	57 (52, 62)	26 (21, 32)
Baseline Characteristic‡				
HIV-RNA > 100,000 copies/mL	48 (40, 56)	16 (8, 26)	47 (39, 55)	13 (7, 23)
≤ 100,000 copies/mL	73 (68, 78)	43 (35, 52)	70 (64, 75)	36 (28, 45)
CD4-count ≤ 50 cells/mm^3	50 (41, 58)	20 (12, 31)	50 (41, 58)	13 (6, 22)
> 50 and ≤ 200 cells/mm^3	67 (59, 74)	39 (28, 50)	65 (57, 72)	32 (22, 44)
> 200 cells/mm^3	76 (68, 83)	44 (32, 56)	71 (62, 78)	41 (29, 53)
Sensitivity score (GSS) §				
0	45 (35, 54)	3 (0, 11)	41 (32, 51)	5 (1, 13)
1	67 (59, 74)	37 (27, 48)	72 (64, 79)	28 (19, 39)
2 and above	75 (68, 82)	59 (46, 71)	65 (56, 72)	53 (40, 66)
Mean CD4 Cell Change (95 % CI), cells/mm^3				
All patients‡	109 (98, 121)	45 (32, 57)	123 (110, 137)	49 (35, 63)
Baseline Characteristic‡				
HIV-RNA > 100,000 copies/mL	126 (107, 144)	36 (17, 55)	140 (115, 165)	40 (16, 65)
≤ 100,000 copies/mL	100 (86, 115)	49 (33, 65)	114 (98, 131)	53 (36, 70)
CD4-count ≤ 50 cells/mm^3	121 (100, 142)	33 (18, 48)	130 (104, 156)	42 (17, 67)
> 50 and ≤ 200 cells/mm^3	104 (88, 119)	47 (28, 66)	123 (103, 144)	56 (34, 79)
> 200 cells/mm^3	104 (80, 129)	54 (24, 84)	117 (90, 143)	48 (23, 73)
Sensitivity score (GSS) §				
0	81 (55, 106)	11 (4, 26)	97 (70, 124)	15 (-0, 31)
1	113 (96, 130)	44 (24, 63)	132 (111, 154)	45 (24, 66)
2 and above	125 (105, 144)	76 (48, 103)	134 (108, 159)	90 (57, 123)

† Non-completer is failure imputation: patients who discontinued prematurely are imputed as failure thereafter. Percent of patients with response and associated 95 % confidence interval (CI) are reported.

‡ For analysis by prognostic factors, virologic failures were carried forward for percent < 400 and 50 copies/mL. For mean CD4 changes, baseline-carry-forward was used for virologic failures.

§ The Genotypic Sensitivity Score (GSS) was defined as the total oral ARTs in the optimised background therapy (OBT) to which a patient's viral isolate showed genotypic sensitivity based upon genotypic resistance test. Enfuvirtide use in OBT in enfuvirtide-naïve patients was counted as one active drug in OBT. Similarly, darunavir use in OBT in darunavir-naïve patients was counted as one active drug in OBT.

Raltegravir achieved virologic responses (using Not Completer=Failure approach) of HIV RNA < 50 copies/mL in 61.7 % of patients at Week 16, in 62.1 % at Week 48 and in 57.0 % at Week 96. Some patients experienced viral rebound between Week 16 and Week 96. Factors associated with failure include high baseline viral load and OBT that did not include at least one potent active agent.

Switch to raltegravir
The SWITCHMRK 1 & 2 (Protocols 032 & 033) studies evaluated HIV-infected patients receiving suppressive (screening HIV RNA < 50 copies/mL; stable regimen > 3 months) therapy with lopinavir 200 mg (+) ritonavir 50 mg 2 tablets twice daily plus at least 2 nucleoside reverse transcriptase inhibitors and randomised them 1:1 to continue lopinavir (+) ritonavir 2 tablets twice daily (n=174 and n=178, respectively) or replace lopinavir (+) ritonavir with raltegravir 400 mg twice daily (n=174 and n=176, respectively). Patients with a prior history of virological failure were not excluded and the number of previous antiretroviral therapies was not limited.

These studies were terminated after the primary efficacy analysis at Week 24 because they failed to demonstrate non-inferiority of raltegravir versus lopinavir (+) ritonavir. In both studies at Week 24, suppression of HIV RNA to less than 50 copies/mL was maintained in 84.4 % of the raltegravir group versus 90.6 % of the lopinavir (+) ritonavir group, (Non-completers = Failure). See section 4.4 regarding the need to administer raltegravir with two other active agents.

Treatment-naïve adult patients
STARTMRK (multi-centre, randomised, double-blind, active-control trial) evaluated the safety and anti-retroviral activity of raltegravir 400 mg twice daily vs. efavirenz 600 mg at bedtime, in a combination with emtricitabine (+) tenofovir disoproxil fumarate, in treatment-naïve HIV-infected patients with HIV RNA > 5,000 copies/mL. Randomisation was stratified by screening HIV RNA level (≤ 50,000 copies/mL; and > 50,000 copies/mL) and by hepatitis B or C status (positive or negative).

Patient demographics (gender, age and race) and baseline characteristics were comparable between the group receiving raltegravir 400 mg twice daily and the group receiving efavirenz 600 mg at bedtime.

Results 48-week and 240-week analyses
With respect to the primary efficacy endpoint, the proportion of patients achieving HIV RNA < 50 copies/mL at Week 48 was 241/280 (86.1 %) in the group receiving raltegravir and 230/281 (81.9 %) in the group receiving efavirenz. The treatment difference (raltegravir – efavirenz) was 4.2 % with an associated 95 % CI of (-1.9, 10.3) establishing that raltegravir is non-inferior to efavirenz (p-value for non-inferiority < 0.001). At Week 240, the treatment difference (raltegravir – efavirenz) was 9.5 % with an associated 95 % CI of (1.7, 17.3). Week 48 and Week 240 outcomes for patients on the recommended dose of raltegravir 400 mg twice daily from STARTMRK are shown in Table 3.

Table 3
Efficacy Outcome at Weeks 48 and 240

STARTMRK Study	48 Weeks		240 Weeks	
Parameter	**Raltegravir 400 mg twice daily (N = 281)**	**Efavirenz 600 mg at bedtime (N = 282)**	**Raltegravir 400 mg twice daily (N = 281)**	**Efavirenz 600 mg at bedtime (N = 282)**
Percent HIV-RNA < 50 copies/mL (95 % CI)				
All patients[†]	86 (81, 90)	82 (77, 86)	71 (65, 76)	61 (55, 67)
Baseline Characteristic[‡]				
HIV-RNA > 100,000 copies/mL	91 (85, 95)	89 (83, 94)	70 (62, 77)	65 (56, 72)
≤ 100,000 copies/mL	93 (86, 97)	89 (82, 94)	72 (64, 80)	58 (49, 66)
CD4-count ≤ 50 cells/mm^3	84 (64, 95)	86 (67, 96)	58 (37, 77)	77 (58, 90)
> 50 and ≤ 200 cells/mm^3	89 (81, 95)	86 (77, 92)	67 (57, 76)	60 (50, 69)
> 200 cells/mm^3	94 (89, 98)	92 (87, 96)	76 (68, 82)	60 (51, 68)
Viral Subtype Clade B	90 (85, 94)	89 (83, 93)	71 (65, 77)	59 (52, 65)
Non-Clade B	96 (87, 100)	91 (78, 97)	68 (54, 79)	70 (54, 82)
Mean CD4 Cell Change (95 % CI), cells/mm^3				
All patients[‡]	189 (174, 204)	163 (148, 178)	374 (345, 403)	312 (284, 339)
Baseline Characteristic[‡]				
HIV-RNA > 100,000 copies/mL	196 (174, 219)	192 (169, 214)	392 (350, 435)	329 (293, 364)
≤ 100,000 copies/mL	180 (160, 200)	134 (115, 153)	350 (312, 388)	294 (251, 337)
CD4-count ≤ 50 cells/mm^3	170 (122, 218)	152 (123, 180)	304 (209, 399)	314 (242, 386)
> 50 and ≤ 200 cells/mm^3	193 (169, 217)	175 (151, 198)	413 (360, 465)	306 (264, 348)
> 200 cells/mm^3	190 (168, 212)	157 (134, 181)	358 (321, 395)	316 (272, 359)
Viral Subtype Clade B	187 (170, 204)	164 (147, 181)	380 (346, 414)	303 (272, 333)
Non-Clade B	189 (153, 225)	156 (121, 190)	332 (275, 388)	329 (260, 398)

[†] Non-completer is failure imputation: patients who discontinued prematurely are imputed as failure thereafter. Percent of patients with response and associated 95 % confidence interval (CI) are reported.
[‡] For analysis by prognostic factors, virologic failures were carried forward for percent < 50 and 400 copies/mL. For mean CD4 changes, baseline-carry-forward was used for virologic failures.
Notes: The analysis is based on all available data.
Raltegravir and efavirenz were administered with emtricitabine (+) tenofovir disoproxil fumarate.

Paediatric population

Children and adolescents 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 to18 years of age. Patients were stratified by age, enrolling adolescents first and then successively younger children. Patients received either the 400 mg tablet formulation (6 to 18 years of age) or the chewable tablet formulation (2 to less than 12 years of age). Raltegravir was administered with an optimised background regimen.

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

Table 4
Baseline Characteristics and Efficacy Outcomes at Weeks 24 and 48 from IMPAACT P1066 (2 to 18 years of age)

Parameter	Final dose population N=96	
Demographics		
Age (years), median [range]	13 [2 – 18]	
Male Gender	49 %	
Race		
Caucasian	34 %	
Black	59 %	
Baseline Characteristics		
Plasma HIV-1 RNA (log_{10} copies/mL), mean [range]	4.3 [2.7 - 6]	
CD4 cell count (cells/mm^3), median [range]	481 [0 – 2361]	
CD4 percent, median [range]	23.3 % [0 – 44]	
HIV-1 RNA >100,000 copies/mL	8 %	
CDC HIV category B or C	59 %	
Prior ART Use by Class		
NNRTI	78 %	
PI	83 %	
Response	**Week 24**	**Week 48**
Achieved ≥1 log_{10} HIV RNA drop from baseline or <400 copies/mL	72 %	79 %
Achieved HIV RNA <50 copies/ mL	54 %	57 %
Mean CD4 cell count (%) increase from baseline	119 cells/mm^3 (3.8 %)	156 cells/mm^3 (4.6 %)

Infants and toddlers 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 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 granules for oral suspension formulation without regard to food in combination with an optimised background regimen that included lopinavir plus ritonavir in two-thirds of patients.

Table 5
Baseline Characteristics and Efficacy Outcomes at Weeks 24 and 48 from IMPAACT P1066 (4 weeks to less than 2 years of age)

Parameter	N=26
Demographics	
Age (weeks), median [range]	28 [4 -100]
Male Gender	65 %
Race	
Caucasian	8 %
Black	85 %
Baseline Characteristics	
Plasma HIV-1 RNA (log_{10} copies/mL), mean [range]	5.7 [3.1 - 7]
CD4 cell count (cells/mm^3), median [range]	1,400 [131 -3,648]
CD4 percent, median [range]	18.6 % [3.3 – 39.3]
HIV-1 RNA >100,000 copies/mL	69 %
CDC HIV category B or C	23 %
Prior ART Use by Class	
NNRTI	73 %
NRTI	46%
PI	19 %

Parameter	N=26	
Response	**Week 24**	**Week 48**
Achieved ≥1 $\log_{10}$ HIV RNA drop from baseline or <400 copies/mL	91 %	85 %
Achieved HIV RNA <50 copies/mL	43 %	53 %
Mean CD4 cell count (%) increase from baseline	500 cells/mm^3 (7.5 %)	492 cells/mm^3 (7.8 %)
Virologic failure	**Week 24**	**Week 48**
Non-responder	0	0
Rebounder	0	4
Number with genotype available*	0	2

*One patient had a mutation at the 155 position.

5.2 Pharmacokinetic properties

Absorption

As demonstrated in healthy volunteers administered single oral doses of raltegravir in the fasted state, raltegravir is rapidly absorbed with a t_{max} of approximately 3 hours postdose. Raltegravir AUC and C_{max} increase dose proportionally over the dose range 100 mg to 1,600 mg. Raltegravir $C_{12\ hr}$ 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 1,600 mg. Dose proportionality has not been established in patients.

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

Raltegravir may be administered with or without food. Raltegravir was administered without regard to food in the pivotal safety and efficacy studies in HIV-infected patients. Administration of multiple doses of raltegravir following a moderate-fat meal did not affect raltegravir AUC to a clinically meaningful degree with an increase of 13 % relative to fasting. Raltegravir $C_{12\ hr}$ was 66 % higher and C_{max} was 5 % higher following a moderate-fat meal compared to fasting. Administration of raltegravir following a high-fat meal increased AUC and C_{max} by approximately 2-fold and increased $C_{12\ hr}$ by 4.1-fold. Administration of raltegravir following a low-fat meal decreased AUC and C_{max} by 46 % and 52 %, respectively; $C_{12\ hr}$ was essentially unchanged. Food appears to increase pharmacokinetic variability relative to fasting.

Overall, considerable variability was observed in the pharmacokinetics of raltegravir. For observed $C_{12\ hr}$ in BENCHMRK 1 and 2 the coefficient of variation (CV) for inter-subject variability = 212 % and the CV for intra-subject variability = 122 %. Sources of variability may include differences in co-administration with food and concomitant medicines.

Distribution

Raltegravir is approximately 83 % bound to human plasma protein over the concentration range of 2 to 10 μM.
Raltegravir readily crossed the placenta in rats, but did not penetrate the brain to any appreciable extent.

In two studies of HIV-1 infected patients who received raltegravir 400 mg twice daily, raltegravir was readily detected in the cerebrospinal fluid. In the first study (n=18), the median cerebrospinal fluid concentration was 5.8 % (range 1 to 53.5 %) of the corresponding plasma concentration. In the second study (n=16), the median cerebrospinal fluid concentration was 3 % (range 1 to 61 %) of the corresponding plasma concentration. These median proportions are approximately 3- to 6-fold lower than the free fraction of raltegravir in plasma.

Biotransformation 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 faeces and urine, respectively. In faeces, only raltegravir was present, most of which is likely to be derived from hydrolysis of raltegravir-glucuronide secreted in bile as observed in preclinical species. Two components, namely raltegravir and raltegravir-glucuronide, were detected in urine and accounted for approximately 9 and 23 % of the dose, respectively. The major circulating entity was raltegravir and represented approximately 70 % of the total radioactivity; the remaining radioactivity in plasma was accounted for by raltegravir-glucuronide. Studies using isoform-selective chemical inhibitors and cDNA-expressed UDP-glucuronosyltransferases (UGT) show that UGT1A1 is the main enzyme responsible for the formation of raltegravir-glucuronide. Thus, the data indicate that the major mechanism of clearance of raltegravir in humans is UGT1A1-mediated glucuronidation.

UGT1A1 Polymorphism
In a comparison of 30 subjects with *28/*28 genotype to 27 subjects with wild-type genotype, the geometric mean ratio (90 % CI) of AUC was 1.41 (0.96, 2.09) and the geometric mean ratio of $C_{12\ hr}$ was 1.91 (1.43, 2.55). Dose adjustment is not considered necessary in subjects with reduced UGT1A1 activity due to genetic polymorphism.

Special populations

Paediatric population
Based on a formulation comparison study in healthy adult volunteers, the chewable tablet and granules for oral suspension have higher oral bioavailability compared to the 400 mg tablet. In this study, administration of the chewable tablet with a high fat meal led to an average 6 % decrease in AUC, 62 % decrease in C_{max}, and 188 % increase in C_{12hr} compared to administration in the fasted state. Administration of the chewable tablet with a high fat meal does not affect raltegravir pharmacokinetics to a clinically meaningful degree and the chewable tablet can be administered without regard to food. The effect of food on the granules for oral suspension formulation was not studied.

Table 6 displays pharmacokinetic parameters in the 400 mg tablet, the chewable tablet, and the granules for oral suspension, by body weight.

Table 6
Raltegravir Pharmacokinetic Parameters IMPAACT P1066 Following Administration of Doses in Section 4.2 (excluding neonates)

Body weight	Formulation	Dose	N*	Geometric mean *(%CV†)* $AUC_{0\text{-}12hr}$ (µM●hr)	Geometric mean *(%CV†)* C_{12hr} (nM)
≥ 25 kg	Film-coated tablet	400 mg twice daily	18	14.1 *(121 %)*	233 (*157 %*)
≥ 25 kg	Chewable tablet	Weight based dosing, see dosing tables for the chewable tablet	9	22.1 (*36 %*)	113 (*80 %*)
11 to less than 25 kg	Chewable tablet	Weight based dosing, see dosing tables for the chewable tablet	13	18.6 (*68 %*)	82 (*123 %*)
3 to less than 20 kg	Oral suspension	Weight based dosing, see dosing table for granules for oral suspension	19	24.5 (*43 %*)	113 (*69 %*)

*Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose.
†Geometric coefficient of variation.

Elderly
There was no clinically meaningful effect of age on raltegravir pharmacokinetics in healthy subjects and patients with HIV-1 infection over the age range studied (19 to 84 years, with few individuals over the age of 65).

Gender, race and BMI
There were no clinically important pharmacokinetic differences due to gender, race or body mass index (BMI) in adults.

Renal impairment
Renal clearance of unchanged medicinal product is a minor pathway of elimination. In adults, there were no clinically important pharmacokinetic differences between patients with severe renal insufficiency and healthy subjects (see section 4.2). Because the extent to which raltegravir may be dialysable is unknown, dosing before a dialysis session should be avoided.

Hepatic impairment
Raltegravir is eliminated primarily by glucuronidation in the liver. In adults, there were no clinically important pharmacokinetic differences between patients with moderate hepatic insufficiency and healthy subjects. The effect of severe hepatic insufficiency on the pharmacokinetics of raltegravir has not been studied (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Non-clinical toxicology studies, including conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, developmental toxicity and juvenile toxicity, have been conducted with raltegravir in mice, rats, dogs and rabbits. Effects at exposure levels sufficiently in excess of clinical exposure levels indicate no special hazard for humans.

Mutagenicity

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.

Carcinogenicity

A carcinogenicity study 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 similar to that at the clinical dose of 400 mg twice daily. In rats, tumours (squamous cell carcinoma) of the nose/nasopharynx were identified at 300 and 600 mg/kg/day in females and at 300 mg/kg/day in males. This neoplasia could result from local deposition and/or aspiration of drug on the mucosa of the nose/nasopharynx during oral gavage dosing and subsequent chronic irritation and inflammation; it is likely that it is of limited relevance for the intended clinical use. At the NOAEL, systemic exposure was similar to that at the clinical dose of 400 mg twice daily. Standard genotoxicity studies to evaluate mutagenicity and clastogenicity were negative.

Developmental toxicity

Raltegravir was not teratogenic in developmental toxicity studies in rats and rabbits. A slight increase in incidence of supernumerary ribs, a variant in the normal developmental process, was observed in rat foetuses of dams exposed to raltegravir at approximately 4.4-fold human exposure at the recommended human dose (RHD) based on $AUC_{0\text{-}24\ hr}$. No development effects were seen at 3.4-fold human exposure at the RHD. Similar findings were not observed in rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
- Microcrystalline cellulose
- Lactose monohydrate
- Calcium phosphate dibasic anhydrous
- Hypromellose 2208
- Poloxamer 407
- Sodium stearyl fumarate
- Magnesium stearate

Film-coating
- Polyvinyl alcohol
- Titanium dioxide
- Polyethylene glycol 3350
- Talc
- Red iron oxide
- Black iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Keep the bottle tightly closed, with the desiccant in order to protect from moisture.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a child-resistant polypropylene closure, induction seal and silica gel desiccant.
Two pack sizes are available: 1 bottle with 60 tablets, and a multipack containing 180 (3 bottles of 60) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/001
EU/1/07/436/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 December 2007
Date of latest renewal: 14 May 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 600 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect
Each 600 mg tablet contains 5.72 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, oval-shaped, dimensions 19.1 mm x 9.7 mm x 6.1 mm, marked with MSD corporate logo and "242" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ISENTRESS 600 mg film-coated tablets is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adults, and paediatric patients weighing at least 40 kg (see sections 4.2, 4.4, 5.1 and 5.2).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

ISENTRESS should be used in combination with other active anti-retroviral therapies (ARTs) (see sections 4.4 and 5.1).

Adults and paediatric population
In adults and paediatric patients (weighing at least 40 kg), the recommended dosage is 1,200 mg (two 600 mg tablets) once daily for treatment-naïve patients or patients who are virologically suppressed on an initial regimen of ISENTRESS 400 mg twice daily.

Additional formulations and strengths available:
ISENTRESS is also available as a 400 mg tablet for twice daily use in HIV infected adults or children and adolescents at least 25 kg. The 400 mg tablet should not be used to administer 1,200 mg once daily regimen (please refer to the 400 mg Summary of Product Characteristics).

ISENTRESS is also available in a chewable tablet formulation and in granules for oral suspension formulation. Refer to the chewable tablet and granules for oral suspension SmPCs for additional dosing information.
The safety and efficacy of raltegravir in preterm (<37 weeks of gestation) and low birth weight (<2,000 g) newborns have not been established. No data are available in this population and no dosing recommendations can be made.

The maximum dose of the chewable tablet is 300 mg twice daily. Because the formulations have different pharmacokinetic profiles neither the chewable tablets nor the granules for oral suspension should be substituted for the 400 mg tablet or the 600 mg tablet (see section 5.2). The chewable tablets and the granules for oral suspension have not been studied in HIV-infected adolescents (12 to 18 years) or adults.

Elderly
There is limited information regarding the use of raltegravir in the elderly (see section 5.2). Therefore, ISENTRESS should be used with caution in this population.

Renal impairment
No dosage adjustment is required for patients with renal impairment (see section 5.2).

Hepatic impairment
No dosage adjustment is required for patients with mild to moderate hepatic impairment. The safety and efficacy of raltegravir have not been established in patients with severe underlying liver disorders. Therefore, ISENTRESS should be used with caution in patients with severe hepatic impairment (see sections 4.4 and 5.2).

ISENTRESS 600 mg film-coated tablet formulation should not be used in children weighing less than 40 kg.

Method of administration

Oral use.
ISENTRESS 600 mg tablets can be administered with or without food as a 1,200 mg once daily dose. The tablets should not be chewed, crushed or split due to anticipated changes in the pharmacokinetic profile.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General

Patients should be advised that current anti-retroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV to others through blood contact.

Raltegravir has a relatively low genetic barrier to resistance. Therefore, whenever possible, raltegravir should be administered with two other active ARTs to minimise the potential for virological failure and the development of resistance (see section 5.1).

In treatment-naïve patients, the clinical study data on use of raltegravir are limited to use in combination with two nucleotide reverse transcriptase inhibitors (NRTIs) (emtricitabine and tenofovir disoproxil fumarate).

Depression

Depression, including suicidal ideation and behaviours, has been reported, particularly in patients with a pre-existing history of depression or psychiatric illness. Caution should be used in patients with a pre-existing history of depression or psychiatric illness.

Hepatic impairment

The safety and efficacy of raltegravir have not been established in patients with severe underlying liver disorders. Therefore, raltegravir should be used with caution in patients with severe hepatic impairment (see sections 4.2 and 5.2).

Patients with pre-existing liver dysfunction including chronic hepatitis have an increased frequency of liver function abnormalities during combination anti-retroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment should be considered.

Patients with chronic hepatitis B or C and treated with combination anti-retroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Osteonecrosis

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

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination anti-retroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and pneumonia caused by *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*). Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation: however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Atazanavir

Co-administration of raltegravir 1,200 mg once daily with atazanavir resulted in increased raltegravir plasma levels; therefore, co-administration is not recommended (see section 4.5).

Tipranavir/ritonavir

Co-administration of raltegravir 1,200 mg once daily with tipranavir/ritonavir could result in decreased raltegravir trough plasma levels; therefore, co-administration is not recommended (see section 4.5).

Antacids

Co-administration of raltegravir 1,200 mg once daily with calcium carbonate and aluminium/magnesium containing antacids resulted in reduced raltegravir plasma levels; therefore, co-administration is not recommended (see section 4.5).

Strong inducers of drug metabolizing enzymes

Strong inducers of drug metabolizing enzymes (e.g., rifampicin) have not been studied with raltegravir 1,200 mg once daily, but could result in decreased raltegravir trough plasma levels; therefore, co-administration with raltegravir 1,200 mg once daily is not recommended.

Myopathy and rhabdomyolysis

Myopathy and rhabdomyolysis have been reported. Use with caution in patients who have had myopathy or rhabdomyolysis in the past or have any predisposing issues including other medicinal products associated with these conditions (see section 4.8).

Severe skin and hypersensitivity reactions

Severe, potentially life-threatening, and fatal skin reactions have been reported in patients taking raltegravir, in most cases concomitantly with other medicinal products associated with these reactions. These include cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. Hypersensitivity reactions have also been reported and were characterised by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure. Discontinue 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 oedema, 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.

Rash

Rash occurred more commonly in treatment-experienced patients receiving regimens containing raltegravir and darunavir compared to patients receiving raltegravir without darunavir or darunavir without raltegravir (see section 4.8).

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro, raltegravir is a weak inhibitor of organic anion transporter (OAT) 1 (IC_{50} of 109 µM) and OAT3 (IC_{50} of 18.8 µM). Caution is recommended when co-administering raltegravir 1,200 mg once daily with sensitive OAT1 and/or OAT3 substrates.

In vitro studies indicate that raltegravir is not a substrate of cytochrome P450 (CYP) enzymes, does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A, does not inhibit UDP glucuronosyltransferases (UGTs) 1A1 and 2B7, does not induce CYP3A4 and is not an inhibitor of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion-transporting polypeptides (OATP) 1B1, OATP1B3, organic cation transporters (OCT)1 and OCT2, or multidrug and toxin extrusion proteins (MATE)1 and MATE2-K. Based on these data, raltegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of these enzymes or transporters.

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

Considerable inter- and intra-individual variability was observed in the pharmacokinetics of raltegravir.

Effect of raltegravir on the pharmacokinetics of other medicinal products

In drug interaction studies performed using raltegravir 400 mg twice daily, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of etravirine, maraviroc, tenofovir disoproxil fumarate, hormonal contraceptives, methadone, midazolam or boceprevir. These findings can be extended to raltegravir 1,200 mg once daily and no dosage adjustment is required for these agents.

In some studies, co-administration of raltegravir 400 mg tablets twice daily with darunavir resulted in a modest but clinically insignificant decrease in darunavir plasma concentrations. Based on the magnitude of effect seen with raltegravir 400 mg tablets twice daily, it is expected that the effect of raltegravir 1,200 mg once daily on darunavir plasma concentrations is likely to be not clinically meaningful.

Effect of other medicinal products on the pharmacokinetics of raltegravir

Inducers of drug metabolizing enzymes
The impact of medicinal products that are strong inducers of UGT1A1 such as rifampicin on raltegravir 1,200 mg once daily is unknown, but co-administration is likely to decrease raltegravir trough levels based on the reduction in trough concentrations observed with raltegravir 400 mg twice daily; therefore, co-administration with raltegravir 1,200 mg once daily is not recommended. The impact of other strong inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown; therefore, co-administration with raltegravir 1,200 mg once daily is not recommended. In drug interaction studies, efavirenz did not have a clinically meaningful effect on the pharmacokinetics of raltegravir 1,200 mg once daily; therefore, other less potent inducers (e.g., efavirenz, nevirapine, rifabutin, glucocorticoids, St. John's wort, pioglitazone) may be used with the recommended dose of raltegravir.

Inhibitors of UGT1A1
Co-administration of atazanavir with raltegravir 1,200 mg once daily significantly increased plasma levels of raltegravir; therefore, co-administration of raltegravir 1,200 mg once daily and atazanavir is not recommended.

Antacids
Co-administration of raltegravir 1,200 mg once daily with aluminium/magnesium and calcium carbonate containing antacids are likely to result in clinically meaningful reductions in the plasma trough levels of raltegravir. Based on these findings, co-administration of aluminium/magnesium and calcium carbonate containing antacids with raltegravir 1,200 mg once daily is not recommended.

Agents that increase gastric pH
Population pharmacokinetic analysis from ONCEMRK (Protocol 292) showed that co-administration of raltegravir 1,200 mg once daily with PPIs or H2 blockers did not result in statistically significant changes in the pharmacokinetics of raltegravir. Comparable efficacy and safety results were obtained in the absence or presence of these gastric pH-altering agents. Based on these data, proton pump inhibitors and H2 blockers may be co-administered with raltegravir 1,200 mg once daily.

Additional considerations
No studies have been conducted to evaluate the drug interactions of ritonavir, tipranavir/ritonavir, boceprevir or etravirine with raltegravir 1,200 mg (2 x 600 mg) once daily. While the magnitudes of change on raltegravir exposure from raltegravir 400 mg twice daily by ritonavir, boceprevir or etravirine were small, the impact from tipranavir/ritonavir was greater (GMR C_{trough}=0.45, GMR AUC=0.76). Co-administration of raltegravir 1,200 mg once daily and tipranavir/ritonavir is not recommended.

Previous studies of raltegravir 400 mg twice daily showed that co-administration of tenofovir disoproxil fumarate (a component of emtricitabine/tenofovir disoproxil fumarate) increased raltegravir exposure. Emtricitabine/tenofovir disoproxil fumarate was identified to increase raltegravir 1,200 mg

once daily bioavailability by 12%, however its impact is not clinically meaningful. Therefore, co-administration of emtricitabine/tenofovir disoproxil fumarate and raltegravir 1,200 mg once daily is permitted.

All interaction studies were performed in adults.
Comprehensive drug interaction studies were performed with raltegravir 400 mg twice daily and a limited number of drug interaction studies were performed for raltegravir 1,200 mg once daily.

Table 1 displays all available interaction study data along with recommendations for co-administration.

Table 1
Pharmacokinetic Interaction Data

Medicinal products by therapeutic area	**Interaction** (mechanism, if known)	**Recommendations concerning co-administration**
ANTI-RETROVIRAL		
Protease inhibitors (PI)		
atazanavir /ritonavir (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 41% raltegravir C_{12hr} ↑ 77% raltegravir C_{max} ↑ 24% (UGT1A1 inhibition)	No dose adjustment required for raltegravir (400 mg twice daily).
atazanavir (raltegravir 1,200 mg single dose)	raltegravir AUC ↑ 67% raltegravir C_{24hr} ↑ 26% raltegravir C_{max} ↑ 16% (UGT1A1 inhibition)	Co-administration of raltegravir (1,200 mg once daily) is not recommended.
tipranavir /ritonavir (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 24% raltegravir C_{12hr} ↓ 55% raltegravir C_{max} ↓ 18% (UGT1A1 induction)	No dose adjustment required for raltegravir (400 mg twice daily).
	Extrapolated from 400 mg twice daily study	Co-administration of raltegravir (1,200 mg once daily) is not recommended.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
efavirenz (raltegravir 400 mg Single Dose)	raltegravir AUC ↓ 36% raltegravir C_{12hr} ↓ 21% raltegravir C_{max} ↓ 36% (UGT1A1 induction)	No dose adjustment required for raltegravir (400 mg twice daily and 1,200 mg once daily).
efavirenz (raltegravir 1,200 mg single dose)	raltegravir AUC ↓ 14% raltegravir C_{24hr} ↓ 6% raltegravir C_{max} ↓ 9% (UGT1A1 induction)	
etravirine (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 10% raltegravir C_{12hr} ↓ 34% raltegravir C_{max} ↓ 11% (UGT1A1 induction) etravirine AUC ↑ 10% etravirine C_{12hr} ↑ 17% etravirine C_{max} ↑ 4%	No dose adjustment required for raltegravir (400 mg twice daily and 1,200 mg once daily) or etravirine.

Medicinal products by therapeutic area	Interaction (mechanism, if known)	Recommendations concerning co-administration
Nucleoside/tide reverse transcriptase inhibitors		
tenofovir disoproxil fumarate (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 49% raltegravir C_{12hr} ↑ 3% raltegravir C_{max} ↑ 64% (mechanism of interaction unknown) tenofovir AUC ↓ 10% tenofovir C_{24hr} ↓ 13% tenofovir C_{max} ↓ 23%	No dose adjustment required for raltegravir (400 mg twice daily and 1,200 mg once daily) or tenofovir disoproxil fumarate.
emtricitabine and tenofovir disoproxil fumarate (raltegravir 1,200 mg (2 x 600 mg) Once Daily)	Population PK analysis showed that the effect of emtricitabine/tenofovir disoproxil fumarate on raltegravir pharmacokinetics was minimal (12% increase in relative bioavailability), and was not statistically or clinically significant. (Mechanism of interaction unknown)	
CCR5 inhibitors		
maraviroc (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 37% raltegravir C_{12hr} ↓ 28% raltegravir C_{max} ↓ 33% (mechanism of interaction unknown) maraviroc AUC ↓ 14% maraviroc C_{12hr} ↓ 10% maraviroc C_{max} ↓ 21%	No dose adjustment required for raltegravir (400 mg twice daily and 1,200 mg once daily) or maraviroc.
HCV ANTIVIRALS		
NS3/4A protease inhibitors (PI)		
boceprevir (raltegravir 400 mg Single Dose)	raltegravir AUC ↑ 4% raltegravir C_{12hr} ↓ 25% raltegravir C_{max} ↑ 11% (mechanism of interaction unknown)	No dose adjustment required for raltegravir (400 mg twice daily and 1,200 mg once daily) or boceprevir.
ANTIMICROBIALS		
Antimycobacterial		
rifampicin (raltegravir 400 mg Single Dose)	raltegravir AUC ↓ 40% raltegravir C_{12hr} ↓ 61% raltegravir C_{max} ↓ 38% (UGT1A1 induction)	Rifampicin reduces plasma levels of raltegravir. If co-administration with rifampicin is unavoidable, a doubling of the dose of raltegravir (400 mg twice daily) can be considered.
	Extrapolated from 400 mg twice daily study	Co-administration of raltegravir (1,200 mg once daily) is not recommended.

Medicinal products by therapeutic area	Interaction (mechanism, if known)	Recommendations concerning co-administration
SEDATIVE		
midazolam (raltegravir 400 mg Twice Daily)	midazolam AUC ↓ 8% midazolam C_{max} ↑ 3%	No dosage adjustment required for raltegravir (400 mg twice daily and 1,200 mg once daily) or midazolam. These results indicate that raltegravir is not an inducer or inhibitor of CYP3A4, and raltegravir is thus not anticipated to affect the pharmacokinetics of medicinal products which are CYP3A4 substrates.
METAL CATION ANTACIDS		
aluminium and magnesium hydroxide antacid (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 49% raltegravir $C_{12\ hr}$ ↓ 63% raltegravir C_{max} ↓ 44% <u>2 hours before raltegravir</u> raltegravir AUC ↓ 51% raltegravir $C_{12\ hr}$ ↓ 56% raltegravir C_{max} ↓ 51% <u>2 hours after raltegravir</u> raltegravir AUC ↓ 30% raltegravir $C_{12\ hr}$ ↓ 57% raltegravir C_{max} ↓ 24% <u>6 hours before raltegravir</u> raltegravir AUC ↓ 13% raltegravir $C_{12\ hr}$ ↓ 50% raltegravir C_{max} ↓ 10% <u>6 hours after raltegravir</u> raltegravir AUC ↓ 11% raltegravir $C_{12\ hr}$ ↓ 49% raltegravir C_{max} ↓ 10% (chelation of metal cations)	Aluminium and magnesium containing antacids reduce raltegravir plasma levels. Co-administration of raltegravir (400 mg twice daily and 1,200 mg once daily) with aluminium and/or magnesium containing antacids is not recommended.
aluminium/magnesium hydroxide antacid (raltegravir 1,200 mg single dose)	<u>12 hours after raltegravir</u> raltegravir AUC ↓ 14% raltegravir $C_{24\ hr}$ ↓ 58% raltegravir C_{max} ↓ 14% (chelation of metal ions)	
calcium carbonate antacid (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 55% raltegravir $C_{12\ hr}$ ↓ 32% raltegravir C_{max} ↓ 52% (chelation of metal cations)	No dose adjustment required for raltegravir (400 mg twice daily).

Medicinal products by therapeutic area	Interaction (mechanism, if known)	Recommendations concerning co-administration
calcium carbonate antacid (raltegravir 1,200 mg single dose)	raltegravir AUC ↓ 72% raltegravir $C_{24\ hr}$ ↓ 48% raltegravir C_{max} ↓ 74% <u>12 hours after raltegravir</u> raltegravir AUC ↓ 10% raltegravir $C_{24\ hr}$ ↓ 57% raltegravir C_{max} ↓ 2% (chelation of metal ions)	Co-administration of raltegravir (1,200 mg once daily) is not recommended.
Other METAL CATION		
Iron salts	Expected: Raltegravir AUC ↓ (chelation of metal cations)	Given simultaneously iron salts are expected to reduce raltegravir plasma levels; taking iron salts at least two hours from the administration of raltegravir may allow to limit this effect.
H2 BLOCKERS AND PROTON PUMP INHIBITORS		
omeprazole (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 37% raltegravir $C_{12\ hr}$ ↑ 24% raltegravir C_{max} ↑ 51% (increased solubility)	No dose adjustment required for raltegravir (400 mg twice daily and 1,200 mg once daily).
famotidine (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 44% raltegravir $C_{12\ hr}$ ↑ 6% raltegravir C_{max} ↑ 60% (increased solubility)	
gastric pH altering agents: proton pump inhibitors (e.g. omeprazole), H2 blockers (e.g. famotidine, ranitidine, cimitedine) (raltegravir 1,200 mg)	Population PK analysis showed that the effect of gastric pH altering agents on raltegravir pharmacokinetics was minimal (8.8% decrease in relative bioavailability), and was not statistically or clinically significant. (Increased drug solubility)	
HORMONAL CONTRACEPTIVES		
Ethinyl Estradiol Norelgestromin (raltegravir 400 mg Twice Daily)	Ethinyl Estradiol AUC ↓ 2% Ethinyl Estradiol C_{max} ↑ 6% Norelgestromin AUC ↑ 14% Norelgestromin C_{max} ↑ 29%	No dosage adjustment required for raltegravir (400 mg twice daily and 1,200 mg once daily) or hormonal contraceptives (estrogen- and/or progesterone-based).
OPIOID ANALGESICS		
methadone (raltegravir 400 mg Twice Daily)	methadone AUC ↔ methadone C_{max} ↔	No dose adjustment required for raltegravir (400 mg twice daily and 1,200 mg once daily) or methadone.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data for the use of raltegravir 1,200 mg once daily in pregnant women. A large amount of data on pregnant women with exposure to raltegravir 400 mg twice daily during the first trimester (more than 1,000 prospective pregnancy outcomes) indicates no malformative toxicity. Animal studies have shown reproductive toxicity (see section 5.3).
A moderate amount of data on pregnant women with exposure to raltegravir 400 mg twice daily during the second and/or third trimester (between 300-1,000 prospective pregnancy outcomes) indicates no increased risk of feto/neonatal toxicity.

Raltegravir 1,200 mg is not recommended during pregnancy.

Anti-retroviral Pregnancy Registry
To monitor maternal-foetal outcomes in patients inadvertently administered raltegravir while pregnant, an Anti-retroviral Pregnancy Registry has been established. Physicians are encouraged to register patients in this registry.

As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account in order to characterise the safety for the foetus.

Breast-feeding

Raltegravir/metabolites are excreted in human milk to such an extent that effects on the breastfed newborns/infants are likely. Available pharmacodynamics/toxicological data in animals have shown excretion of raltegravir/metabolites in milk (for details see section 5.3).

A risk to the newborns/infants cannot be excluded.

It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

Fertility

No effect on fertility was seen in male and female rats at doses up to 600 mg/kg/day which resulted in 3-fold exposure above the exposure at the recommended human dose.

4.7 Effects on ability to drive and use machines

Dizziness has been reported in some patients during treatment with regimens containing raltegravir. Dizziness may influence some patients' ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

In randomised clinical trials raltegravir 400 mg twice daily was administered in combination with fixed or optimised background treatment regimens to treatment-naïve (N=547) and treatment-experienced (N=462) adults for up to 96 weeks. A further 531 treatment-naïve adults have received raltegravir 1,200 mg once daily with emtricitabine and tenofovir disoproxil fumarate for up to 96 weeks. See section 5.1.

The most frequently reported adverse reactions during treatment were headache, nausea and abdominal pain. The most frequently reported serious adverse reactions were immune reconstitution syndrome and rash. The rates of discontinuation of raltegravir due to adverse reactions were 5% or less in clinical trials.

Rhabdomyolysis was an uncommonly reported serious adverse reaction in post-marketing use of raltegravir 400 mg twice daily.

Tabulated summary of adverse reactions

Adverse reactions considered by investigators to be causally related to raltegravir (alone or in combination with other ART), as well as adverse reactions established in post-marketing experience, are listed below by System Organ Class. Frequencies are defined as common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reactions Raltegravir (alone or in combination with other ART)
Infections and infestations	Uncommon	genital herpes, folliculitis, gastroenteritis, herpes simplex, herpes virus infection, herpes zoster, influenza, lymph node abscess, molluscum contagiosum, nasopharyngitis, upper respiratory tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Uncommon	skin papilloma
Blood and lymphatic system disorders	Uncommon	anaemia, iron deficiency anaemia, lymph node pain, lymphadenopathy, neutropenia, thrombocytopenia
Immune system disorders	Uncommon	immune reconstitution syndrome, drug hypersensitivity, hypersensitivity
Metabolism and nutrition disorders	Common	decreased appetite
	Uncommon	cachexia, diabetes mellitus, dyslipidaemia, hypercholesterolaemia, hyperglycaemia, hyperlipidaemia, hyperphagia, increased appetite, polydipsia, body fat disorder
Psychiatric disorders	Common	abnormal dreams, insomnia, nightmare, abnormal behaviour, depression
	Uncommon	mental disorder, suicide attempt, anxiety, confusional state, depressed mood, major depression, middle insomnia, mood altered, panic attack, sleep disorder, suicidal ideation, suicidal behaviour (particularly in patients with a pre-existing history of psychiatric illness)
Nervous system disorders	Common	dizziness, headache, psychomotor hyperactivity
	Uncommon	amnesia, carpal tunnel syndrome, cognitive disorder, disturbance in attention, dizziness postural, dysgeusia, hypersomnia, hypoaesthesia, lethargy, memory impairment, migraine, neuropathy peripheral, paraesthesia, somnolence, tension headache, tremor, poor quality sleep

System Organ Class	Frequency	Adverse reactions Raltegravir (alone or in combination with other ART)
Eye disorders	Uncommon	visual impairment
Ear and labyrinth disorders	Common Uncommon	vertigo tinnitus
Cardiac disorders	Uncommon	palpitations, sinus bradycardia, ventricular extrasystoles
Vascular disorders	Uncommon	hot flush, hypertension
Respiratory, thoracic and mediastinal disorders	Uncommon	dysphonia, epistaxis, nasal congestion
Gastrointestinal disorders	Common Uncommon	abdominal distention, abdominal pain, diarrhoea, flatulence, nausea, vomiting, dyspepsia gastritis, abdominal discomfort, abdominal pain upper, abdominal tenderness, anorectal discomfort, constipation, dry mouth, epigastric discomfort, erosive duodenitis, eructation, gastroesophageal reflux disease, gingivitis, glossitis, odynophagia, pancreatitis acute, peptic ulcer, rectal haemorrhage
Hepato-biliary disorders	Uncommon	hepatitis, hepatic steatosis, hepatitis alcoholic, hepatic failure
Skin and subcutaneous tissue disorders	Common	rash
	Uncommon	acne, alopecia, dermatitis acneiforme, dry skin, erythema, facial wasting, hyperhidrosis, lipoatrophy, lipodystrophy acquired, lipohypertrophy, night sweats, prurigo, pruritus, pruritus generalised, rash macular, rash maculo-papular, rash pruritic, skin lesion, urticaria, xeroderma, Stevens Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Uncommon	arthralgia, arthritis, back pain, flank pain, musculoskeletal pain, myalgia, neck pain, osteopenia, pain in extremity, tendonitis, rhabdomyolysis
Renal and urinary disorders	Uncommon	renal failure, nephritis, nephrolithiasis, nocturia, renal cyst, renal impairment, tubulointerstitial nephritis
Reproductive system and breast disorders	Uncommon	erectile dysfunction, gynaecomastia, menopausal symptoms
General disorders and administration site conditions	Common Uncommon	asthenia, fatigue, pyrexia chest discomfort, chills, face oedema, fat tissue increased, feeling jittery, malaise, submandibular mass, oedema peripheral, pain

System Organ Class	Frequency	Adverse reactions Raltegravir (alone or in combination with other ART)
Investigations	Common	alanine aminotransferase increased, atypical lymphocytes, aspartate aminotransferase increased, blood triglycerides increased, lipase increased, blood pancreatic amylase increased
	Uncommon	absolute neutrophil count decreased, alkaline phosphatase increased, blood albumin decreased, blood amylase increased, blood bilirubin increased, blood cholesterol increased, blood creatinine increased, blood glucose increased, blood urea nitrogen increased, creatine phosphokinase increased, fasting blood glucose increased, glucose urine present, high density lipoprotein increased, international normalised ratio increased, low density lipoprotein increased, platelet count decreased, red blood cells urine positive, waist circumference increased, weight increased, white blood cell count decreased
Injury, poisoning and procedural complications	Uncommon	accidental overdose

Description of selected adverse reactions

In studies of raltegravir 400 mg twice daily, cancers were reported in treatment-experienced and treatment-naïve patients who initiated raltegravir in conjunction with other antiretroviral agents. The types and rates of specific cancers were those expected in a highly immunodeficient population. The risk of developing cancer in these studies was similar in the groups receiving raltegravir and in the groups receiving comparators.

Grade 2-4 creatine kinase laboratory abnormalities were observed in patients treated with raltegravir. Myopathy and rhabdomyolysis have been reported. Use with caution in patients who have had myopathy or rhabdomyolysis in the past or have any predisposing issues including other medicinal products associated with these conditions (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

For each of the following clinical adverse reactions there was at least one serious occurrence: genital herpes, anaemia, immune reconstitution syndrome, depression, mental disorder, suicide attempt, gastritis, hepatitis, renal failure, accidental overdose.

In clinical studies of treatment-experienced patients, rash, irrespective of causality, was more commonly observed with regimens containing raltegravir and darunavir compared to those containing raltegravir without darunavir or darunavir without raltegravir. Rash considered by the investigator to be drug-related occurred at similar rates. The exposure-adjusted rates of rash (all causality) were 10.9, 4.2, and 3.8 per 100 patient-years (PYR), respectively; and for drug-related rash were 2.4, 1.1, and 2.3

per 100 PYR, respectively. The rashes observed in clinical studies were mild to moderate in severity and did not result in discontinuation of therapy (see section 4.4).

Patients co-infected with hepatitis B and/or hepatitis C virus
In clinical trials, there were 79 patients co-infected with hepatitis B, 84 co-infected with hepatitis C, and 8 patients co-infected with hepatitis B and C who were treated with raltegravir in combination with other agents for HIV-1. In general, the safety profile of raltegravir in patients with hepatitis B and/or hepatitis C virus co-infection was similar to that in patients without hepatitis B and/or hepatitis C virus co-infection, although the rates of AST and ALT abnormalities were somewhat higher in the subgroup co-infected with hepatitis B and/or hepatitis C virus.

At 96-weeks, in treatment-experienced patients, 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 patients treated with raltegravir as compared to 11 %, 10 % and 9 % of all other patients treated with raltegravir. At 240-weeks, in treatment-naïve patients, 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 patients treated with raltegravir as compared to 13 %, 13 % and 5 % of all other patients treated with raltegravir.

Paediatric population

ISENTRESS 600 mg tablet formulation has not been studied in paediatric patients (see section 4.2).

Children and adolescents 2 to 18 years of age
Raltegravir twice daily has been studied in 126 antiretroviral treatment-experienced HIV-1 infected children and adolescents 2 to 18 years of age, in combination with other antiretroviral agents in IMPAACT P1066 (see sections 5.1 and 5.2). Of the 126 patients, 96 received the recommended dose of raltegravir twice daily.

In these 96 children and adolescents, frequency, type and severity of drug related adverse reactions through Week 48 were comparable to those observed in adults.

One patient experienced drug related clinical adverse reactions of Grade 3 psychomotor hyperactivity, abnormal behaviour and insomnia; one patient experienced a Grade 2 serious drug related allergic rash.

One patient experienced drug related laboratory abnormalities, Grade 4 AST and Grade 3 ALT, which were considered serious.

Infants and toddlers 4 weeks to less than 2 years of age
Raltegravir twice daily has 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 sections 5.1 and 5.2).

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
In IMPAACT P1110 (see section 5.2) eligible infants were at least 37 weeks gestation and at least 2 kg in weight. Sixteen (16) neonates received 2 doses of ISENTRESS in first 2 weeks of life, and 26 neonates received 6 weeks of daily dosing; all were followed for 24 weeks. There were no drug related clinical adverse experiences and three drug-related laboratory adverse experiences (one a transient Grade 4 neutropenia in a subject receiving zidovudine containing 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).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No specific information is available on the treatment of overdose with raltegravir.

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. It should be taken into account that raltegravir is presented for clinical use as the potassium salt. The extent to which raltegravir may be dialysable is unknown.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, integrase inhibitors, ATC code: J05AJ01.

Mechanism of action

Raltegravir is an integrase strand transfer inhibitor active against the Human Immunodeficiency Virus (HIV-1). Raltegravir inhibits the catalytic activity of integrase, an HIV-encoded enzyme that is required for viral replication. Inhibition of integrase prevents the covalent insertion, or integration, of the HIV genome into the host cell genome. HIV genomes that fail to integrate cannot direct the production of new infectious viral particles, so inhibiting integration prevents propagation of the viral infection.

Antiviral activity *in vitro*

Raltegravir at concentrations of 31 ± 20 nM resulted in 95 % inhibition (IC_{95}) of HIV-1 replication (relative to an untreated virus-infected culture) in human T-lymphoid cell cultures infected with the cell-line adapted HIV-1 variant H9IIIB. In addition, raltegravir inhibited viral replication in cultures of mitogen-activated human peripheral blood mononuclear cells infected with diverse, primary clinical isolates of HIV-1, including isolates from 5 non-B subtypes, and isolates resistant to reverse transcriptase inhibitors and protease inhibitors. In a single-cycle infection assay, raltegravir inhibited infection of 23 HIV isolates representing 5 non-B subtypes and 5 circulating recombinant forms with IC_{50} values ranging from 5 to 12 nM.

Resistance

Most viruses isolated from patients failing raltegravir had high-level raltegravir resistance resulting from the appearance of two or more mutations in integrase. Most had a signature mutation at amino acid 155 (N155 changed to H), amino acid 148 (Q148 changed to H, K, or R), or amino acid 143 (Y143 changed to H, C, or R), along with one or more additional integrase mutations (e.g., L74M, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, S230R). The signature mutations decrease viral susceptibility to raltegravir and addition of other mutations results in a further decrease in raltegravir susceptibility. Factors that reduced the likelihood of developing resistance included lower baseline viral load and use of other active anti-retroviral agents. Mutations conferring resistance to raltegravir generally also confer resistance to the integrase strand transfer inhibitor elvitegravir. Mutations at

amino acid 143 confer greater resistance to raltegravir than to elvitegravir, and the E92Q mutation confers greater resistance to elvitegravir than to raltegravir. Viruses harbouring a mutation at amino acid 148, along with one or more other raltegravir resistance mutations, may also have clinically significant resistance to dolutegravir.

Clinical experience

The evidence of efficacy of raltegravir was based on the analyses of 96-week data from two randomised, double-blind, placebo-controlled trials (BENCHMRK 1 and BENCHMRK 2, Protocols 018 and 019) in antiretroviral treatment-experienced HIV-1 infected adult patients, the analysis of 240-week data from randomised, double-blind, active-control trial (STARTMRK, Protocol 021) in antiretroviral treatment-naïve HIV-1 infected adult patients and the analysis of 96-week data from randomised, double-blind, active-control trial (ONCEMRK, Protocol 292) in antiretroviral treatment-naïve HIV-1 infected adult patients.

Efficacy

Treatment-experienced adult patients (400 mg twice daily)
BENCHMRK 1 and BENCHMRK 2 (multi-centre, randomised, double-blind, placebo-controlled trials) evaluated the safety and anti-retroviral activity of raltegravir 400 mg twice daily vs. placebo in a combination with optimised background therapy (OBT), in HIV-infected patients, 16 years or older, with documented resistance to at least 1 drug in each of 3 classes (NRTIs, NNRTIs, PIs) of anti-retroviral therapies. Prior to randomisation, OBT were selected by the investigator based on the patient's prior treatment history, as well as baseline genotypic and phenotypic viral resistance testing.

Patient demographics (gender, age and race) and baseline characteristics were comparable between the groups receiving raltegravir 400 mg twice daily and placebo. Patients had prior exposure to a median of 12 anti-retrovirals for a median of 10 years. A median of 4 ARTs was used in OBT.

Results 48-week and 96-week analyses
Durable outcomes (Week 48 and Week 96) for patients on the recommended dose raltegravir 400 mg twice daily from the pooled studies BENCHMRK 1 and BENCHMRK 2 are shown in Table 2.

Table 2
Efficacy Outcome at Weeks 48 and 96

BENCHMRK 1 and 2 Pooled	**48 Weeks**		**96 Weeks**	
Parameter	**Raltegravir 400 mg twice daily + OBT (N = 462)**	**Placebo + OBT (N = 237)**	**Raltegravir 400 mg twice daily + OBT (N = 462)**	**Placebo + OBT (N = 237)**
Percent HIV-RNA < 400 copies/mL (95 % CI)				
All patients[†]	72 (68, 76)	37 (31, 44)	62 (57, 66)	28 (23, 34)
Baseline Characteristic[‡]				
HIV-RNA > 100,000 copies/mL	62 (53, 69)	17 (9, 27)	53 (45, 61)	15 (8, 25)
≤ 100,000 copies/mL	82 (77, 86)	49 (41, 58)	74 (69, 79)	39 (31, 47)
CD4-count ≤ 50 cells/mm^3	61 (53, 69)	21 (13, 32)	51 (42, 60)	14 (7, 24)
> 50 and ≤ 200 cells/mm^3	80 (73, 85)	44 (33, 55)	70 (62, 77)	36 (25, 48)
> 200 cells/mm^3	83 (76, 89)	51 (39, 63)	78 (70, 85)	42 (30, 55)
Sensitivity score (GSS) [§]				
0	52 (42, 61)	8 (3, 17)	46 (36, 56)	5 (1, 13)
1	81 (75, 87)	40 (30, 51)	76 (69, 83)	31 (22, 42)
2 and above	84 (77, 89)	65 (52, 76)	71 (63, 78)	56 (43, 69)

BENCHMRK 1 and 2 Pooled	48 Weeks		96 Weeks	
Parameter	**Raltegravir 400 mg twice daily + OBT (N = 462)**	**Placebo + OBT (N = 237)**	**Raltegravir 400 mg twice daily + OBT (N = 462)**	**Placebo + OBT (N = 237)**
Percent HIV-RNA < 50 copies/mL (95 % CI)				
All patients[†]	62 (57, 67)	33 (27, 39)	57 (52, 62)	26 (21, 32)
Baseline Characteristic[‡]				
HIV-RNA > 100,000 copies/mL	48 (40, 56)	16 (8, 26)	47 (39, 55)	13 (7, 23)
≤ 100,000 copies/mL	73 (68, 78)	43 (35, 52)	70 (64, 75)	36 (28, 45)
CD4-count ≤ 50 cells/mm^3	50 (41, 58)	20 (12, 31)	50 (41, 58)	13 (6, 22)
> 50 and ≤ 200 cells/mm^3	67 (59, 74)	39 (28, 50)	65 (57, 72)	32 (22, 44)
> 200 cells/mm^3	76 (68, 83)	44 (32, 56)	71 (62, 78)	41 (29, 53)
Sensitivity score (GSS) [§]				
0	45 (35, 54)	3 (0, 11)	41 (32, 51)	5 (1, 13)
1	67 (59, 74)	37 (27, 48)	72 (64, 79)	28 (19, 39)
2 and above	75 (68, 82)	59 (46, 71)	65 (56, 72)	53 (40, 66)
Mean CD4 Cell Change (95 % CI), cells/mm^3				
All patients[‡]	109 (98, 121)	45 (32, 57)	123 (110, 137)	49 (35, 63)
Baseline Characteristic[‡]				
HIV-RNA > 100,000 copies/mL	126 (107, 144)	36 (17, 55)	140 (115, 165)	40 (16, 65)
≤ 100,000 copies/mL	100 (86, 115)	49 (33, 65)	114 (98, 131)	53 (36, 70)
CD4-count ≤ 50 cells/mm^3	121 (100, 142)	33 (18, 48)	130 (104, 156)	42 (17, 67)
> 50 and ≤ 200 cells/mm^3	104 (88, 119)	47 (28, 66)	123 (103, 144)	56 (34, 79)
> 200 cells/mm^3	104 (80, 129)	54 (24, 84)	117 (90, 143)	48 (23, 73)
Sensitivity score (GSS) [§]				
0	81 (55, 106)	11 (4, 26)	97 (70, 124)	15 (-0, 31)
1	113 (96, 130)	44 (24, 63)	132 (111, 154)	45 (24, 66)
2 and above	125 (105, 144)	76 (48, 103)	134 (108, 159)	90 (57, 123)

[†] Non-completer is failure imputation: patients who discontinued prematurely are imputed as failure thereafter. Percent of patients with response and associated 95 % confidence interval (CI) are reported.

[‡] For analysis by prognostic factors, virologic failures were carried forward for percent < 400 and 50 copies/mL. For mean CD4 changes, baseline-carry-forward was used for virologic failures.

[§] The Genotypic Sensitivity Score (GSS) was defined as the total oral ARTs in the optimised background therapy (OBT) to which a patient's viral isolate showed genotypic sensitivity based upon genotypic resistance test. Enfuvirtide use in OBT in enfuvirtide-naïve patients was counted as one active drug in OBT. Similarly, darunavir use in OBT in darunavir-naïve patients was counted as one active drug in OBT.

Raltegravir achieved virologic responses (using Not Completer=Failure approach) of HIV RNA < 50 copies/mL in 61.7 % of patients at Week 16, in 62.1 % at Week 48 and in 57.0 % at Week 96. Some patients experienced viral rebound between Week 16 and Week 96. Factors associated with failure include high baseline viral load and OBT that did not include at least one potent active agent.

Switch to raltegravir (400 mg twice daily)

The SWITCHMRK 1 & 2 (Protocols 032 & 033) studies evaluated HIV-infected patients receiving suppressive (screening HIV RNA < 50 copies/mL; stable regimen > 3 months) therapy with lopinavir 200 mg (+) ritonavir 50 mg 2 tablets twice daily plus at least 2 nucleoside reverse transcriptase inhibitors and randomised them 1:1 to continue lopinavir (+) ritonavir 2 tablets twice daily (n=174 and n=178, respectively) or replace lopinavir (+) ritonavir with raltegravir 400 mg twice daily (n=174 and n=176, respectively). Patients with a prior history of virological failure were not excluded and the number of previous antiretroviral therapies was not limited.

These studies were terminated after the primary efficacy analysis at Week 24 because they failed to demonstrate non-inferiority of raltegravir versus lopinavir (+) ritonavir. In both studies at Week 24, suppression of HIV RNA to less than 50 copies/mL was maintained in 84.4 % of the raltegravir group versus 90.6 % of the lopinavir (+) ritonavir group, (Non-completers = Failure). See section 4.4 regarding the need to administer raltegravir with two other active agents.

Treatment-naïve adult patients (400 mg twice daily)
STARTMRK (multi-centre, randomised, double-blind, active-control trial) evaluated the safety and anti-retroviral activity of raltegravir 400 mg twice daily vs. efavirenz 600 mg at bedtime, in a combination with emtricitabine (+) tenofovir disoproxil fumarate, in treatment-naïve HIV-infected patients with HIV RNA > 5,000 copies/mL. Randomisation was stratified by screening HIV RNA level (≤ 50,000 copies/mL; and > 50,000 copies/mL) and by hepatitis B or C status (positive or negative).

Patient demographics (gender, age and race) and baseline characteristics were comparable between the group receiving raltegravir 400 mg twice daily and the group receiving efavirenz 600 mg at bedtime.

Results 48-week and 240-week analyses
With respect to the primary efficacy endpoint, the proportion of patients achieving HIV RNA < 50 copies/mL at Week 48 was 241/280 (86.1 %) in the group receiving raltegravir and 230/281 (81.9 %) in the group receiving efavirenz. The treatment difference (raltegravir – efavirenz) was 4.2 % with an associated 95 % CI of (-1.9, 10.3) establishing that raltegravir is non-inferior to efavirenz (p-value for non-inferiority < 0.001). At Week 240, the treatment difference (raltegravir – efavirenz) was 9.5 % with an associated 95 % CI of (1.7, 17.3). Week 48 and Week 240 outcomes for patients on the recommended dose of raltegravir 400 mg twice daily from STARTMRK are shown in Table 3.

Table 3
Efficacy Outcome at Weeks 48 and 240

STARTMRK Study	**48 Weeks**		**240 Weeks**	
Parameter	**Raltegravir 400 mg twice daily (N = 281)**	**Efavirenz 600 mg at bedtime (N = 282)**	**Raltegravir 400 mg twice daily (N = 281)**	**Efavirenz 600 mg at bedtime (N = 282)**
Percent HIV-RNA < 50 copies/mL (95 % CI)				
All patients[†]	86 (81, 90)	82 (77, 86)	71 (65, 76)	61 (55, 67)
Baseline Characteristic[‡]				
HIV-RNA > 100,000 copies/mL	91 (85, 95)	89 (83, 94)	70 (62, 77)	65 (56, 72)
≤ 100,000 copies/mL	93 (86, 97)	89 (82, 94)	72 (64, 80)	58 (49, 66)
CD4-count ≤ 50 cells/mm^3	84 (64, 95)	86 (67, 96)	58 (37, 77)	77 (58, 90)
> 50 and ≤ 200 cells/mm^3	89 (81, 95)	86 (77, 92)	67 (57, 76)	60 (50, 69)
> 200 cells/mm^3	94 (89, 98)	92 (87, 96)	76 (68, 82)	60 (51, 68)
Viral Subtype Clade B	90 (85, 94)	89 (83, 93)	71 (65, 77)	59 (52, 65)
Non-Clade B	96 (87, 100)	91 (78, 97)	68 (54, 79)	70 (54, 82)
Mean CD4 Cell Change (95 % CI), cells/mm^3				
All patients[‡]	189 (174, 204)	163 (148, 178)	374 (345, 403)	312 (284, 339)
Baseline Characteristic[‡]				
HIV-RNA > 100,000 copies/mL	196 (174, 219)	192 (169, 214)	392 (350, 435)	329 (293, 364)
≤ 100,000 copies/mL	180 (160, 200)	134 (115, 153)	350 (312, 388)	294 (251, 337)
CD4-count ≤ 50 cells/mm^3	170 (122, 218)	152 (123, 180)	304 (209, 399)	314 (242, 386)
> 50 and ≤ 200 cells/mm^3	193 (169, 217)	175 (151, 198)	413 (360, 465)	306 (264, 348)
> 200 cells/mm^3	190 (168, 212)	157 (134, 181)	358 (321, 395)	316 (272, 359)
Viral Subtype Clade B	187 (170, 204)	164 (147, 181)	380 (346, 414)	303 (272, 333)
Non-Clade B	189 (153, 225)	156 (121, 190)	332 (275, 388)	329 (260, 398)

[†] Non-completer is failure imputation: patients who discontinued prematurely are imputed as failure thereafter. Percent of patients with response and associated 95 % confidence interval (CI) are reported.
[‡] For analysis by prognostic factors, virologic failures were carried forward for percent < 50 and 400 copies/mL. For mean CD4 changes, baseline-carry-forward was used for virologic failures.
Notes: The analysis is based on all available data.
Raltegravir and efavirenz were administered with emtricitabine (+) tenofovir disoproxil fumarate.

Treatment-naïve adult patients (1,200 mg [2 x 600 mg] once daily)
ONCEMRK (multi-centre, randomised, double-blind, active-control trial; Protocol 292) evaluated the safety and anti-retroviral activity of raltegravir 1,200 mg once daily + emtricitabine (+) tenofovir disoproxil fumarate vs. raltegravir 400 mg twice daily, in combination with emtricitabine (+) tenofovir disoproxil fumarate, in treatment-naïve HIV-infected patients with HIV RNA > 1,000 copies/mL. Randomisation was stratified by screening HIV RNA level (≤ 100,000 copies/mL; and > 100,000 copies/mL) and by hepatitis B or C status (positive or negative).

Patient demographics (gender, age and race) and baseline characteristics were comparable between the group receiving raltegravir 1,200 mg once daily and the group receiving raltegravir 400 mg twice daily.

Results of Week 48 and 96 analyses
With respect to the primary efficacy endpoint, the proportion of patients achieving HIV RNA < 40 copies/mL at Week 48 was 472/531(88.9 %) in the group receiving raltegravir 1,200 mg once daily and 235/266 (88.3 %) in the group receiving raltegravir 400 mg twice daily. The treatment difference (raltegravir 1,200 mg once daily-raltegravir 400 mg twice daily) was 0.5 % with an associated 95 % CI of (-4.2, 5.2) establishing that raltegravir 1,200 mg once daily is non-inferior to raltegravir 400 mg twice daily.

At Week 96, the proportion of patients achieving HIV RNA < 40 copies/mL was 433/531(81.5 %) in the group receiving raltegravir 1,200 mg once daily and 213/266 (80.1 %) in the group receiving raltegravir 400 mg twice daily. The treatment difference (raltegravir 1,200 mg once daily-raltegravir 400 mg twice daily) was 1.5 % with an associated 95 % CI of (-4.4, 7.3). Week 48 and Week 96 outcomes from ONCEMRK are shown in Table 4.

Table 4
Efficacy Outcome at Weeks 48 and 96

ONCEMRK Study	**48 Weeks**		**96 Weeks**	
Parameter	**Raltegravir 600 mg (1,200 mg once daily) (N = 531)**	**Raltegravir 400 mg twice daily (N = 266)**	**Raltegravir 600 mg (1,200 mg once daily) (N = 531)**	**Raltegravir 400 mg twice daily (N = 266)**
Percent HIV-RNA < 40 copies/mL (95 % CI)				
All patients[†]	88.9 (85.9, 91.4)	88.3 (83.9, 91.9)	81.5 (78.0, 84.8)	80.1 (74.8, 84.7)
Baseline Characteristic[‡]				
HIV-RNA > 100,000 copies/mL	86.7 (80.0, 91.8)	83.8 (73.4, 91.3)	84.7 (77.5, 90.3)	82.9 (72.0, 90.8)
≤ 100,000 copies/mL	97.2 (94.9, 98.7)	97.7 (94.3, 99.4)	91.9 (88.5, 94.5)	93.0 (89.1, 97.1)
CD4-count ≤ 200 cells/mm^3	85.1 (74.3, 92.6)	87.9 (71.8, 96.6)	79.0 (66.8, 88.3)	80 (61.4, 92.3)
> 200 cells/mm^3	95.6 (93.2, 97.3)	94.5 (90.6, 97.1)	91.4 (88.3, 93.9)	92.2 (87.6, 95.5)
Viral Subtype Clade B	94.6 (91.4, 96.8)	93.7 (89.0, 96.8)	90.0 (86.0, 93.2)	88.9 (83.0, 93.3)
Non-Clade B	93.6 (89.1, 96.6)	93.2 (84.9, 97.8)	89.5 (84.1, 93.6)	94.4 (86.2, 98.4)

ONCEMRK Study	48 Weeks		96 Weeks	
Parameter	**Raltegravir 600 mg (1,200 mg once daily) (N = 531)**	**Raltegravir 400 mg twice daily (N = 266)**	**Raltegravir 600 mg (1,200 mg once daily) (N = 531)**	**Raltegravir 400 mg twice daily (N = 266)**
Mean CD4 Cell Change (95 % CI), cells/mm^3				
All patients‡	232 (215, 249)	234 (213, 255)	262 (243, 280)	262 (236, 288)
Baseline Characteristic‡				
HIV-RNA > 100,000 copies/mL	276 (245, 308)	256 (218, 294)	297 (263, 332)	281 (232, 329)
≤ 100,000 copies/mL	214 (194, 235)	225 (199, 251)	248 (225, 270)	254 (224, 285)
CD4 count ≤ 200 cells/mm^3	209 (176, 243)	209 (172, 245)	239 (196, 281)	242 (188, 296)
> 200 cells/mm^3	235 (216, 255)	238 (214, 262)	265 (245, 286)	265 (237, 294)
Viral Subtype Clade B	232 (209, 254)	240 (213, 266)	270 (245, 296)	267 (236, 297)
Non-Clade B	233 (205, 261)	226 (191, 261)	246 (219, 274)	259 (211, 307)

† Non-completer is failure imputation: patients who discontinued prematurely are imputed as failure thereafter. Percent of patients with response and associated 95 % confidence interval (CI) are reported.
‡ For analysis by prognostic factors, virologic failures were carried forward for percent < 40 copies/mL. For mean CD4 changes, baseline-carry-forward was used for virologic failures.
Raltegravir 1,200 mg QD and raltegravir 400 mg BID were administered with emtricitabine (+) tenofovir disoproxil fumarate.

5.2 Pharmacokinetic properties

Absorption

As demonstrated in healthy volunteers administered single oral doses of raltegravir in the fasted state, raltegravir is rapidly absorbed with a t_{max} of approximately 3 hours postdose. Raltegravir AUC and C_{max} increase dose proportionally over the dose range 100 mg to 1,600 mg. Raltegravir $C_{12\ hr}$ 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 1,600 mg.

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

Raltegravir 1,200 mg once daily is also rapidly absorbed with median T_{max} ~1.5 to 2 hours in the fasted state and generates a sharper absorption peak with a tendency to higher C_{max} in comparison to raltegravir twice daily (1 x 400 mg tablet twice daily). In addition, relative to the raltegravir 400 mg formulation the raltegravir 600 mg formulation used in the 1,200 mg (2 x 600 mg) once daily dosing regimen has higher relative bioavailability (by 21 to 66%). Once absorbed, both formulations of raltegravir exhibit similar systemic pharmacokinetics. In patients, after 1,200 mg once daily raltegravir dosing, steady state AUC_{0-24} was 53.7 h·µM, C_{24} was 75.6 nM, and median T_{max} was 1.50 h.

Raltegravir 400 mg twice daily may be administered with or without food. Raltegravir was administered without regard to food in the pivotal safety and efficacy studies in HIV-infected patients. Administration of multiple doses of raltegravir following a moderate-fat meal did not affect raltegravir AUC to a clinically meaningful degree with an increase of 13 % relative to fasting. Raltegravir $C_{12\ hr}$ was 66 % higher and C_{max} was 5 % higher following a moderate-fat meal compared to fasting. Administration of raltegravir following a high-fat meal increased AUC and C_{max} by approximately 2-fold and increased $C_{12\ hr}$ by 4.1-fold. Administration of raltegravir following a low-fat meal decreased AUC and C_{max} by 46 % and 52 %, respectively; $C_{12\ hr}$ was essentially unchanged. Food appears to increase pharmacokinetic variability relative to fasting.

Raltegravir 600 mg tablets (2 x 600 mg once daily) may be administered with or without food. A single dose food effect study demonstrated that the 1,200 mg once daily had similar or smaller food effects when studied under high-fat and low-fat meal conditions when compared to the 400 mg twice

daily. Administration of a low-fat meal with raltegravir 1,200 mg once daily resulted in a 42% decrease in $AUC_{0\text{-last}}$, 52% decrease in C_{max}, and 16% decrease in $C_{24\ hr}$. Administration of a high fat meal resulted in a 1.9% increase in $AUC_{0\text{-last}}$, 28% decrease in C_{max}, and 12% decrease in $C_{24\ hr}$.

Overall, considerable variability was observed in the pharmacokinetics of raltegravir. For observed $C_{12\ hr}$ in BENCHMRK 1 and 2 the coefficient of variation (CV) for inter-subject variability = 212 % and the CV for intra-subject variability = 122 %. Sources of variability may include differences in co-administration with food and concomitant medicines.

Distribution

Raltegravir is approximately 83 % bound to human plasma protein over the concentration range of 2 to 10 μM.
Raltegravir readily crossed the placenta in rats, but did not penetrate the brain to any appreciable extent.

In two studies of HIV-1 infected patients who received raltegravir 400 mg twice daily, raltegravir was readily detected in the cerebrospinal fluid. In the first study (n=18), the median cerebrospinal fluid concentration was 5.8 % (range 1 to 53.5 %) of the corresponding plasma concentration. In the second study (n=16), the median cerebrospinal fluid concentration was 3 % (range 1 to 61 %) of the corresponding plasma concentration. These median proportions are approximately 3- to 6-fold lower than the free fraction of raltegravir in plasma.

Biotransformation 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 faeces and urine, respectively. In faeces, only raltegravir was present, most of which is likely to be derived from hydrolysis of raltegravir-glucuronide secreted in bile as observed in preclinical species. Two components, namely raltegravir and raltegravir-glucuronide, were detected in urine and accounted for approximately 9 and 23 % of the dose, respectively. The major circulating entity was raltegravir and represented approximately 70 % of the total radioactivity; the remaining radioactivity in plasma was accounted for by raltegravir-glucuronide. Studies using isoform-selective chemical inhibitors and cDNA-expressed UDP-glucuronosyltransferases (UGT) show that UGT1A1 is the main enzyme responsible for the formation of raltegravir-glucuronide. Thus, the data indicate that the major mechanism of clearance of raltegravir in humans is UGT1A1-mediated glucuronidation.

UGT1A1 Polymorphism
In a comparison of 30 subjects with *28/*28 genotype to 27 subjects with wild-type genotype, the geometric mean ratio (90 % CI) of AUC was 1.41 (0.96, 2.09) and the geometric mean ratio of $C_{12\ hr}$ was 1.91 (1.43, 2.55). Dose adjustment is not considered necessary in subjects with reduced UGT1A1 activity due to genetic polymorphism.

Special populations

Paediatric population
Based on a formulation comparison study in healthy adult volunteers, the chewable tablet and granules for oral suspension have higher oral bioavailability compared to the 400 mg tablet. In this study, administration of the chewable tablet with a high fat meal led to an average 6 % decrease in AUC, 62 % decrease in C_{max}, and 188 % increase in $C_{12\ hr}$ 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 granules for oral suspension formulation was not studied.

Table 5 displays pharmacokinetic parameters in the 400 mg tablet, the chewable tablet, and the granules for oral suspension, by body weight.

Table 5
Raltegravir Pharmacokinetic Parameters IMPAACT P1066 Following Administration of Doses in Section 4.2 (excluding neonates)

Body weight	Formulation	Dose	N*	Geometric mean *(%CV†)* $AUC_{0\text{-}12hr}$ (µM●hr)	Geometric mean *(%CV†)* C_{12hr} (nM)
≥ 25 kg	Film-coated tablet	400 mg twice daily	18	14.1 *(121 %)*	233 (*157 %*)
≥ 25 kg	Chewable tablet	Weight based dosing, see dosing tables for the chewable tablet	9	22.1 (*36 %*)	113 (*80 %*)
11 to less than 25 kg	Chewable tablet	Weight based dosing, see dosing tables for the chewable tablet	13	18.6 (*68 %*)	82 (*123 %*)
3 to less than 20 kg	Oral suspension	Weight based dosing, see dosing table for granules for oral suspension	19	24.5 (*43 %*)	113 (*69 %*)
*Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose. †Geometric coefficient of variation.					

Elderly
There was no clinically meaningful effect of age on raltegravir pharmacokinetics over the age range studied with raltegravir 400 mg twice daily. There was no clinically meaningful effect of age on raltegravir pharmacokinetics over the age range studied in ONCEMRK with raltegravir 1,200 mg (2 x 600 mg) once daily.

Gender, race, ethnicity and body weight
There were no clinically important pharmacokinetic differences due to gender, race, ethnicity or body weight in adults for raltegravir 400 mg twice daily, and no clinically meaningful effect on raltegravir pharmacokinetics was concluded. For raltegravir 1,200 mg (2 x 600 mg) once daily, population PK analysis also demonstrated that the impacts of gender, race, ethnicity and body weight are not clinically meaningful.

Renal impairment
Renal clearance of unchanged medicinal product is a minor pathway of elimination. In adults, there were no clinically important pharmacokinetic differences between patients with severe renal insufficiency and healthy subjects (see section 4.2 of the 400 mg twice daily SmPC). Because the extent to which raltegravir may be dialysable is unknown, dosing before a dialysis session should be avoided. No renal impairment study was conducted with raltegravir 1,200 mg once daily however, based on results with the 400 mg twice daily tablet, no clinically meaningful effect is anticipated.

Hepatic impairment
Raltegravir is eliminated primarily by glucuronidation in the liver. In adults, there were no clinically important pharmacokinetic differences between patients with moderate hepatic insufficiency and healthy subjects. The effect of severe hepatic insufficiency on the pharmacokinetics of raltegravir has not been studied (see sections 4.2 and 4.4 of the 400 mg twice daily SmPC). No hepatic impairment study has been conducted with raltegravir 1,200 mg once daily, however, based on results with the 400 mg twice daily tablet, no clinically meaningful effect is expected for mild and moderate hepatic impairment.

5.3 Preclinical safety data

Non-clinical toxicology studies, including conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, developmental toxicity and juvenile toxicity, have been conducted with raltegravir in mice, rats, dogs and rabbits. Effects at exposure levels sufficiently in excess of clinical exposure levels indicate no special hazard for humans.

Mutagenicity

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.

Carcinogenicity

A carcinogenicity study 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 similar to that at the clinical dose of 1,200 mg once daily. In rats, tumours (squamous cell carcinoma) of the nose/nasopharynx were identified at 300 and 600 mg/kg/day in females and at 300 mg/kg/day in males. This neoplasia could result from local deposition and/or aspiration of drug on the mucosa of the nose/nasopharynx during oral gavage dosing and subsequent chronic irritation and inflammation; it is likely that it is of limited relevance for the intended clinical use. At the NOAEL, systemic exposure was similar to that at the clinical dose of 1,200 mg once daily. Standard genotoxicity studies to evaluate mutagenicity and clastogenicity were negative.

Developmental toxicity

Raltegravir was not teratogenic in developmental toxicity studies in rats and rabbits. A slight increase in incidence of supernumerary ribs, a variant in the normal developmental process, was observed in rat foetuses of dams exposed to raltegravir at approximately 4.4-fold human exposure at the recommended human dose (RHD) based on $AUC_{0\text{-}24\ hr}$. No development effects were seen at 3.4-fold human exposure at the RHD. Similar findings were not observed in rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
- Microcrystalline cellulose
- Hypromellose 2910
- Magnesium stearate
- Croscarmellose sodium

Film-coating
- Lactose monohydrate
- Hypromellose 2910
- Titanium dioxide
- Triacetin
- Iron oxide yellow
- Black iron oxide

The tablet may also contain trace amount of carnauba wax.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Keep the bottle tightly closed, with the desiccant in order to protect from moisture.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a child-resistant polypropylene closure, induction seal and silica gel desiccant.
Two pack sizes are available: 1 bottle with 60 tablets, and a multipack containing 180 (3 bottles of 60) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/006
EU/1/07/436/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 December 2007
Date of latest renewal: 14 May 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 25 mg chewable tablets
ISENTRESS 100 mg chewable tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains 25 mg of raltegravir (as potassium).
Each chewable tablet contains 100 mg of raltegravir (as potassium).

Excipients with known effect 25 mg
Each chewable tablet contains up to: 0.54 mg fructose, 0.47 mg aspartame (E 951), 3.5 mg sucrose and 1.5 mg sorbitol (E 420).

Excipients with known effect 100 mg
Each chewable tablet contains up to: 1.07 mg fructose, 0.93 mg aspartame (E 951), 7 mg sucrose and 2.9 mg sorbitol (E 420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablet

Chewable tablet 25 mg
Pale yellow, round, chewable tablet with MSD corporate logo on one side and “473” on the other side.

Chewable tablet 100 mg
Pale orange coloured, oval shaped, chewable tablet scored on both sides with the MSD corporate logo and "477" on one side and without inscription on the other side.
The tablet can be divided into equal 50 mg doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ISENTRESS is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection (see sections 4.2, 4.4, 5.1 and 5.2).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

ISENTRESS should be used in combination with other active anti-retroviral therapies (ARTs) (see sections 4.4 and 5.1).
The maximum dose of the chewable tablet is 300 mg twice daily.
Because the formulations have different pharmacokinetic profiles neither the chewable tablets nor the granules for oral suspension should be substituted for the 400 mg tablet or 600 mg tablet (see section 5.2). The chewable tablets and the granules for oral suspension have not been studied in HIV-infected adolescents (12 to 18 years) or adults.

Paediatric Population
Children at least 11 kg: weight-based dose of the chewable tablet to a maximum dose of 300 mg, twice daily as specified in Tables 1 and 2. The chewable tablets are available in 25 mg and scored 100 mg strengths.
See section 5.2 regarding the limited data on which these dose recommendations are based.

Table 1
Recommended Dose* for ISENTRESS Chewable Tablets for Paediatric 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 (see section 5.2).
†The 100 mg chewable tablet can be divided into equal 50 mg doses. However, breaking the tablets should be avoided whenever possible.

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 (see section 5.1).

Table 2
Recommended Dose* for ISENTRESS Granules For Oral Suspension and Chewable Tablets in Paediatric Patients at least 4 weeks of age and weighing 3 to 25 kg

Body Weight (kg)	Volume (Dose) of Suspension to be Administered	Number of Chewable Tablets
3 to less than 4	2.5 mL (25 mg) twice daily	
4 to less than 6	3 mL (30 mg) twice daily	
6 to less than 8	4 mL (40 mg) twice daily	
8 to less than 11	6 mL (60 mg) twice daily	
11 to less than 14†	8 mL (80 mg) twice daily	3 x 25 mg twice daily
14 to less than 20†	10 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 in 10 mL of water is based on approximately 6 mg/kg/dose twice daily (see section 5.2).
†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 50 mg doses.
However, breaking the tablets should be avoided whenever possible.

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

Patients should be instructed to keep scheduled appointments because the ISENTRESS dosage should be adjusted as the child grows.

Additional formulations and strengths available
ISENTRESS is also available in a 400 mg tablet and as granules for oral suspension for use. Refer to the 400 mg tablet and granules for oral suspension SmPCs for additional dosing information.
The safety and efficacy of raltegravir in preterm (<37 weeks of gestation) and low birth weight (<2,000 g) newborns have not been established. No data are available in this population and no dosing recommendations can be made.

ISENTRESS is also available for adults and paediatric patients (weighing at least 40 kg), as a 600 mg tablet to be administered as 1,200 mg once daily (two 600 mg tablets) for treatment-naïve patients or patients who are virologically suppressed on an initial regimen of ISENTRESS 400 mg twice daily. Refer to the 600 mg tablet SmPCs for additional dosing information.

Elderly
There is limited information regarding the use of raltegravir in the elderly (see section 5.2). Therefore, ISENTRESS should be used with caution in this population.

Renal impairment
No dosage adjustment is required for patients with renal impairment (see section 5.2).

Hepatic impairment
No dosage adjustment is required for patients with mild to moderate hepatic impairment. The safety and efficacy of raltegravir have not been established in patients with severe underlying liver disorders. Therefore, ISENTRESS should be used with caution in patients with severe hepatic impairment (see sections 4.4 and 5.2).

Method of administration

Oral use.
ISENTRESS chewable tablets can be administered with or without food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General

Patients should be advised that current anti-retroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV to others through blood contact.

Raltegravir has a relatively low genetic barrier to resistance. Therefore, whenever possible, raltegravir should be administered with two other active ARTs to minimise the potential for virological failure and the development of resistance (see section 5.1).

In treatment-naïve patients, the clinical study data on use of raltegravir are limited to use in combination with two nucleotide reverse transcriptase inhibitors (NRTIs) (emtricitabine and tenofovir disoproxil fumarate).

Depression

Depression, including suicidal ideation and behaviours, has been reported, particularly in patients with a pre-existing history of depression or psychiatric illness. Caution should be used in patients with a pre-existing history of depression or psychiatric illness.

Hepatic impairment

The safety and efficacy of raltegravir have not been established in patients with severe underlying liver disorders. Therefore, raltegravir should be used with caution in patients with severe hepatic impairment (see sections 4.2 and 5.2).

Patients with pre-existing liver dysfunction including chronic hepatitis have an increased frequency of liver function abnormalities during combination anti-retroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment should be considered.

Patients with chronic hepatitis B or C and treated with combination anti-retroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Osteonecrosis

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

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination anti-retroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and pneumonia caused by *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*). Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation: however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Antacids

Co-administration of raltegravir with aluminium and magnesium antacids resulted in reduced raltegravir plasma levels. Co-administration of raltegravir with aluminium and/or magnesium antacids is not recommended (see section 4.5).

Rifampicin

Caution should be used when co-administering raltegravir with strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 (e.g., rifampicin). Rifampicin reduces plasma levels of raltegravir; the impact on the efficacy of raltegravir is unknown. However, if co-administration with rifampicin is unavoidable, a doubling of the dose of raltegravir can be considered in adults. There are no data to guide co-administration of raltegravir with rifampicin in patients below 18 years of age (see section 4.5).

Myopathy and rhabdomyolysis

Myopathy and rhabdomyolysis have been reported. Use with caution in patients who have had myopathy or rhabdomyolysis in the past or have any predisposing issues including other medicinal products associated with these conditions (see section 4.8).

Severe skin and hypersensitivity reactions

Severe, potentially life-threatening, and fatal skin reactions have been reported in patients taking raltegravir, in most cases concomitantly with other medicinal products associated with these reactions. These include cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. Hypersensitivity reactions have also been reported and were characterised by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure. Discontinue 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 oedema, 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.

Rash

Rash occurred more commonly in treatment-experienced patients receiving regimens containing raltegravir and darunavir compared to patients receiving raltegravir without darunavir or darunavir without raltegravir (see section 4.8).

Chewable tablet 25 mg

Fructose

This medicinal product contains fructose up to 0.54 mg per tablet.
Fructose may damage teeth.

Sorbitol

This medicinal product contains sorbitol (E 420) up to 1.5 mg per tablet.
In medicinal products for oral use, sorbitol may affect the bioavailability of other medicinal products for oral use administered concomitantly.

Aspartame

This medicinal product contains aspartame (E 951), a source of phenylalanine. Each 25 mg chewable tablet contains up to 0.47 mg aspartame, corresponding to up to 0.05 mg phenylalanine. It may be harmful for patients with phenylketonuria.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

Sucrose

This medicinal product contains up to 3.5 mg sucrose in each 25 mg chewable tablet.
May be harmful to the teeth.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Chewable tablet 100 mg

Fructose

This medicinal product contains fructose up to 1.07 mg per tablet.
Fructose may damage teeth.

Sorbitol

This medicinal product contains sorbitol (E 420) up to 2.9 mg per tablet.
In medicinal products for oral use, sorbitol may affect the bioavailability of other medicinal products for oral use administered concomitantly.

Aspartame

This medicinal product contains aspartame (E 951), a source of phenylalanine. Each 100 mg chewable tablet contains up to 0.93 mg aspartame, corresponding to up to 0.10 mg phenylalanine. It may be harmful for patients with phenylketonuria.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Sucrose

This medicinal product contains up to 7 mg sucrose in each 100 mg chewable tablet.
May be harmful to the teeth.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies indicate that raltegravir is not a substrate of cytochrome P450 (CYP) enzymes, does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A, does not inhibit UDP glucuronosyltransferases (UGTs) 1A1 and 2B7, does not induce CYP3A4 and does not inhibit P-glycoprotein-mediated transport. Based on these data, raltegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of these enzymes or P-glycoprotein.

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

Considerable inter- and intra-individual variability was observed in the pharmacokinetics of raltegravir.

Effect of raltegravir on the pharmacokinetics of other medicinal products

In interaction studies, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of etravirine, maraviroc, tenofovir disoproxil fumarate, hormonal contraceptives, methadone, midazolam or boceprevir.

In some studies, co-administration of raltegravir with darunavir resulted in a modest decrease in darunavir plasma concentrations; the mechanism for this effect is unknown. However, the effect of raltegravir on darunavir plasma concentrations does not appear to be clinically meaningful.

Effect of other medicinal products on the pharmacokinetics of raltegravir

Given that raltegravir is metabolised primarily via UGT1A1, caution should be used when co-administering raltegravir with strong inducers of UGT1A1 (e.g., rifampicin). Rifampicin reduces plasma levels of raltegravir; the impact on the efficacy of raltegravir is unknown. However, if co-administration with rifampicin is unavoidable, a doubling of the dose of raltegravir can be considered in adults. There are no data to guide co-administration of raltegravir with rifampicin in patients below 18 years of age (see section 4.4). The impact of other strong inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown. Less potent inducers (e.g., efavirenz, nevirapine, etravirine, rifabutin, glucocorticoids, St. John's wort, pioglitazone) may be used with the recommended dose of raltegravir.

Co-administration of raltegravir with medicinal products that are known to be potent UGT1A1 inhibitors (e.g., atazanavir) may increase plasma levels of raltegravir. Less potent UGT1A1 inhibitors (e.g., indinavir, saquinavir) may also increase plasma levels of raltegravir, but to a lesser extent compared with atazanavir. In addition, tenofovir disoproxil fumarate may increase plasma levels of raltegravir, however, the mechanism for this effect is unknown (see Table 3). From the clinical trials, a large proportion of patients used atazanavir and / or tenofovir disoproxil fumarate, both agents that result in increases in raltegravir plasma levels, in the optimised background regimens. The safety profile observed in patients who used atazanavir and / or tenofovir disoproxil fumarate was generally similar to the safety profile of patients who did not use these agents. Therefore, no dose adjustment is required.

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

Co-administration of raltegravir with other agents that increase gastric pH (e.g., omeprazole and famotidine) may increase the rate of raltegravir absorption and result in increased plasma levels of raltegravir (see Table 3). Safety profiles in the subgroup of patients in Phase III trials taking proton pump inhibitors or H2 antagonists were comparable with those who were not taking these antacids. Therefore, no dose adjustment is required with use of proton pump inhibitors or H2 antagonists.

All interaction studies have been performed in adults.

Table 3
Pharmacokinetic Interaction Data in Adults

Medicinal products by therapeutic area	**Interaction** (mechanism, if known)	**Recommendations concerning co-administration**
ANTI-RETROVIRAL		
Protease inhibitors (PI)		
atazanavir /ritonavir (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 41 % raltegravir C_{12hr} ↑ 77 % raltegravir C_{max} ↑ 24 % (UGT1A1 inhibition)	No dose adjustment required for raltegravir.

Medicinal products by therapeutic area	**Interaction** (mechanism, if known)	**Recommendations concerning co-administration**
tipranavir /ritonavir (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 24 % raltegravir C_{12hr} ↓ 55 % raltegravir C_{max} ↓ 18 % (UGT1A1 induction)	No dose adjustment required for raltegravir.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
efavirenz (raltegravir 400 mg Single Dose)	raltegravir AUC ↓ 36 % raltegravir C_{12hr} ↓ 21 % raltegravir C_{max} ↓ 36 % (UGT1A1 induction)	No dose adjustment required for raltegravir.
etravirine (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 10 % raltegravir C_{12hr} ↓ 34 % raltegravir C_{max} ↓ 11 % (UGT1A1 induction) etravirine AUC ↑ 10 % etravirine C_{12hr} ↑ 17 % etravirine C_{max} ↑ 4 %	No dose adjustment required for raltegravir or etravirine.
Nucleoside/tide reverse transcriptase inhibitors		
tenofovir disoproxil fumarate (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 49 % raltegravir C_{12hr} ↑ 3 % raltegravir C_{max} ↑ 64 % (mechanism of interaction unknown) tenofovir AUC ↓ 10 % tenofovir C_{24hr} ↓ 13 % tenofovir C_{max} ↓ 23 %	No dose adjustment required for raltegravir or tenofovir disoproxil fumarate.
CCR5 inhibitors		
maraviroc (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 37 % raltegravir C_{12hr} ↓ 28 % raltegravir C_{max} ↓ 33 % (mechanism of interaction unknown) maraviroc AUC ↓ 14 % maraviroc C_{12hr} ↓ 10 % maraviroc C_{max} ↓ 21 %	No dose adjustment required for raltegravir or maraviroc.
HCV ANTIVIRALS		
NS3/4A protease inhibitors (PI)		
boceprevir (raltegravir 400 mg Single Dose)	raltegravir AUC ↑ 4 % raltegravir C_{12hr} ↓ 25 % raltegravir C_{max} ↑ 11 % (mechanism of interaction unknown)	No dose adjustment required for raltegravir or boceprevir.

Medicinal products by therapeutic area	Interaction (mechanism, if known)	Recommendations concerning co-administration
ANTIMICROBIALS		
Antimycobacterial		
rifampicin (raltegravir 400 mg Single Dose)	raltegravir AUC ↓ 40 % raltegravir C_{12hr} ↓ 61 % raltegravir C_{max} ↓ 38 % (UGT1A1 induction)	Rifampicin reduces plasma levels of raltegravir. If co-administration with rifampicin is unavoidable, a doubling of the dose of raltegravir can be considered (see section 4.4).
SEDATIVE		
midazolam (raltegravir 400 mg Twice Daily)	midazolam AUC ↓ 8 % midazolam C_{max} ↑ 3 %	No dosage adjustment required for raltegravir or midazolam. These results indicate that raltegravir is not an inducer or inhibitor of CYP3A4, and raltegravir is thus not anticipated to affect the pharmacokinetics of medicinal products which are CYP3A4 substrates.
METAL CATION ANTACIDS		
aluminium and magnesium hydroxide antacid (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 49 % raltegravir $C_{12\ hr}$ ↓ 63 % raltegravir C_{max} ↓ 44 % <u>2 hours before raltegravir</u> raltegravir AUC ↓ 51 % raltegravir $C_{12\ hr}$ ↓ 56 % raltegravir C_{max} ↓ 51 % <u>2 hours after raltegravir</u> raltegravir AUC ↓ 30 % raltegravir $C_{12\ hr}$ ↓ 57 % raltegravir C_{max} ↓ 24 % <u>6 hours before raltegravir</u> raltegravir AUC ↓ 13 % raltegravir $C_{12\ hr}$ ↓ 50 % raltegravir C_{max} ↓ 10 % <u>6 hours after raltegravir</u> raltegravir AUC ↓ 11 % raltegravir $C_{12\ hr}$ ↓ 49 % raltegravir C_{max} ↓ 10 % (chelation of metal cations)	Aluminium and magnesium containing antacids reduce raltegravir plasma levels. Co-administration of raltegravir with aluminium and/or magnesium containing antacids is not recommended.
calcium carbonate antacid (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 55 % raltegravir $C_{12\ hr}$ ↓ 32 % raltegravir C_{max} ↓ 52 % (chelation of metal cations)	No dose adjustment required for raltegravir.
Other METAL CATION		

Medicinal products by therapeutic area	Interaction (mechanism, if known)	Recommendations concerning co-administration
Iron salts	Expected: Raltegravir AUC ↓ (chelation of metal cations)	Given simultaneously iron salts are expected to reduce raltegravir plasma levels; taking iron salts at least two hours from the administration of raltegravir may allow to limit this effect.
H2 BLOCKERS AND PROTON PUMP INHIBITORS		
omeprazole (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 37 % raltegravir $C_{12\ hr}$ ↑ 24 % raltegravir C_{max} ↑ 51 % (increased solubility)	No dose adjustment required for raltegravir.
famotidine (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 44 % raltegravir $C_{12\ hr}$ ↑ 6 % raltegravir C_{max} ↑ 60 % (increased solubility)	No dose adjustment required for raltegravir.
HORMONAL CONTRACEPTIVES		
Ethinyl Estradiol **Norelgestromin** (raltegravir 400 mg Twice Daily)	Ethinyl Estradiol AUC ↓ 2 % Ethinyl Estradiol C_{max} ↑ 6 % Norelgestromin AUC ↑ 14 % Norelgestromin C_{max} ↑ 29 %	No dosage adjustment required for raltegravir or hormonal contraceptives (estrogen- and/or progesterone-based).
OPIOID ANALGESICS		
methadone (raltegravir 400 mg Twice Daily)	methadone AUC ↔ methadone C_{max} ↔	No dose adjustment required for raltegravir or methadone.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data for the use of raltegravir chewable tablets in pregnant women. A large amount of data on pregnant women with exposure to raltegravir 400 mg twice daily during the first trimester (more than 1,000 prospective pregnancy outcomes) indicates no malformative toxicity. Animal studies have shown reproductive toxicity (see section 5.3).
A moderate amount of data on pregnant women with exposure to raltegravir 400 mg twice daily during the second and/or third trimester (between 300-1,000 prospective pregnancy outcomes) indicates no increased risk of feto/neonatal toxicity.

Raltegravir chewable tablets should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus. See section 4.2 for dosing recommendations.

Anti-retroviral Pregnancy Registry
To monitor maternal-foetal outcomes in patients inadvertently administered raltegravir while pregnant, an Anti-retroviral Pregnancy Registry has been established. Physicians are encouraged to register patients in this registry.

As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account in order to characterise the safety for the foetus.

Breast-feeding

Raltegravir/metabolites are excreted in human milk to such an extent that effects on the breastfed newborns/infants are likely. Available pharmacodynamics/toxicological data in animals have shown excretion of raltegravir/metabolites in milk (for details see section 5.3).

A risk to the newborns/infants cannot be excluded.

It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

Fertility

No effect on fertility was seen in male and female rats at doses up to 600 mg/kg/day which resulted in 3-fold exposure above the exposure at the recommended human dose.

4.7 Effects on ability to drive and use machines

Dizziness has been reported in some patients during treatment with regimens containing raltegravir. Dizziness may influence some patients' ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

In randomised clinical trials raltegravir 400 mg twice daily was administered in combination with fixed or optimised background treatment regimens to treatment-naïve (N=547) and treatment-experienced (N=462) adults for up to 96 weeks. A further 531 treatment-naïve adults have received raltegravir 1,200 mg once daily with emtricitabine and tenofovir disoproxil fumarate for up to 96 weeks. See section 5.1.

The most frequently reported adverse reactions during treatment were headache, nausea and abdominal pain. The most frequently reported serious adverse reaction was immune reconstitution syndrome and rash. The rates of discontinuation of raltegravir due to adverse reactions were 5 % or less in clinical trials.

Rhabdomyolysis was an uncommonly reported serious adverse reaction in post-marketing use of raltegravir 400 mg twice daily.

Tabulated summary of adverse reactions

Adverse reactions considered by investigators to be causally related to raltegravir (alone or in combination with other ART), as well as adverse reactions established in post-marketing experience, are listed below by System Organ Class. Frequencies are defined as common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reactions Raltegravir (alone or in combination with other ART)
Infections and infestations	Uncommon	genital herpes, folliculitis, gastroenteritis, herpes simplex, herpes virus infection, herpes zoster, influenza, lymph node abscess, molluscum contagiosum, nasopharyngitis, upper respiratory tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Uncommon	skin papilloma

System Organ Class	Frequency	Adverse reactions Raltegravir (alone or in combination with other ART)
Blood and lymphatic system disorders	Uncommon	anaemia, iron deficiency anaemia, lymph node pain, lymphadenopathy, neutropenia, thrombocytopenia
Immune system disorders	Uncommon	immune reconstitution syndrome, drug hypersensitivity, hypersensitivity
Metabolism and nutrition disorders	Common Uncommon	decreased appetite cachexia, diabetes mellitus, dyslipidaemia, hypercholesterolaemia, hyperglycaemia, hyperlipidaemia, hyperphagia, increased appetite, polydipsia, body fat disorder
Psychiatric disorders	Common Uncommon	abnormal dreams, insomnia, nightmare, abnormal behaviour, depression mental disorder, suicide attempt, anxiety, confusional state, depressed mood, major depression, middle insomnia, mood altered, panic attack, sleep disorder, suicidal ideation, suicidal behaviour (particularly in patients with a pre-existing history of psychiatric illness)
Nervous system disorders	Common Uncommon	dizziness, headache, psychomotor hyperactivity amnesia, carpal tunnel syndrome, cognitive disorder, disturbance in attention, dizziness postural, dysgeusia, hypersomnia, hypoaesthesia, lethargy, memory impairment, migraine, neuropathy peripheral, paraesthesia, somnolence, tension headache, tremor, poor quality sleep
Eye disorders	Uncommon	visual impairment
Ear and labyrinth disorders	Common Uncommon	vertigo tinnitus
Cardiac disorders	Uncommon	palpitations, sinus bradycardia, ventricular extrasystoles
Vascular disorders	Uncommon	hot flush, hypertension
Respiratory, thoracic and mediastinal disorders	Uncommon	dysphonia, epistaxis, nasal congestion
Gastrointestinal disorders	Common Uncommon	abdominal distention, abdominal pain, diarrhoea, flatulence, nausea, vomiting, dyspepsia gastritis, abdominal discomfort, abdominal pain upper, abdominal tenderness, anorectal discomfort, constipation, dry mouth, epigastric discomfort, erosive duodenitis, eructation, gastroesophageal reflux disease, gingivitis, glossitis, odynophagia, pancreatitis acute, peptic ulcer, rectal haemorrhage
Hepato-biliary disorders	Uncommon	hepatitis, hepatic steatosis, hepatitis alcoholic, hepatic failure

System Organ Class	Frequency	Adverse reactions Raltegravir (alone or in combination with other ART)
Skin and subcutaneous tissue disorders	Common Uncommon	rash acne, alopecia, dermatitis acneiforme, dry skin, erythema, facial wasting, hyperhidrosis, lipoatrophy, lipodystrophy acquired, lipohypertrophy, night sweats, prurigo, pruritus, pruritus generalised, rash macular, rash maculo-papular, rash pruritic, skin lesion, urticaria, xeroderma, Stevens Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Uncommon	arthralgia, arthritis, back pain, flank pain, musculoskeletal pain, myalgia, neck pain, osteopenia, pain in extremity, tendonitis, rhabdomyolysis
Renal and urinary disorders	Uncommon	renal failure, nephritis, nephrolithiasis, nocturia, renal cyst, renal impairment, tubulointerstitial nephritis
Reproductive system and breast disorders	Uncommon	erectile dysfunction, gynaecomastia, menopausal symptoms
General disorders and administration site conditions	Common Uncommon	asthenia, fatigue, pyrexia chest discomfort, chills, face oedema, fat tissue increased, feeling jittery, malaise, submandibular mass, oedema peripheral, pain
Investigations	Common Uncommon	alanine aminotransferase increased, atypical lymphocytes, aspartate aminotransferase increased, blood triglycerides increased, lipase increased, blood pancreatic amylase increased absolute neutrophil count decreased, alkaline phosphatase increased, blood albumin decreased, blood amylase increased, blood bilirubin increased, blood cholesterol increased, blood creatinine increased, blood glucose increased, blood urea nitrogen increased, creatine phosphokinase increased, fasting blood glucose increased, glucose urine present, high density lipoprotein increased, international normalised ratio increased, low density lipoprotein increased, platelet count decreased, red blood cells urine positive, waist circumference increased, weight increased, white blood cell count decreased
Injury, poisoning and procedural complications	Uncommon	accidental overdose

Description of selected adverse reactions

Cancers were reported in treatment-experienced and treatment-naïve patients who initiated raltegravir in conjunction with other antiretroviral agents. The types and rates of specific cancers were those expected in a highly immunodeficient population. The risk of developing cancer in these studies was similar in the groups receiving raltegravir and in the groups receiving comparators.

Grade 2-4 creatine kinase laboratory abnormalities were observed in patients treated with raltegravir. Myopathy and rhabdomyolysis have been reported. Use with caution in patients who have had myopathy or rhabdomyolysis in the past or have any predisposing issues including other medicinal products associated with these conditions (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

For each of the following clinical adverse reactions there was at least one serious occurrence: genital herpes, anaemia, immune reconstitution syndrome, depression, mental disorder, suicide attempt, gastritis, hepatitis, renal failure, accidental overdose.

In clinical studies of treatment-experienced patients, rash, irrespective of causality, was more commonly observed with regimens containing raltegravir and darunavir compared to those containing raltegravir without darunavir or darunavir without raltegravir. Rash considered by the investigator to be drug-related occurred at similar rates. The exposure-adjusted rates of rash (all causality) were 10.9, 4.2, and 3.8 per 100 patient-years (PYR), respectively; and for drug-related rash were 2.4, 1.1, and 2.3 per 100 PYR, respectively. The rashes observed in clinical studies were mild to moderate in severity and did not result in discontinuation of therapy (see section 4.4).

Patients co-infected with hepatitis B and/or hepatitis C virus
In clinical trials, there were 79 patients co-infected with hepatitis B, 84 co-infected with hepatitis C, and 8 patients co-infected with hepatitis B and C who were treated with raltegravir in combination with other agents for HIV-1. In general, the safety profile of raltegravir in patients with hepatitis B and/or hepatitis C virus co-infection was similar to that in patients without hepatitis B and/or hepatitis C virus co-infection, although the rates of AST and ALT abnormalities were somewhat higher in the subgroup co-infected with hepatitis B and/or hepatitis C virus

At 96-weeks, in treatment-experienced patients, 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 patients treated with raltegravir as compared to 11 %, 10 % and 9 % of all other patients treated with raltegravir. At 240-weeks, in treatment-naïve patients, 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 patients treated with raltegravir as compared to 13 %, 13 % and 5 % of all other patients treated with raltegravir.

Paediatric population

Children and adolescents 2 to 18 years of age
Raltegravir has been studied in 126 antiretroviral treatment-experienced HIV-1 infected children and adolescents 2 to 18 years of age, in combination with other antiretroviral agents in IMPAACT P1066 (see sections 5.1 and 5.2). Of the 126 patients, 96 received the recommended dose of raltegravir.

In these 96 children and adolescents, frequency, type and severity of drug related adverse reactions through Week 48 were comparable to those observed in adults.

One patient experienced drug related clinical adverse reactions of Grade 3 psychomotor hyperactivity, abnormal behaviour and insomnia; one patient experienced a Grade 2 serious drug related allergic rash.

One patient experienced drug related laboratory abnormalities, Grade 4 AST and Grade 3 ALT, which were considered serious.

Infants and toddlers 4 weeks to less than 2 years of age
Raltegravir has 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 sections 5.1 and 5.2).

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
In IMPAACT P1110 (see section 5.2) eligible infants were at least 37 weeks gestation and at least 2 kg in weight. Sixteen (16) neonates received 2 doses of ISENTRESS in first 2 weeks of life, and 26 neonates received 6 weeks of daily dosing; all were followed for 24 weeks. There were no drug related clinical adverse experiences and three drug-related laboratory adverse experiences (one a transient Grade 4 neutropenia in a subject receiving zidovudine containing 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).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No specific information is available on the treatment of overdose with raltegravir.

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. It should be taken into account that raltegravir is presented for clinical use as the potassium salt. The extent to which raltegravir may be dialysable is unknown.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, integrase inhibitors, ATC code: J05AJ01.

Mechanism of action

Raltegravir is an integrase strand transfer inhibitor active against the Human Immunodeficiency Virus (HIV-1). Raltegravir inhibits the catalytic activity of integrase, an HIV-encoded enzyme that is required for viral replication. Inhibition of integrase prevents the covalent insertion, or integration, of the HIV genome into the host cell genome. HIV genomes that fail to integrate cannot direct the production of new infectious viral particles, so inhibiting integration prevents propagation of the viral infection.

Antiviral activity *in vitro*

Raltegravir at concentrations of 31 ± 20 nM resulted in 95 % inhibition (IC_{95}) of HIV-1 replication (relative to an untreated virus-infected culture) in human T-lymphoid cell cultures infected with the cell-line adapted HIV-1 variant H9IIIB. In addition, raltegravir inhibited viral replication in cultures of mitogen-activated human peripheral blood mononuclear cells infected with diverse, primary clinical isolates of HIV-1, including isolates from 5 non-B subtypes, and isolates resistant to reverse transcriptase inhibitors and protease inhibitors. In a single-cycle infection assay, raltegravir inhibited infection of 23 HIV isolates representing 5 non-B subtypes and 5 circulating recombinant forms with IC_{50} values ranging from 5 to 12 nM.

Resistance

Most viruses isolated from patients failing raltegravir had high-level raltegravir resistance resulting from the appearance of two or more mutations in integrase. Most had a signature mutation at amino acid 155 (N155 changed to H), amino acid 148 (Q148 changed to H, K, or R), or amino acid 143 (Y143 changed to H, C, or R), along with one or more additional integrase mutations (e.g., L74M, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, S230R). The signature mutations decrease viral susceptibility to raltegravir and addition of other mutations results in a further decrease in raltegravir susceptibility. Factors that reduced the likelihood of developing resistance included lower baseline viral load and use of other active anti-retroviral agents. Mutations conferring resistance to raltegravir generally also confer resistance to the integrase strand transfer inhibitor elvitegravir. Mutations at amino acid 143 confer greater resistance to raltegravir than to elvitegravir, and the E92Q mutation confers greater resistance to elvitegravir than to raltegravir. Viruses harbouring a mutation at amino acid 148, along with one or more other raltegravir resistance mutations, may also have clinically significant resistance to dolutegravir.

Clinical experience

The evidence of efficacy of raltegravir was based on the analyses of 96-week data from two randomised, double-blind, placebo-controlled trials (BENCHMRK 1 and BENCHMRK 2, Protocols 018 and 019) in antiretroviral treatment-experienced HIV-1 infected adult patients and the analysis of 240-week data from a randomised, double-blind, active-control trial (STARTMRK, Protocol 021) in antiretroviral treatment-naïve HIV-1 infected adult patients.

Efficacy

Treatment-experienced adult patients
BENCHMRK 1 and BENCHMRK 2 (multi-centre, randomised, double-blind, placebo-controlled trials) evaluated the safety and anti-retroviral activity of raltegravir 400 mg twice daily vs. placebo in a combination with optimised background therapy (OBT), in HIV-infected patients, 16 years or older, with documented resistance to at least 1 drug in each of 3 classes (NRTIs, NNRTIs, PIs) of anti-retroviral therapies. Prior to randomisation, OBT were selected by the investigator based on the patient's prior treatment history, as well as baseline genotypic and phenotypic viral resistance testing

Patient demographics (gender, age and race) and baseline characteristics were comparable between the groups receiving raltegravir 400 mg twice daily and placebo. Patients had prior exposure to a median of 12 anti-retrovirals for a median of 10 years. A median of 4 ARTs was used in OBT.

Results 48 week and 96 week analyses
Durable outcomes (Week 48 and Week 96) for patients on the recommended dose raltegravir 400 mg twice daily from the pooled studies BENCHMRK 1 and BENCHMRK 2 are shown in Table 4.

Table 4
Efficacy Outcome at Weeks 48 and 96

BENCHMRK 1 and 2 Pooled	48 Weeks		96 Weeks	
Parameter	**Raltegravir 400 mg twice daily + OBT (N = 462)**	**Placebo + OBT (N = 237)**	**Raltegravir 400 mg twice daily + OBT (N = 462)**	**Placebo + OBT (N = 237)**
Percent HIV-RNA < 400 copies/mL (95 % CI)				
All patients†	72 (68, 76)	37 (31, 44)	62 (57, 66)	28 (23, 34)
Baseline Characteristic‡				
HIV-RNA > 100,000 copies/mL	62 (53, 69)	17 (9, 27)	53 (45, 61)	15 (8, 25)
≤ 100,000 copies/mL	82 (77, 86)	49 (41, 58)	74 (69, 79)	39 (31, 47)
CD4-count ≤ 50 cells/mm^3	61 (53, 69)	21 (13, 32)	51 (42, 60)	14 (7, 24)
> 50 and ≤ 200 cells/mm^3	80 (73, 85)	44 (33, 55)	70 (62, 77)	36 (25, 48)
> 200 cells/mm^3	83 (76, 89)	51 (39, 63)	78 (70, 85)	42 (30, 55)
Sensitivity score (GSS) §				
0	52 (42, 61)	8 (3, 17)	46 (36, 56)	5 (1, 13)
1	81 (75, 87)	40 (30, 51)	76 (69, 83)	31 (22, 42)
2 and above	84 (77, 89)	65 (52, 76)	71 (63, 78)	56 (43, 69)
Percent HIV-RNA < 50 copies/mL (95 % CI)				
All patients†	62 (57, 67)	33 (27, 39)	57 (52, 62)	26 (21, 32)
Baseline Characteristic‡				
HIV-RNA > 100,000 copies/mL	48 (40, 56)	16 (8, 26)	47 (39, 55)	13 (7, 23)
≤ 100,000 copies/mL	73 (68, 78)	43 (35, 52)	70 (64, 75)	36 (28, 45)
CD4-count ≤ 50 cells/mm^3	50 (41, 58)	20 (12, 31)	50 (41, 58)	13 (6, 22)
> 50 and ≤ 200 cells/mm^3	67 (59, 74)	39 (28, 50)	65 (57, 72)	32 (22, 44)
> 200 cells/mm^3	76 (68, 83)	44 (32, 56)	71 (62, 78)	41 (29, 53)
Sensitivity score (GSS) §				
0	45 (35, 54)	3 (0, 11)	41 (32, 51)	5 (1, 13)
1	67 (59, 74)	37 (27, 48)	72 (64, 79)	28 (19, 39)
2 and above	75 (68, 82)	59 (46, 71)	65 (56, 72)	53 (40, 66)
Mean CD4 Cell Change (95 % CI), cells/mm^3				
All patients‡	109 (98, 121)	45 (32, 57)	123 (110, 137)	49 (35, 63)
Baseline Characteristic‡				
HIV-RNA > 100,000 copies/mL	126 (107, 144)	36 (17, 55)	140 (115, 165)	40 (16, 65)
≤ 100,000 copies/mL	100 (86, 115)	49 (33, 65)	114 (98, 131)	53 (36, 70)
CD4-count ≤ 50 cells/mm^3	121 (100, 142)	33 (18, 48)	130 (104, 156)	42 (17, 67)
> 50 and ≤ 200 cells/mm^3	104 (88, 119)	47 (28, 66)	123 (103, 144)	56 (34, 79)
> 200 cells/mm^3	104 (80, 129)	54 (24, 84)	117 (90, 143)	48 (23, 73)
Sensitivity score (GSS) §				
0	81 (55, 106)	11 (4, 26)	97 (70, 124)	15 (-0, 31)
1	113 (96, 130)	44 (24, 63)	132 (111, 154)	45 (24, 66)
2 and above	125 (105, 144)	76 (48, 103)	134 (108, 159)	90 (57, 123)

† Non-completer is failure imputation: patients who discontinued prematurely are imputed as failure thereafter. Percent of patients with response and associated 95 % confidence interval (CI) are reported.

‡ For analysis by prognostic factors, virologic failures were carried forward for percent < 400 and 50 copies/mL. For mean CD4 changes, baseline-carry-forward was used for virologic failures.

§ The Genotypic Sensitivity Score (GSS) was defined as the total oral ARTs in the optimised background therapy (OBT) to which a patient's viral isolate showed genotypic sensitivity based upon genotypic resistance test. Enfuvirtide use in OBT in enfuvirtide-naïve patients was counted as one active drug in OBT. Similarly, darunavir use in OBT in darunavir-naïve patients was counted as one active drug in OBT.

Raltegravir achieved virologic responses (using Not Completer=Failure approach) of HIV RNA < 50 copies/mL in 61.7 % of patients at Week 16, in 62.1 % at Week 48 and in 57.0 % at Week 96. Some patients experienced viral rebound between Week 16 and Week 96. Factors associated with failure include high baseline viral load and OBT that did not include at least one potent active agent.

Switch to raltegravir
The SWITCHMRK 1 & 2 (Protocols 032 & 033) studies evaluated HIV-infected patients receiving suppressive (screening HIV RNA < 50 copies/mL; stable regimen > 3 months) therapy with lopinavir 200 mg (+) ritonavir 50 mg 2 tablets twice daily plus at least 2 nucleoside reverse transcriptase inhibitors and randomised them 1:1 to continue lopinavir (+) ritonavir 2 tablets twice daily (n=174 and n=178, respectively) or replace lopinavir (+) ritonavir with raltegravir 400 mg twice daily (n=174 and n=176, respectively). Patients with a prior history of virological failure were not excluded and the number of previous antiretroviral therapies was not limited.

These studies were terminated after the primary efficacy analysis at Week 24 because they failed to demonstrate non-inferiority of raltegravir versus lopinavir (+) ritonavir. In both studies at Week 24, suppression of HIV RNA to less than 50 copies/mL was maintained in 84.4 % of the raltegravir group versus 90.6 % of the lopinavir (+) ritonavir group, (Non-completers = Failure). See section 4.4 regarding the need to administer raltegravir with two other active agents.

Treatment-naïve adult patients
STARTMRK (multi-centre, randomised, double-blind, active-control trial) evaluated the safety and anti-retroviral activity of raltegravir 400 mg twice daily vs. efavirenz 600 mg at bedtime, in a combination with emtricitabine (+) tenofovir disoproxil fumarate, in treatment-naïve HIV-infected patients with HIV RNA > 5,000 copies/mL. Randomisation was stratified by screening HIV RNA level (≤ 50,000 copies/mL; and > 50,000 copies/mL) and by hepatitis B or C status (positive or negative).

Patient demographics (gender, age and race) and baseline characteristics were comparable between the group receiving raltegravir 400 mg twice daily and the group receiving efavirenz 600 mg at bedtime.

Results 48-week and 240-week analyses
With respect to the primary efficacy endpoint, the proportion of patients achieving HIV RNA < 50 copies/mL at Week 48 was 241/280 (86.1 %) in the group receiving raltegravir and 230/281 (81.9 %) in the group receiving efavirenz. The treatment difference (raltegravir – efavirenz) was 4.2 % with an associated 95 % CI of (-1.9, 10.3) establishing that raltegravir is non-inferior to efavirenz (p-value for non-inferiority < 0.001). At Week 240, the treatment difference (raltegravir – efavirenz) was 9.5 % with an associated 95 % CI of (1.7, 17.3). Week 48 and Week 240 outcomes for patients on the recommended dose of raltegravir 400 mg twice daily from STARTMRK are shown in Table 5.

Table 5
Efficacy Outcome at Weeks 48 and 240

STARTMRK Study	**48 Weeks**		**240 Weeks**	
Parameter	**Raltegravir 400 mg twice daily (N = 281)**	**Efavirenz 600 mg at bedtime (N = 282)**	**Raltegravir 400 mg twice daily (N = 281)**	**Efavirenz 600 mg at bedtime (N = 282)**
Percent HIV-RNA < 50 copies/mL (95 % CI)				
All patients[†]	86 (81, 90)	82 (77, 86)	71 (65, 76)	61 (55, 67)
Baseline Characteristic[‡]				
HIV-RNA > 100,000 copies/mL	91 (85, 95)	89 (83, 94)	70 (62, 77)	65 (56, 72)
≤ 100,000 copies/mL	93 (86, 97)	89 (82, 94)	72 (64, 80)	58 (49, 66)
CD4-count ≤ 50 cells/mm^3	84 (64, 95)	86 (67, 96)	58 (37, 77)	77 (58, 90)
> 50 and ≤ 200 cells/mm^3	89 (81, 95)	86 (77, 92)	67 (57, 76)	60 (50, 69)
> 200 cells/mm^3	94 (89, 98)	92 (87, 96)	76 (68, 82)	60 (51, 68)
Viral Subtype Clade B	90 (85, 94)	89 (83, 93)	71 (65, 77)	59 (52, 65)
Non-Clade B	96 (87, 100)	91 (78, 97)	68 (54, 79)	70 (54, 82)

STARTMRK Study	48 Weeks		240 Weeks	
Parameter	**Raltegravir 400 mg twice daily (N = 281)**	**Efavirenz 600 mg at bedtime (N = 282)**	**Raltegravir 400 mg twice daily (N = 281)**	**Efavirenz 600 mg at bedtime (N = 282)**
Mean CD4 Cell Change (95 % CI), cells/mm^3				
All patients‡	189 (174, 204)	163 (148, 178)	374 (345, 403)	312 (284, 339)
Baseline Characteristic‡				
HIV-RNA > 100,000 copies/mL	196 (174, 219)	192 (169, 214)	392 (350, 435)	329 (293, 364)
≤ 100,000 copies/mL	180 (160, 200)	134 (115, 153)	350 (312, 388)	294 (251, 337)
CD4-count ≤ 50 cells/mm^3	170 (122, 218)	152 (123, 180)	304 (209, 399)	314 (242, 386)
> 50 and ≤ 200 cells/mm^3	193 (169, 217)	175 (151, 198)	413 (360, 465)	306 (264, 348)
> 200 cells/mm^3	190 (168, 212)	157 (134, 181)	358 (321, 395)	316 (272, 359)
Viral Subtype Clade B	187 (170, 204)	164 (147, 181)	380 (346, 414)	303 (272, 333)
Non-Clade B	189 (153, 225)	156 (121, 190)	332 (275, 388)	329 (260, 398)

† Non-completer is failure imputation: patients who discontinued prematurely are imputed as failure thereafter. Percent of patients with response and associated 95 % confidence interval (CI) are reported.

‡ For analysis by prognostic factors, virologic failures were carried forward for percent < 50 and 400 copies/mL. For mean CD4 changes, baseline-carry-forward was used for virologic failures.

Notes: The analysis is based on all available data.

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

Paediatric population

Children and adolescents 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. Patients were stratified by age, enrolling adolescents first and then successively younger children. Patients received either the 400 mg tablet formulation (6 to 18 years of age) or the chewable tablet formulation (2 to less than 12 years of age). Raltegravir was administered with an optimised background regimen.

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

Table 6
Baseline Characteristics and Efficacy Outcomes at Weeks 24 and 48 from IMPAACT P1066 (2 to 18 years of age)

Parameter	**Final dose population N=96**
Demographics	
Age (years), median [range]	13 [2 – 18]
Male Gender	49 %
Race	
Caucasian	34 %
Black	59 %
Baseline Characteristics	
Plasma HIV-1 RNA (log_{10} copies/mL), mean [range]	4.3 [2.7 - 6]
CD4 cell count (cells/mm^3), median [range]	481 [0 – 2361]
CD4 percent, median [range]	23.3 % [0 – 44]
HIV-1 RNA >100,000 copies/mL	8 %
CDC HIV category B or C	59 %

Parameter	Final dose population	
	N=96	
Prior ART Use by Class		
NNRTI	78 %	
PI	83 %	
Response	**Week 24**	**Week 48**
Achieved ≥1 log_{10} HIV RNA drop from baseline or <400 copies/mL	72 %	79 %
Achieved HIV RNA <50 copies/mL	54 %	57 %
Mean CD4 cell count (%) increase from baseline	119 cells/mm^3 (3.8 %)	156 cells/mm^3 (4.6 %)

Infants and toddlers 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 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 granules for oral suspension formulation without regard to food in combination with an optimised background regimen that included lopinavir plus ritonavir in two-thirds of patients.

Table 7
Baseline Characteristics and Efficacy Outcomes at Weeks 24 and 48 from IMPAACT P1066 (4 weeks to less than 2 years of age)

Parameter	N=26	
Demographics		
Age (weeks), median [range]	28 [4 -100]	
Male Gender	65 %	
Race		
Caucasian	8 %	
Black	85 %	
Baseline Characteristics		
Plasma HIV-1 RNA (log_{10} copies/mL), mean [range]	5.7 [3.1 - 7]	
CD4 cell count (cells/mm^3), median [range]	1,400 [131 -3,648]	
CD4 percent, median [range]	18.6 % [3.3 – 39.3]	
HIV-1 RNA >100,000 copies/mL	69 %	
CDC HIV category B or C	23 %	
Prior ART Use by Class		
NNRTI	73 %	
NRTI	46%	
PI	19 %	
Response	**Week 24**	**Week 48**
Achieved ≥1 log_{10} HIV RNA drop from baseline or <400 copies/mL	91 %	85 %
Achieved HIV RNA <50 copies/mL	43 %	53 %
Mean CD4 cell count (%) increase from baseline	500 cells/mm^3 (7.5 %)	492 cells/mm^3 (7.8 %)
Virologic failure	**Week 24**	**Week 48**
Non-responder	0	0
Rebounder	0	4
Number with genotype available*	0	2

*One patient had a mutation at the 155 position.

5.2 Pharmacokinetic properties

Absorption

As demonstrated in healthy volunteers administered single oral doses of raltegravir in the fasted state, raltegravir is rapidly absorbed with a t_{max} of approximately 3 hours postdose. Raltegravir AUC and C_{max} increase dose proportionally over the dose range 100 mg to 1,600 mg. Raltegravir $C_{12\ hr}$ 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 1,600 mg. Dose proportionality has not been established in patients.

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

Raltegravir may be administered with or without food. Raltegravir was administered without regard to food in the pivotal safety and efficacy studies in HIV-infected patients. Administration of multiple doses of raltegravir following a moderate-fat meal did not affect raltegravir AUC to a clinically meaningful degree with an increase of 13 % relative to fasting. Raltegravir $C_{12\ hr}$ was 66 % higher and C_{max} was 5 % higher following a moderate-fat meal compared to fasting. Administration of raltegravir following a high-fat meal increased AUC and C_{max} by approximately 2-fold and increased $C_{12\ hr}$ by 4.1-fold. Administration of raltegravir following a low-fat meal decreased AUC and C_{max} by 46 % and 52 %, respectively; $C_{12\ hr}$ was essentially unchanged. Food appears to increase pharmacokinetic variability relative to fasting.

Overall, considerable variability was observed in the pharmacokinetics of raltegravir. For observed $C_{12\ hr}$ in BENCHMRK 1 and 2 the coefficient of variation (CV) for inter-subject variability = 212 % and the CV for intra-subject variability = 122 %. Sources of variability may include differences in co-administration with food and concomitant medicines.

Distribution

Raltegravir is approximately 83 % bound to human plasma protein over the concentration range of 2 to 10 μM.
Raltegravir readily crossed the placenta in rats, but did not penetrate the brain to any appreciable extent.

In two studies of HIV-1 infected patients who received raltegravir 400 mg twice daily, raltegravir was readily detected in the cerebrospinal fluid. In the first study (n=18), the median cerebrospinal fluid concentration was 5.8 % (range 1 to 53.5 %) of the corresponding plasma concentration. In the second study (n=16), the median cerebrospinal fluid concentration was 3 % (range 1 to 61 %) of the corresponding plasma concentration. These median proportions are approximately 3- to 6-fold lower than the free fraction of raltegravir in plasma.

Biotransformation 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 faeces and urine, respectively. In faeces, only raltegravir was present, most of which is likely to be derived from hydrolysis of raltegravir-glucuronide secreted in bile as observed in preclinical species. Two components, namely raltegravir and raltegravir-glucuronide, were detected in urine and accounted for approximately 9 and 23 % of the dose, respectively. The major circulating entity was raltegravir and represented approximately 70 % of the total radioactivity; the remaining radioactivity in plasma was accounted for by raltegravir-glucuronide. Studies using isoform-selective chemical inhibitors and cDNA-expressed UDP-glucuronosyltransferases (UGT) show that UGT1A1 is the main enzyme responsible for the

formation of raltegravir-glucuronide. Thus, the data indicate that the major mechanism of clearance of raltegravir in humans is UGT1A1-mediated glucuronidation.

UGT1A1 Polymorphism
In a comparison of 30 subjects with *28/*28 genotype to 27 subjects with wild-type genotype, the geometric mean ratio (90 % CI) of AUC was 1.41 (0.96, 2.09) and the geometric mean ratio of $C_{12\ hr}$ was 1.91 (1.43, 2.55). Dose adjustment is not considered necessary in subjects with reduced UGT1A1 activity due to genetic polymorphism.

Special populations

Paediatric population
Based on a formulation comparison study in healthy adult volunteers, the chewable tablet and granules for oral suspension have higher oral bioavailability compared to the 400 mg tablet. In this study, administration of the chewable tablet with a high fat meal led to an average 6 % decrease in AUC, 62 % decrease in C_{max}, and 188 % increase in C_{12hr} compared to administration in the fasted state. Administration of the chewable tablet with a high fat meal does not affect raltegravir pharmacokinetics to a clinically meaningful degree and the chewable tablet can be administered without regard to food. The effect of food on the granules for oral suspension formulation was not studied.

Table 8 displays pharmacokinetic parameters in the 400 mg tablet, the chewable tablet), and the granules for oral suspension, by body weight.

Table 8
Raltegravir Pharmacokinetic Parameters IMPAACT P1066 Following Administration of Doses in Section 4.2 (excluding neonates)

Body weight	Formulation	Dose	N*	Geometric mean *(%CV†)* AUC_{0-12hr} (µM●hr)	Geometric mean *(%CV†)* C_{12hr} (nM)
≥ 25 kg	Film-coated tablet	400 mg twice daily	18	14.1 *(121 %)*	233 (*157 %*)
≥ 25 kg	Chewable tablet	Weight based dosing, see dosing Table 1	9	22.1 (*36 %*)	113 (*80 %*)
11 to less than 25 kg	Chewable tablet	Weight based dosing, see dosing Table 2	13	18.6 (*68 %*)	82 (*123 %*)
3 to less than 20 kg	Oral suspension	Weight based dosing, see dosing table for granules for oral suspension	19	24.5 (*43 %*)	113 (*69 %*)
*Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose. †Geometric coefficient of variation.					

Elderly
There was no clinically meaningful effect of age on raltegravir pharmacokinetics in healthy subjects and patients with HIV-1 infection over the age range studied (19 to 84 years, with few individuals over the age of 65).

Gender, race and BMI
There were no clinically important pharmacokinetic differences due to gender, race or body mass index (BMI) in adults.

Renal impairment
Renal clearance of unchanged medicinal product is a minor pathway of elimination. In adults, there were no clinically important pharmacokinetic differences between patients with severe renal insufficiency and healthy subjects (see section 4.2). Because the extent to which raltegravir may be dialysable is unknown, dosing before a dialysis session should be avoided.

Hepatic impairment
Raltegravir is eliminated primarily by glucuronidation in the liver. In adults, there were no clinically important pharmacokinetic differences between patients with moderate hepatic insufficiency and healthy subjects. The effect of severe hepatic insufficiency on the pharmacokinetics of raltegravir has not been studied (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Non-clinical toxicology studies, including conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, developmental toxicity and juvenile toxicity, have been conducted with raltegravir in mice, rats, dogs and rabbits. Effects at exposure levels sufficiently in excess of clinical exposure levels indicate no special hazard for humans.

Mutagenicity

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.

Carcinogenicity

A carcinogenicity study 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 similar to that at the clinical dose of 400 mg twice daily. In rats, tumours (squamous cell carcinoma) of the nose/nasopharynx were identified at 300 and 600 mg/kg/day in females and at 300 mg/kg/day in males. This neoplasia could result from local deposition and/or aspiration of drug on the mucosa of the nose/nasopharynx during oral gavage dosing and subsequent chronic irritation and inflammation; it is likely that it is of limited relevance for the intended clinical use. At the NOAEL, systemic exposure was similar to that at the clinical dose of 400 mg twice daily. Standard genotoxicity studies to evaluate mutagenicity and clastogenicity were negative.

Developmental toxicity

Raltegravir was not teratogenic in developmental toxicity studies in rats and rabbits. A slight increase in incidence of supernumerary ribs, a variant in the normal developmental process, was observed in rat foetuses of dams exposed to raltegravir at approximately 4.4-fold human exposure at 400 mg twice daily based on $AUC_{0\text{-}24\ hr}$. No development effects were seen at 3.4-fold human exposure at 400 mg twice daily based on $AUC_{0\text{-}24\ hr}$. Similar findings were not observed in rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Chewable tablet 25 mg
- Hydroxypropyl cellulose
- Sucralose
- Saccharin sodium
- Sodium citrate dihydrate
- Mannitol (E 421)
- Monoammonium glycyrrhizinate
- Sorbitol (E 420)
- Fructose
- Banana flavour
- Orange flavour
- Masking flavour

- Aspartame (E951)
- Sucrose
- Crospovidone, Type A
- Sodium stearyl fumarate
- Magnesium stearate
- Hypromellose 2910/6cP
- Macrogol/PEG 400
- Ethylcellulose 20 cP
- Ammonium hydroxide
- Medium chain triglycerides
- Oleic acid
- Yellow iron oxide

Chewable tablet 100 mg
- Hydroxypropyl cellulose
- Sucralose
- Saccharin sodium
- Sodium citrate dihydrate
- Mannitol (E 421)
- Monoammonium glycyrrhizinate
- Sorbitol (E 420)
- Fructose
- Banana flavour
- Orange flavour
- Masking flavour
- Aspartame (E 951)
- Sucrose
- Crospovidone, Type A
- Sodium stearyl fumarate
- Magnesium stearate
- Hypromellose 2910/6cP
- Macrogol/PEG 400
- Ethylcellulose 20 cP
- Ammonium hydroxide
- Medium chain triglycerides
- Oleic acid
- Red iron oxide
- Yellow iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep the bottle tightly closed, with the desiccant in order to protect from moisture.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a child-resistant polypropylene closure, induction seal and silica gel desiccant: 60 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/003 – 25 mg
EU/1/07/436/004 – 100 mg

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 December 2007
Date of latest renewal: 14 May 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 100 mg granules for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 100 mg of raltegravir (as potassium). Following reconstitution, the oral suspension has a concentration of 10 mg per mL.

Excipients with known effect
Each sachet contains up to: 0.5 mg fructose, 1.5 mg sorbitol and 4.7 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules for oral suspension.
White to off-white, granular powder that may contain yellow or beige to tan particles, in a single-use sachet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ISENTRESS is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection (see sections 4.2, 4.4, 5.1 and 5.2).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

ISENTRESS should be used in combination with other active anti-retroviral therapies (ARTs) (see sections 4.4 and 5.1).

Because the formulations have different pharmacokinetic profiles neither the granules for oral suspension nor the chewable tablets should be substituted for the 400 mg tablet or 600 mg tablet (see section 5.2). The granules for oral suspension and the chewable tablets have not been studied in HIV-infected adolescents (12 to 18 years) or adults.

Neonates, Infants and Toddlers
Dosing is weight based from birth as specified in Table 1 and Table 2. Patients can remain on the granules for oral suspension as long as their weight is below 20 kg.
For patients weighing between 11 and 20 kg, either the granules for oral suspension or the chewable tablet can be used as specified in Table 1 (see section 5.2). Refer to the chewable tablet SmPC for additional dosing information.
The safety and efficacy of raltegravir in preterm (<37 weeks of gestation) and low birth weight (<2,000 g) newborns have not been established. No data are available in this population and no dosing recommendations can be made.

Table 1
Recommended Dose* for ISENTRESS Granules For Oral Suspension and Chewable Tablets in Paediatric Patients at least 4 weeks of age and weighing 3 to 25 kg

Body Weight (kg)	Volume (Dose) of Suspension to be Administered	Number of Chewable Tablets
3 to less than 4	2.5 mL (25 mg) twice daily	
4 to less than 6	3 mL (30 mg) twice daily	
6 to less than 8	4 mL (40 mg) twice daily	
8 to less than 11	6 mL (60 mg) twice daily	
11 to less than 14†	8 mL (80 mg) twice daily	3 x 25 mg twice daily
14 to less than 20†	10 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 in 10 mL of water is based on approximately 6 mg/kg/dose twice daily (see section 5.2) †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 50 mg doses. However, breaking the tablets should be avoided whenever possible.		

Table 2
Recommended Dose for ISENTRESS For Oral Suspension in Full-Term Neonates (Birth to 4 weeks [28 days] of age*

Note: If the mother has taken ISENTRESS 2-24 hours before delivery, the infant's first dose should be given between 24-48 hours after birth.

Body Weight (kg)	Volume (Dose) of Suspension to be Administered
Birth to 1 Week - Once daily dosing†	
2 to less than 3	0.4 mL (4 mg) once daily
3 to less than 4	0.5 mL (5 mg) once daily
4 to less than 5	0.7 mL (7 mg) once daily
1 to 4 Weeks - Twice daily dosing‡	
2 to less than 3	0.8 mL (8 mg) twice daily
3 to less than 4	1 mL (10 mg) twice daily
4 to less than 5	1.5 mL (15 mg) twice daily
*No data are available in pre-term neonates. The use of ISENTRESS is not recommended in pre-term neonates. †The dosing recommendations are based on approximately: 1.5 mg/kg/dose. ‡The dosing recommendations are based on approximately: 3 mg/kg/dose.	

Maximum dose of oral suspension is 100 mg twice daily.

Each single-use sachet contains 100 mg of raltegravir which is to be suspended in 10 mL of water giving a final concentration of 10 mg per mL (see section 6.6).

Scheduled appointments for the patient should be kept because the ISENTRESS dosage should be adjusted as the child grows.

Additional formulations and strengths available:
ISENTRESS is also available in a 400 mg tablet for use in adults, adolescents and children weighing at least 25 kg and able to swallow a tablet. For patients weighing at least 25 kg but are unable to swallow a tablet, consider the chewable tablet. Refer to the 400 mg and chewable tablet SmPCs for additional dosing information.

ISENTRESS is also available for adults and paediatric patients (weighing at least 40 kg), as a 600 mg tablet to be administered as 1,200 mg once daily (two 600 mg tablets) for treatment-naïve patients or patients who are virologically suppressed on an initial regimen of ISENTRESS 400 mg twice daily. Refer to the 600 mg tablet SmPC for additional dosing information.

Elderly
There is limited information regarding the use of raltegravir in the elderly (see section 5.2). Therefore, ISENTRESS should be used with caution in this population.

Renal impairment
No dosage adjustment is required for patients with renal impairment (see section 5.2).

Hepatic impairment
No dosage adjustment is required for patients with mild to moderate hepatic impairment. The safety and efficacy of raltegravir have not been established in patients with severe underlying liver disorders. Therefore, ISENTRESS should be used with caution in patients with severe hepatic impairment (see sections 4.4 and 5.2).

Method of administration

Oral use.
ISENTRESS granules for oral suspension can be administered with or without food (see section 5.2).

For details on preparation and administration of the suspension, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General

Patients should be advised that current anti-retroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV to others through blood contact.

Raltegravir has a relatively low genetic barrier to resistance. Therefore, whenever possible, raltegravir should be administered with two other active ARTs to minimise the potential for virological failure and the development of resistance (see section 5.1).

In treatment-naïve patients, the clinical study data on use of raltegravir are limited to use in combination with two nucleotide reverse transcriptase inhibitors (NRTIs) (emtricitabine and tenofovir disoproxil fumarate).

Depression

Depression, including suicidal ideation and behaviours, has been reported, particularly in patients with a pre-existing history of depression or psychiatric illness. Caution should be used in patients with a pre-existing history of depression or psychiatric illness.

Hepatic impairment

The safety and efficacy of raltegravir have not been established in patients with severe underlying liver disorders. Therefore, raltegravir should be used with caution in patients with severe hepatic impairment (see sections 4.2 and 5.2).

Patients with pre-existing liver dysfunction including chronic hepatitis have an increased frequency of liver function abnormalities during combination anti-retroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment should be considered.

Patients with chronic hepatitis B or C and treated with combination anti-retroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Osteonecrosis

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

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination anti-retroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and pneumonia caused by *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*). Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation: however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Antacids

Co-administration of raltegravir with aluminium and magnesium antacids resulted in reduced raltegravir plasma levels. Co-administration of raltegravir with aluminium and/or magnesium antacids is not recommended (see section 4.5).

Rifampicin

Caution should be used when co-administering raltegravir with strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 (e.g., rifampicin). Rifampicin reduces plasma levels of raltegravir; the impact on the efficacy of raltegravir is unknown. However, if co-administration with rifampicin is unavoidable, a doubling of the dose of raltegravir can be considered in adults. There are no data to guide co-administration of raltegravir with rifampicin in patients below 18 years of age (see section 4.5).

Myopathy and rhabdomyolysis

Myopathy and rhabdomyolysis have been reported. Use with caution in patients who have had myopathy or rhabdomyolysis in the past or have any predisposing issues including other medicinal products associated with these conditions (see section 4.8).

Severe skin and hypersensitivity reactions

Severe, potentially life-threatening, and fatal skin reactions have been reported in patients taking raltegravir, in most cases concomitantly with other medicinal products associated with these reactions. These include cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. Hypersensitivity reactions have also been reported and were characterised by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure. Discontinue 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 oedema, 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.

Rash

Rash occurred more commonly in treatment-experienced patients receiving regimens containing raltegravir and darunavir compared to patients receiving raltegravir without darunavir or darunavir without raltegravir (see section 4.8).

Fructose

This medicinal product contains up to 0.5 mg fructose per sachet.
Fructose may damage teeth.

Sucrose

This medicinal product contains up to 4.7 mg sucrose per sachet.
Sucrose may be harmful to the teeth.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Sorbitol

This medicine contains sorbitol (E 420) up to 1.5 mg per sachet.
In medicinal products for oral use, sorbitol may affect the bioavailability of other medicinal products for oral use administered concomitantly.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per sachet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies indicate that raltegravir is not a substrate of cytochrome P450 (CYP) enzymes, does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A, does not inhibit UDP glucuronosyltransferases (UGTs) 1A1 and 2B7, does not induce CYP3A4 and does not inhibit P-glycoprotein-mediated transport. Based on these data, raltegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of these enzymes or P-glycoprotein.

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

Considerable inter- and intra-individual variability was observed in the pharmacokinetics of raltegravir.

Effect of raltegravir on the pharmacokinetics of other medicinal products

In interaction studies, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of etravirine, maraviroc, tenofovir disoproxil fumarate, hormonal contraceptives, methadone, midazolam or boceprevir.

In some studies, co-administration of raltegravir with darunavir resulted in a modest decrease in darunavir plasma concentrations; the mechanism for this effect is unknown. However, the effect of raltegravir on darunavir plasma concentrations does not appear to be clinically meaningful.

Effect of other medicinal products on the pharmacokinetics of raltegravir

Given that raltegravir is metabolised primarily via UGT1A1, caution should be used when co-administering raltegravir with strong inducers of UGT1A1 (e.g., rifampicin). Rifampicin reduces plasma levels of raltegravir; the impact on the efficacy of raltegravir is unknown. However, if co-administration with rifampicin is unavoidable, a doubling of the dose of raltegravir can be considered in adults. There are no data to guide co-administration of raltegravir with rifampicin in patients below 18 years of age (see section 4.4). The impact of other strong inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown. Less potent inducers (e.g., efavirenz, nevirapine, etravirine, rifabutin, glucocorticoids, St. John's wort, pioglitazone) may be used with the recommended dose of raltegravir.

Co-administration of raltegravir with medicinal products that are known to be potent UGT1A1 inhibitors (e.g., atazanavir) may increase plasma levels of raltegravir. Less potent UGT1A1 inhibitors (e.g., indinavir, saquinavir) may also increase plasma levels of raltegravir, but to a lesser extent compared with atazanavir. In addition, tenofovir disoproxil fumarate may increase plasma levels of raltegravir, however, the mechanism for this effect is unknown (see Table 3). From the clinical trials, a large proportion of patients used atazanavir and / or tenofovir disoproxil fumarate, both agents that result in increases in raltegravir plasma levels, in the optimised background regimens. The safety profile observed in patients who used atazanavir and / or tenofovir disoproxil fumarate was generally similar to the safety profile of patients who did not use these agents. Therefore, no dose adjustment is required.

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

Co-administration of raltegravir with other agents that increase gastric pH (e.g., omeprazole and famotidine) may increase the rate of raltegravir absorption and result in increased plasma levels of raltegravir (see Table 3). Safety profiles in the subgroup of patients in Phase III trials taking proton pump inhibitors or H2 antagonists were comparable with those who were not taking these antacids. Therefore, no dose adjustment is required with use of proton pump inhibitors or H2 antagonists.

All interaction studies were performed in adults.

Table 3
Pharmacokinetic Interaction Data

Medicinal products by therapeutic area	**Interaction** (mechanism, if known)	**Recommendations concerning co-administration**
ANTI-RETROVIRAL		
Protease inhibitors (PI)		
atazanavir /ritonavir (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 41 % raltegravir C_{12hr} ↑ 77 % raltegravir C_{max} ↑ 24 % (UGT1A1 inhibition)	No dose adjustment required for raltegravir.
tipranavir /ritonavir (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 24 % raltegravir C_{12hr} ↓ 55 % raltegravir C_{max} ↓ 18 % (UGT1A1 induction)	No dose adjustment required for raltegravir.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
efavirenz (raltegravir 400 mg Single Dose)	raltegravir AUC ↓ 36 % raltegravir C_{12hr} ↓ 21 % raltegravir C_{max} ↓ 36 % (UGT1A1 induction)	No dose adjustment required for raltegravir.
etravirine (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 10 % raltegravir C_{12hr} ↓ 34 % raltegravir C_{max} ↓ 11 % (UGT1A1 induction) etravirine AUC ↑ 10 % etravirine C_{12hr} ↑ 17 % etravirine C_{max} ↑ 4 %	No dose adjustment required for raltegravir or etravirine.
Nucleoside/tide reverse transcriptase inhibitors		
tenofovir disoproxil fumarate (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 49 % raltegravir C_{12hr} ↑ 3 % raltegravir C_{max} ↑ 64 % (mechanism of interaction unknown) tenofovir AUC ↓ 10 % tenofovir C_{24hr} ↓ 13 % tenofovir C_{max} ↓ 23 %	No dose adjustment required for raltegravir or tenofovir disoproxil fumarate.
CCR5 inhibitors		
maraviroc (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 37 % raltegravir C_{12hr} ↓ 28 % raltegravir C_{max} ↓ 33 % (mechanism of interaction unknown) maraviroc AUC ↓ 14 % maraviroc C_{12hr} ↓ 10 % maraviroc C_{max} ↓ 21 %	No dose adjustment required for raltegravir or maraviroc.

Medicinal products by therapeutic area	**Interaction** (mechanism, if known)	**Recommendations concerning co-administration**
HCV ANTIVIRALS		
NS3/4A protease inhibitors (PI)		
boceprevir (raltegravir 400 mg Single Dose)	raltegravir AUC ↑ 4 % raltegravir C_{12hr} ↓ 25 % raltegravir C_{max} ↑ 11 % (mechanism of interaction unknown)	No dose adjustment required for raltegravir or boceprevir.
ANTIMICROBIALS		
Antimycobacterial		
rifampicin (raltegravir 400 mg Single Dose)	raltegravir AUC ↓ 40 % raltegravir C_{12hr} ↓ 61 % raltegravir C_{max} ↓ 38 % (UGT1A1 induction)	Rifampicin reduces plasma levels of raltegravir. If co-administration with rifampicin is unavoidable, a doubling of the dose of raltegravir can be considered (see section 4.4).
SEDATIVE		
midazolam (raltegravir 400 mg Twice Daily)	midazolam AUC ↓ 8 % midazolam C_{max} ↑ 3 %	No dosage adjustment required for raltegravir or midazolam. These results indicate that raltegravir is not an inducer or inhibitor of CYP3A4, and raltegravir is thus not anticipated to affect the pharmacokinetics of medicinal products which are CYP3A4 substrates.
METAL CATION ANTACIDS		
aluminium and magnesium hydroxide antacid (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 49 % raltegravir $C_{12\ hr}$ ↓ 63 % raltegravir C_{max} ↓ 44 % <u>2 hours before raltegravir</u> raltegravir AUC ↓ 51 % raltegravir $C_{12\ hr}$ ↓ 56 % raltegravir C_{max} ↓ 51 % <u>2 hours after raltegravir</u> raltegravir AUC ↓ 30 % raltegravir $C_{12\ hr}$ ↓ 57 % raltegravir C_{max} ↓ 24 % <u>6 hours before raltegravir</u> raltegravir AUC ↓ 13 % raltegravir $C_{12\ hr}$ ↓ 50 % raltegravir C_{max} ↓ 10 % <u>6 hours after raltegravir</u> raltegravir AUC ↓ 11 % raltegravir $C_{12\ hr}$ ↓ 49 % raltegravir C_{max} ↓ 10 % (chelation of metal cations)	Aluminium and magnesium containing antacids reduce raltegravir plasma levels. Co-administration of raltegravir with aluminium and/or magnesium containing antacids is not recommended.

Medicinal products by therapeutic area	Interaction (mechanism, if known)	Recommendations concerning co-administration
calcium carbonate antacid (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 55 % raltegravir $C_{12\ hr}$ ↓ 32 % raltegravir C_{max} ↓ 52 % (chelation of metal cations)	No dose adjustment required for raltegravir.
Other METAL CATION		
Iron salts	Expected: Raltegravir AUC ↓ (chelation of metal cations)	Given simultaneously iron salts are expected to reduce raltegravir plasma levels; taking iron salts at least two hours from the administration of raltegravir may allow to limit this effect.
H2 BLOCKERS AND PROTON PUMP INHIBITORS		
omeprazole (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 37 % raltegravir $C_{12\ hr}$ ↑ 24 % raltegravir C_{max} ↑ 51 % (increased solubility)	No dose adjustment required for raltegravir.
famotidine (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 44 % raltegravir $C_{12\ hr}$ ↑ 6 % raltegravir C_{max} ↑ 60 % (increased solubility)	No dose adjustment required for raltegravir.
HORMONAL CONTRACEPTIVES		
Ethinyl Estradiol Norelgestromin (raltegravir 400 mg Twice Daily)	Ethinyl Estradiol AUC ↓ 2 % Ethinyl Estradiol C_{max} ↑ 6 % Norelgestromin AUC ↑ 14 % Norelgestromin C_{max} ↑ 29 %	No dosage adjustment required for raltegravir or hormonal contraceptives (estrogen- and/or progesterone-based).
OPIOID ANALGESICS		
methadone (raltegravir 400 mg Twice Daily)	methadone AUC ↔ methadone C_{max} ↔	No dose adjustment required for raltegravir or methadone.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data for the use of raltegravir granules for oral suspension in pregnant women. A large amount of data on pregnant women with exposure to raltegravir 400 mg twice daily during the first trimester (more than 1,000 prospective pregnancy outcomes) indicates no malformative toxicity. Animal studies have shown reproductive toxicity (see section 5.3).
A moderate amount of data on pregnant women with exposure to raltegravir 400 mg twice daily during the second and/or third trimester (between 300-1,000 prospective pregnancy outcomes) indicates no increased risk of feto/neonatal toxicity.

Raltegravir granules for oral suspension should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus. See section 4.2 for dosing recommendations.

Anti-retroviral Pregnancy Registry
To monitor maternal-foetal outcomes in patients inadvertently administered raltegravir while pregnant, an Anti-retroviral Pregnancy Registry has been established. Physicians are encouraged to register patients in this registry.

As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account in order to characterise the safety for the foetus.

Breast-feeding

Raltegravir/metabolites are excreted in human milk to such an extent that effects on the breastfed newborns/infants are likely. Available pharmacodynamics/toxicological data in animals have shown excretion of raltegravir/metabolites in milk (for details see section 5.3).

A risk to the newborns/infants cannot be excluded.

It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

Fertility

No effect on fertility was seen in male and female rats at doses up to 600 mg/kg/day which resulted in 3-fold exposure above the exposure at the recommended human dose.

4.7 Effects on ability to drive and use machines

Dizziness has been reported in some patients during treatment with regimens containing raltegravir. Dizziness may influence some patients' ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

In randomised clinical trials raltegravir 400 mg twice daily was administered in combination with fixed or optimised background treatment regimens to treatment-naïve (N=547) and treatment-experienced (N=462) adults for up to 96 weeks. A further 531 treatment-naïve adults have received raltegravir 1,200 mg once daily with emtricitabine and tenofovir disoproxil fumarate for up to 96 weeks. See section 5.1.

The most frequently reported adverse reactions during treatment were headache, nausea and abdominal pain. The most frequently reported serious adverse reaction was immune reconstitution syndrome and rash. The rates of discontinuation of raltegravir due to adverse reactions were 5% or less in clinical trials.

Rhabdomyolysis was an uncommonly reported serious adverse reaction in post-marketing use of raltegravir 400 mg twice daily.

Tabulated summary of adverse reactions

Adverse reactions considered by investigators to be causally related to raltegravir (alone or in combination with other ART), as well as adverse reactions established in post-marketing experience, are listed below by System Organ Class. Frequencies are defined as common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reactions Raltegravir (alone or in combination with other ART)
Infections and infestations	Uncommon	genital herpes, folliculitis, gastroenteritis, herpes simplex, herpes virus infection, herpes zoster, influenza, lymph node abscess, molluscum contagiosum, nasopharyngitis, upper respiratory tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Uncommon	skin papilloma
Blood and lymphatic system disorders	Uncommon	anaemia, iron deficiency anaemia, lymph node pain, lymphadenopathy, neutropenia, thrombocytopenia
Immune system disorders	Uncommon	immune reconstitution syndrome, drug hypersensitivity, hypersensitivity
Metabolism and nutrition disorders	Common Uncommon	decreased appetite cachexia, diabetes mellitus, dyslipidaemia, hypercholesterolaemia, hyperglycaemia, hyperlipidaemia, hyperphagia, increased appetite, polydipsia, body fat disorder
Psychiatric disorders	Common Uncommon	abnormal dreams, insomnia, nightmare, abnormal behaviour, depression mental disorder, suicide attempt, anxiety, confusional state, depressed mood, major depression, middle insomnia, mood altered, panic attack, sleep disorder, suicidal ideation, suicidal behaviour (particularly in patients with a pre-existing history of psychiatric illness)
Nervous system disorders	Common Uncommon	dizziness, headache, psychomotor hyperactivity amnesia, carpal tunnel syndrome, cognitive disorder, disturbance in attention, dizziness postural, dysgeusia, hypersomnia, hypoaesthesia, lethargy, memory impairment, migraine, neuropathy peripheral, paraesthesia, somnolence, tension headache, tremor, poor quality sleep
Eye disorders	Uncommon	visual impairment
Ear and labyrinth disorders	Common Uncommon	vertigo tinnitus
Cardiac disorders	Uncommon	palpitations, sinus bradycardia, ventricular extrasystoles
Vascular disorders	Uncommon	hot flush, hypertension
Respiratory, thoracic and mediastinal disorders	Uncommon	dysphonia, epistaxis, nasal congestion

System Organ Class	Frequency	Adverse reactions Raltegravir (alone or in combination with other ART)
Gastrointestinal disorders	Common Uncommon	abdominal distention, abdominal pain, diarrhoea, flatulence, nausea, vomiting, dyspepsia gastritis, abdominal discomfort, abdominal pain upper, abdominal tenderness, anorectal discomfort, constipation, dry mouth, epigastric discomfort, erosive duodenitis, eructation, gastroesophageal reflux disease, gingivitis, glossitis, odynophagia, pancreatitis acute, peptic ulcer, rectal haemorrhage
Hepato-biliary disorders	Uncommon	hepatitis, hepatic steatosis, hepatitis alcoholic, hepatic failure
Skin and subcutaneous tissue disorders	Common Uncommon	rash acne, alopecia, dermatitis acneiforme, dry skin, erythema, facial wasting, hyperhidrosis, lipoatrophy, lipodystrophy acquired, lipohypertrophy, night sweats, prurigo, pruritus, pruritus generalised, rash macular, rash maculo-papular, rash pruritic, skin lesion, urticaria, xeroderma, Stevens Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Uncommon	arthralgia, arthritis, back pain, flank pain, musculoskeletal pain, myalgia, neck pain, osteopenia, pain in extremity, tendonitis, rhabdomyolysis
Renal and urinary disorders	Uncommon	renal failure, nephritis, nephrolithiasis, nocturia, renal cyst, renal impairment, tubulointerstitial nephritis
Reproductive system and breast disorders	Uncommon	erectile dysfunction, gynaecomastia, menopausal symptoms
General disorders and administration site conditions	Common Uncommon	asthenia, fatigue, pyrexia chest discomfort, chills, face oedema, fat tissue increased, feeling jittery, malaise, submandibular mass, oedema peripheral, pain

System Organ Class	Frequency	Adverse reactions Raltegravir (alone or in combination with other ART)
Investigations	Common	alanine aminotransferase increased, atypical lymphocytes, aspartate aminotransferase increased, blood triglycerides increased, lipase increased, blood pancreatic amylase increased
	Uncommon	absolute neutrophil count decreased, alkaline phosphatase increased, blood albumin decreased, blood amylase increased, blood bilirubin increased, blood cholesterol increased, blood creatinine increased, blood glucose increased, blood urea nitrogen increased, creatine phosphokinase increased, fasting blood glucose increased, glucose urine present, high density lipoprotein increased, international normalised ratio increased, low density lipoprotein increased, platelet count decreased, red blood cells urine positive, waist circumference increased, weight increased, white blood cell count decreased
Injury, poisoning and procedural complications	Uncommon	accidental overdose

Description of selected adverse reactions

Cancers were reported in treatment-experienced and treatment-naïve patients who initiated raltegravir in conjunction with other antiretroviral agents. The types and rates of specific cancers were those expected in a highly immunodeficient population. The risk of developing cancer in these studies was similar in the groups receiving raltegravir and in the groups receiving comparators.

Grade 2-4 creatine kinase laboratory abnormalities were observed in patients treated with raltegravir. Myopathy and rhabdomyolysis have been reported. Use with caution in patients who have had myopathy or rhabdomyolysis in the past or have any predisposing issues including other medicinal products associated with these conditions (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

For each of the following clinical adverse reactions there was at least one serious occurrence: genital herpes, anaemia, immune reconstitution syndrome, depression, mental disorder, suicide attempt, gastritis, hepatitis, renal failure, accidental overdose.

In clinical studies of treatment-experienced patients, rash, irrespective of causality, was more commonly observed with regimens containing raltegravir and darunavir compared to those containing raltegravir without darunavir or darunavir without raltegravir. Rash considered by the investigator to be drug-related occurred at similar rates. The exposure-adjusted rates of rash (all causality) were 10.9, 4.2, and 3.8 per 100 patient-years (PYR), respectively; and for drug-related rash were 2.4, 1.1, and 2.3

per 100 PYR, respectively. The rashes observed in clinical studies were mild to moderate in severity and did not result in discontinuation of therapy (see section 4.4).

Patients co-infected with hepatitis B and/or hepatitis C virus
In clinical trials, there were 79 patients co-infected with hepatitis B, 84 co-infected with hepatitis C, and 8 patients co-infected with hepatitis B and C who were treated with raltegravir in combination with other agents for HIV-1. In general, the safety profile of raltegravir in patients with hepatitis B and/or hepatitis C virus co-infection was similar to that in patients without hepatitis B and/or hepatitis C virus co-infection, although the rates of AST and ALT abnormalities were somewhat higher in the subgroup co-infected with hepatitis B and/or hepatitis C virus
At 96-weeks, in treatment-experienced patients, 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 patients treated with raltegravir as compared to 11 %, 10 % and 9 % of all other patients treated with raltegravir. At 240-weeks, in treatment-naïve patients, 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 patients treated with raltegravir as compared to 13 %, 13 % and 5 % of all other patients treated with raltegravir.

Paediatric population

Children and adolescents 2 to 18 years of age
Raltegravir has been studied in 126 antiretroviral treatment-experienced HIV-1 infected children and adolescents 2 to 18 years of age, in combination with other antiretroviral agents in IMPAACT P1066 (see sections 5.1 and 5.2). Of the 126 patients, 96 received the recommended dose of raltegravir.

In these 96 children and adolescents, frequency, type and severity of drug related adverse reactions through Week 48 were comparable to those observed in adults.

One patient experienced drug related clinical adverse reactions of Grade 3 psychomotor hyperactivity, abnormal behaviour and insomnia; one patient experienced a Grade 2 serious drug related allergic rash.

One patient experienced drug related laboratory abnormalities, Grade 4 AST and Grade 3 ALT, which were considered serious.

Infants and toddlers 4 weeks to less than 2 years of age
Raltegravir has 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 sections 5.1 and 5.2).

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
In IMPAACT P1110 (see section 5.2) eligible infants were at least 37 weeks gestation and at least 2 kg in weight. Sixteen (16) neonates received 2 doses of ISENTRESS in first 2 weeks of life, and 26 neonates received 6 weeks of daily dosing; all were followed for 24 weeks. There were no drug related clinical adverse experiences and three drug-related laboratory adverse experiences (one a transient Grade 4 neutropenia in a subject receiving zidovudine containing 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).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No specific information is available on the treatment of overdose with raltegravir.

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. It should be taken into account that raltegravir is presented for clinical use as the potassium salt. The extent to which raltegravir may be dialysable is unknown.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, integrase inhibitors, ATC code: J05AJ01.

Mechanism of action

Raltegravir is an integrase strand transfer inhibitor active against the Human Immunodeficiency Virus (HIV-1). Raltegravir inhibits the catalytic activity of integrase, an HIV-encoded enzyme that is required for viral replication. Inhibition of integrase prevents the covalent insertion, or integration, of the HIV genome into the host cell genome. HIV genomes that fail to integrate cannot direct the production of new infectious viral particles, so inhibiting integration prevents propagation of the viral infection.

Antiviral activity *in vitro*

Raltegravir at concentrations of 31 ± 20 nM resulted in 95 % inhibition (IC_{95}) of HIV-1 replication (relative to an untreated virus-infected culture) in human T-lymphoid cell cultures infected with the cell-line adapted HIV-1 variant H9IIIB. In addition, raltegravir inhibited viral replication in cultures of mitogen-activated human peripheral blood mononuclear cells infected with diverse, primary clinical isolates of HIV-1, including isolates from 5 non-B subtypes, and isolates resistant to reverse transcriptase inhibitors and protease inhibitors. In a single-cycle infection assay, raltegravir inhibited infection of 23 HIV isolates representing 5 non-B subtypes and 5 circulating recombinant forms with IC_{50} values ranging from 5 to 12 nM.

Resistance

Most viruses isolated from patients failing raltegravir had high-level raltegravir resistance resulting from the appearance of two or more mutations in integrase. Most had a signature mutation at amino acid 155 (N155 changed to H), amino acid 148 (Q148 changed to H, K, or R), or amino acid 143 (Y143 changed to H, C, or R), along with one or more additional integrase mutations (e.g., L74M, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, S230R). The signature mutations decrease viral susceptibility to raltegravir and addition of other mutations results in a further decrease in raltegravir susceptibility. Factors that reduced the likelihood of developing resistance included lower baseline viral load and use of other active anti-retroviral agents. Mutations conferring resistance to raltegravir generally also confer resistance to the integrase strand transfer inhibitor elvitegravir. Mutations at amino acid 143 confer greater resistance to raltegravir than to elvitegravir, and the E92Q mutation confers greater resistance to elvitegravir than to raltegravir. Viruses harbouring a mutation at amino

acid 148, along with one or more other raltegravir resistance mutations, may also have clinically significant resistance to dolutegravir.

Clinical experience

The evidence of efficacy of raltegravir was based on the analyses of 96-week data from two randomised, double-blind, placebo-controlled trials (BENCHMRK 1 and BENCHMRK 2, Protocols 018 and 019) in antiretroviral treatment-experienced HIV-1 infected adult patients and the analysis of 240-week data from a randomised, double-blind, active-control trial (STARTMRK, Protocol 021) in antiretroviral treatment-naïve HIV-1 infected adult patients.

Efficacy

Treatment-experienced adult patients
BENCHMRK 1 and BENCHMRK 2 (multi-centre, randomised, double-blind, placebo-controlled trials) evaluated the safety and anti-retroviral activity of raltegravir 400 mg twice daily vs. placebo in a combination with optimised background therapy (OBT), in HIV-infected patients, 16 years or older, with documented resistance to at least 1 drug in each of 3 classes (NRTIs, NNRTIs, PIs) of anti-retroviral therapies. Prior to randomisation, OBT were selected by the investigator based on the patient's prior treatment history, as well as baseline genotypic and phenotypic viral resistance testing.

Patient demographics (gender, age and race) and baseline characteristics were comparable between the groups receiving raltegravir 400 mg twice daily and placebo. Patients had prior exposure to a median of 12 anti-retrovirals for a median of 10 years. A median of 4 ARTs was used in OBT.

Results 48 week and 96 week analyses
Durable outcomes (Week 48 and Week 96) for patients on the recommended dose raltegravir 400 mg twice daily from the pooled studies BENCHMRK 1 and BENCHMRK 2 are shown in Table 3.

Table 4
Efficacy Outcome at Weeks 48 and 96

BENCHMRK 1 and 2 Pooled	48 Weeks		96 Weeks	
Parameter	**Raltegravir 400 mg twice daily + OBT (N = 462)**	**Placebo + OBT (N = 237)**	**Raltegravir 400 mg twice daily + OBT (N = 462)**	**Placebo + OBT (N = 237)**
Percent HIV-RNA < 400 copies/mL (95 % CI)				
All patients[†]	72 (68, 76)	37 (31, 44)	62 (57, 66)	28 (23, 34)
Baseline Characteristic[‡]				
HIV-RNA > 100,000 copies/mL	62 (53, 69)	17 (9, 27)	53 (45, 61)	15 (8, 25)
≤ 100,000 copies/mL	82 (77, 86)	49 (41, 58)	74 (69, 79)	39 (31, 47)
CD4-count ≤ 50 cells/mm^3	61 (53, 69)	21 (13, 32)	51 (42, 60)	14 (7, 24)
> 50 and ≤ 200 cells/mm^3	80 (73, 85)	44 (33, 55)	70 (62, 77)	36 (25, 48)
> 200 cells/mm^3	83 (76, 89)	51 (39, 63)	78 (70, 85)	42 (30, 55)
Sensitivity score (GSS) [§]				
0	52 (42, 61)	8 (3, 17)	46 (36, 56)	5 (1, 13)
1	81 (75, 87)	40 (30, 51)	76 (69, 83)	31 (22, 42)
2 and above	84 (77, 89)	65 (52, 76)	71 (63, 78)	56 (43, 69)
Percent HIV-RNA < 50 copies/mL (95 % CI)				
All patients[†]	62 (57, 67)	33 (27, 39)	57 (52, 62)	26 (21, 32)
Baseline Characteristic[‡]				
HIV-RNA > 100,000 copies/mL	48 (40, 56)	16 (8, 26)	47 (39, 55)	13 (7, 23)
≤ 100,000 copies/mL	73 (68, 78)	43 (35, 52)	70 (64, 75)	36 (28, 45)
CD4-count ≤ 50 cells/mm^3	50 (41, 58)	20 (12, 31)	50 (41, 58)	13 (6, 22)
> 50 and ≤ 200 cells/mm^3	67 (59, 74)	39 (28, 50)	65 (57, 72)	32 (22, 44)
> 200 cells/mm^3	76 (68, 83)	44 (32, 56)	71 (62, 78)	41 (29, 53)
Sensitivity score (GSS) [§]				
0	45 (35, 54)	3 (0, 11)	41 (32, 51)	5 (1, 13)
1	67 (59, 74)	37 (27, 48)	72 (64, 79)	28 (19, 39)
2 and above	75 (68, 82)	59 (46, 71)	65 (56, 72)	53 (40, 66)
Mean CD4 Cell Change (95 % CI), cells/mm^3				
All patients[‡]	109 (98, 121)	45 (32, 57)	123 (110, 137)	49 (35, 63)
Baseline Characteristic[‡]				
HIV-RNA > 100,000 copies/mL	126 (107, 144)	36 (17, 55)	140 (115, 165)	40 (16, 65)
≤ 100,000 copies/mL	100 (86, 115)	49 (33, 65)	114 (98, 131)	53 (36, 70)
CD4-count ≤ 50 cells/mm^3	121 (100, 142)	33 (18, 48)	130 (104, 156)	42 (17, 67)
> 50 and ≤ 200 cells/mm^3	104 (88, 119)	47 (28, 66)	123 (103, 144)	56 (34, 79)
> 200 cells/mm^3	104 (80, 129)	54 (24, 84)	117 (90, 143)	48 (23, 73)
Sensitivity score (GSS) [§]				
0	81 (55, 106)	11 (4, 26)	97 (70, 124)	15 (-0, 31)
1	113 (96, 130)	44 (24, 63)	132 (111, 154)	45 (24, 66)
2 and above	125 (105, 144)	76 (48, 103)	134 (108, 159)	90 (57, 123)

[†] Non-completer is failure imputation: patients who discontinued prematurely are imputed as failure thereafter. Percent of patients with response and associated 95 % confidence interval (CI) are reported.

[‡] For analysis by prognostic factors, virologic failures were carried forward for percent < 400 and 50 copies/mL. For mean CD4 changes, baseline-carry-forward was used for virologic failures.

[§] The Genotypic Sensitivity Score (GSS) was defined as the total oral ARTs in the optimised background therapy (OBT) to which a patient's viral isolate showed genotypic sensitivity based upon genotypic resistance test. Enfuvirtide use in OBT in enfuvirtide-naïve patients was counted as one active drug in OBT. Similarly, darunavir use in OBT in darunavir-naïve patients was counted as one active drug in OBT.

Raltegravir achieved virologic responses (using Not Completer=Failure approach) of HIV RNA < 50 copies/mL in 61.7 % of patients at Week 16, in 62.1 % at Week 48 and in 57.0 % at Week 96. Some patients experienced viral rebound between Week 16 and Week 96. Factors associated with failure include high baseline viral load and OBT that did not include at least one potent active agent.

Switch to raltegravir
The SWITCHMRK 1 & 2 (Protocols 032 & 033) studies evaluated HIV-infected patients receiving suppressive (screening HIV RNA < 50 copies/mL; stable regimen > 3 months) therapy with lopinavir 200 mg (+) ritonavir 50 mg 2 tablets twice daily plus at least 2 nucleoside reverse transcriptase inhibitors and randomised them 1:1 to continue lopinavir (+) ritonavir 2 tablets twice daily (n=174 and n=178, respectively) or replace lopinavir (+) ritonavir with raltegravir 400 mg twice daily (n=174 and n=176, respectively). Patients with a prior history of virological failure were not excluded and the number of previous antiretroviral therapies was not limited.

These studies were terminated after the primary efficacy analysis at Week 24 because they failed to demonstrate non-inferiority of raltegravir versus lopinavir (+) ritonavir. In both studies at Week 24, suppression of HIV RNA to less than 50 copies/mL was maintained in 84.4 % of the raltegravir group versus 90.6 % of the lopinavir (+) ritonavir group, (Non-completers = Failure). See section 4.4 regarding the need to administer raltegravir with two other active agents.

Treatment-naïve adult patients
STARTMRK (multi-centre, randomised, double-blind, active-control trial) evaluated the safety and anti-retroviral activity of raltegravir 400 mg twice daily vs. efavirenz 600 mg at bedtime, in a combination with emtricitabine (+) tenofovir disoproxil fumarate, in treatment-naïve HIV-infected patients with HIV RNA > 5,000 copies/mL. Randomisation was stratified by screening HIV RNA level (≤ 50,000 copies/mL; and > 50,000 copies/mL) and by hepatitis B or C status (positive or negative).
Patient demographics (gender, age and race) and baseline characteristics were comparable between the group receiving raltegravir 400 mg twice daily and the group receiving efavirenz 600 mg at bedtime.

Results 48-week and 240-week analyses
With respect to the primary efficacy endpoint, the proportion of patients achieving HIV RNA < 50 copies/mL at Week 48 was 241/280 (86.1 %) in the group receiving raltegravir and 230/281 (81.9 %) in the group receiving efavirenz. The treatment difference (raltegravir – efavirenz) was 4.2 % with an associated 95 % CI of (-1.9, 10.3) establishing that raltegravir is non-inferior to efavirenz (p-value for non-inferiority < 0.001). At Week 240, the treatment difference (raltegravir – efavirenz) was 9.5 % with an associated 95 % CI of (1.7, 17.3). Week 48 and Week 240 outcomes for patients on the recommended dose of raltegravir 400 mg twice daily from STARTMRK are shown in Table 5.

Table 5
Efficacy Outcome at Weeks 48 and 240

STARTMRK Study	48 Weeks		240 Weeks	
Parameter	**Raltegravir 400 mg twice daily (N = 281)**	**Efavirenz 600 mg at bedtime (N = 282)**	**Raltegravir 400 mg twice daily (N = 281)**	**Efavirenz 600 mg at bedtime (N = 282)**
Percent HIV-RNA < 50 copies/mL (95 % CI)				
All patients[†]	86 (81, 90)	82 (77, 86)	71 (65, 76)	61 (55, 67)
Baseline Characteristic[‡]				
HIV-RNA > 100,000 copies/mL	91 (85, 95)	89 (83, 94)	70 (62, 77)	65 (56, 72)
≤ 100,000 copies/mL	93 (86, 97)	89 (82, 94)	72 (64, 80)	58 (49, 66)
CD4-count ≤ 50 cells/mm^3	84 (64, 95)	86 (67, 96)	58 (37, 77)	77 (58, 90)
> 50 and ≤ 200 cells/mm^3	89 (81, 95)	86 (77, 92)	67 (57, 76)	60 (50, 69)
> 200 cells/mm^3	94 (89, 98)	92 (87, 96)	76 (68, 82)	60 (51, 68)
Viral Subtype Clade B	90 (85, 94)	89 (83, 93)	71 (65, 77)	59 (52, 65)
Non-Clade B	96 (87, 100)	91 (78, 97)	68 (54, 79)	70 (54, 82)
Mean CD4 Cell Change (95 % CI), cells/mm^3				
All patients[‡]	189 (174, 204)	163 (148, 178)	374 (345, 403)	312 (284, 339)
Baseline Characteristic[‡]				
HIV-RNA > 100,000 copies/mL	196 (174, 219)	192 (169, 214)	392 (350, 435)	329 (293, 364)
≤ 100,000 copies/mL	180 (160, 200)	134 (115, 153)	350 (312, 388)	294 (251, 337)
CD4-count ≤ 50 cells/mm^3	170 (122, 218)	152 (123, 180)	304 (209, 399)	314 (242, 386)
> 50 and ≤ 200 cells/mm^3	193 (169, 217)	175 (151, 198)	413 (360, 465)	306 (264, 348)
> 200 cells/mm^3	190 (168, 212)	157 (134, 181)	358 (321, 395)	316 (272, 359)
Viral Subtype Clade B	187 (170, 204)	164 (147, 181)	380 (346, 414)	303 (272, 333)
Non-Clade B	189 (153, 225)	156 (121, 190)	332 (275, 388)	329 (260, 398)

[†] Non-completer is failure imputation: patients who discontinued prematurely are imputed as failure thereafter. Percent of patients with response and associated 95 % confidence interval (CI) are reported.

[‡] For analysis by prognostic factors, virologic failures were carried forward for percent < 50 and 400 copies/mL. For mean CD4 changes, baseline-carry-forward was used for virologic failures.

Notes: The analysis is based on all available data.

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

Paediatric population

Children and adolescents 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. Patients were stratified by age, enrolling adolescents first and then successively younger children. Patients received either the 400 mg tablet formulation (6 to 18 years of age) or the chewable tablet formulation (2 to less than 12 years of age). Raltegravir was administered with an optimised background regimen.

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

Table 6
Baseline Characteristics and Efficacy Outcomes at Weeks 24 and 48 from IMPAACT P1066 (2 to 18 years of age)

Parameter	Final dose population N=96	
Demographics		
Age (years), median [range]	13 [2 – 18]	
Male Gender	49 %	
Race		
Caucasian	34 %	
Black	59 %	
Baseline Characteristics		
Plasma HIV-1 RNA (log_{10} copies/mL), mean [range]	4.3 [2.7 - 6]	
CD4 cell count (cells/mm^3), median [range]	481 [0 – 2361]	
CD4 percent, median [range]	23.3 % [0 – 44]	
HIV-1 RNA >100,000 copies/mL	8 %	
CDC HIV category B or C	59 %	
Prior ART Use by Class		
NNRTI	78 %	
PI	83 %	
Response	**Week 24**	**Week 48**
Achieved ≥1 log_{10} HIV RNA drop from baseline or <400 copies/mL	72 %	79 %
Achieved HIV RNA <50 copies/mL	54 %	57 %
Mean CD4 cell count (%) increase from baseline	119 cells/mm^3 (3.8 %)	156 cells/mm^3 (4.6 %)

Infants and toddlers 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 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 granules for oral suspension formulation without regard to food in combination with an optimised background regimen that included lopinavir plus ritonavir in two-thirds of patients.

Table 7
Baseline Characteristics and Efficacy Outcomes at Weeks 24 and 48 from IMPAACT P1066 (4 weeks to less than 2 years of age)

Parameter	N=26	
Demographics		
Age (weeks), median [range]	28 [4 -100]	
Male Gender	65 %	
Race		
Caucasian	8 %	
Black	85 %	
Baseline Characteristics		
Plasma HIV-1 RNA (log_{10} copies/mL), mean [range]	5.7 [3.1 - 7]	
CD4 cell count (cells/mm^3), median [range]	1,400 [131 -3,648]	
CD4 percent, median [range]	18.6 % [3.3 – 39.3]	
HIV-1 RNA >100,000 copies/mL	69 %	
CDC HIV category B or C	23 %	
Prior ART Use by Class		
NNRTI	73 %	
NRTI	46%	
PI	19 %	
Response	**Week 24**	**Week 48**
Achieved ≥1 log_{10} HIV RNA drop from baseline or <400 copies/mL	91 %	85 %
Achieved HIV RNA <50 copies/mL	43 %	53 %
Mean CD4 cell count (%) increase from baseline	500 cells/mm^3 (7.5 %)	492 cells/mm^3 (7.8 %)
Virologic failure	**Week 24**	**Week 48**
Non-responder	0	0
Rebounder	0	4
Number with genotype available*	0	2

*One patient had a mutation at the 155 position.

5.2 Pharmacokinetic properties

Absorption

As demonstrated in healthy volunteers administered single oral doses of raltegravir in the fasted state, raltegravir is rapidly absorbed with a t_{max} of approximately 3 hours postdose. Raltegravir AUC and C_{max} increase dose proportionally over the dose range 100 mg to 1,600 mg. Raltegravir $C_{12\ hr}$ 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 1,600 mg. Dose proportionality has not been established in patients.

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

Raltegravir may be administered with or without food. Raltegravir was administered without regard to food in the pivotal safety and efficacy studies in HIV-infected patients. Administration of multiple doses of raltegravir following a moderate-fat meal did not affect raltegravir AUC to a clinically meaningful degree with an increase of 13 % relative to fasting. Raltegravir $C_{12\ hr}$ was 66 % higher and C_{max} was 5 % higher following a moderate-fat meal compared to fasting. Administration of raltegravir following a high-fat meal increased AUC and C_{max} by approximately 2-fold and increased $C_{12\ hr}$ by 4.1-fold. Administration of raltegravir following a low-fat meal decreased AUC and C_{max} by 46 % and 52 %, respectively; $C_{12\ hr}$ was essentially unchanged. Food appears to increase pharmacokinetic variability relative to fasting.

Overall, considerable variability was observed in the pharmacokinetics of raltegravir. For observed $C_{12\ hr}$ in BENCHMRK 1 and 2 the coefficient of variation (CV) for inter-subject variability = 212 % and the CV for intra-subject variability = 122 %. Sources of variability may include differences in co-administration with food and concomitant medicines.

Distribution

Raltegravir is approximately 83 % bound to human plasma protein over the concentration range of 2 to 10 μM.
Raltegravir readily crossed the placenta in rats, but did not penetrate the brain to any appreciable extent.

In two studies of HIV-1 infected patients who received raltegravir 400 mg twice daily, raltegravir was readily detected in the cerebrospinal fluid. In the first study (n=18), the median cerebrospinal fluid concentration was 5.8 % (range 1 to 53.5 %) of the corresponding plasma concentration. In the second study (n=16), the median cerebrospinal fluid concentration was 3 % (range 1 to 61 %) of the corresponding plasma concentration. These median proportions are approximately 3- to 6-fold lower than the free fraction of raltegravir in plasma.

Biotransformation 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 faeces and urine, respectively. In faeces, only raltegravir was present, most of which is likely to be derived from hydrolysis of raltegravir-glucuronide secreted in bile as observed in preclinical species. Two components, namely raltegravir and raltegravir-glucuronide, were detected in urine and accounted for approximately 9 and 23 % of the dose, respectively. The major circulating entity was raltegravir and represented approximately 70 % of the total radioactivity; the remaining radioactivity in plasma was accounted for by raltegravir-glucuronide. Studies using isoform-selective chemical inhibitors and cDNA-expressed UDP-glucuronosyltransferases (UGT) show that UGT1A1 is the main enzyme responsible for the formation of raltegravir-glucuronide. Thus, the data indicate that the major mechanism of clearance of raltegravir in humans is UGT1A1-mediated glucuronidation.

UGT1A1 Polymorphism
In a comparison of 30 subjects with *28/*28 genotype to 27 subjects with wild-type genotype, the geometric mean ratio (90 % CI) of AUC was 1.41 (0.96, 2.09) and the geometric mean ratio of $C_{12\ hr}$ was 1.91 (1.43, 2.55). Dose adjustment is not considered necessary in subjects with reduced UGT1A1 activity due to genetic polymorphism.

Special populations

Paediatric population
Based on a formulation comparison study in healthy adult volunteers, the chewable tablet and granules for oral suspension have higher oral bioavailability compared to the 400 mg tablet. In this study, administration of the chewable tablet with a high fat meal led to an average 6 % decrease in AUC, 62 % decrease in C_{max}, and 188 % increase in $C_{12\ hr}$ 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 granules for oral suspension formulation was not studied.

Table 8 displays pharmacokinetic parameters in the 400 mg tablet, the chewable tablet, and the granules for oral suspension, by body weight.

Table 8
Raltegravir Pharmacokinetic Parameters IMPAACT P1066 Following Administration of Doses in Section 4.2

Body weight	Formulation	Dose	N*	Geometric mean *(%CV†)* $AUC_{0\text{-}12hr}$ (µM●hr)	Geometric mean *(%CV†)* C_{12hr} (nM)
≥ 25 kg	Film-coated tablet	400 mg twice daily	18	14.1 *(121 %)*	233 (*157 %*)
≥ 25 kg	Chewable tablet	Weight based dosing, see dosing tables for the chewable tablet	9	22.1 (*36 %*)	113 (*80 %*)
11 to less than 25 kg	Chewable tablet	Weight based dosing, see dosing tables for the chewable tablet	13	18.6 (*68 %*)	82 (*123 %*)
3 to less than 20 kg	Oral suspension	Weight based dosing, see dosing Table 1	19	24.5 (*43 %*)	113 (*69 %*)

*Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose.
†Geometric coefficient of variation.

HIV-1 Exposed Neonates
IMPAACT P1110 is a Phase I trial to evaluate the safety and pharmacokinetics of raltegravir granules for suspension (GFS) with standard care PMTCT in full term HIV-1-exposed neonates. Cohort 1 (N=16, 10 exposed and 6 unexposed to raltegravir in utero) received 2 single doses of raltegravir GFS (within 48 hours and 7 - 10 days after birth); Cohort 2 (N=26, all raltegravir unexposed in utero) received raltegravir GFS for 6 weeks: 1.5 mg/kg once daily starting within 48 hours of birth through Week 1; 3 mg/kg twice daily Weeks 2 to 4; and 6 mg/kg twice daily Weeks 5 and 6.

Table 9 displays pharmacokinetic parameters for neonates in Cohort 2 at birth and at 2 weeks of age. Elimination of raltegravir *in vivo* in human is primarily through the UGT1A1-mediated glucuronidation pathway. UGT1A1 catalytic activity is negligible at birth and matures after birth. The dose recommended for neonates less than 4 weeks of age takes into consideration the rapidly increasing UGT1A1 activity and drug clearance from birth to 4 weeks of age.

Table 9: Raltegravir Pharmacokinetic Parameters IMPAACT P1110 Following Age and Weight Based Dosing of the Granules for Suspension

Age (hours/days) at PK Sampling	Dose (See Table 2)	N*	Geometric Mean (%CV†) AUC (mg*hr/L)	Geometric Mean (% CV†) C_{trough} (ng/mL)
Birth – 48 hours	1.5 mg/kg once daily	25	38.2 (38.4%)‡	947.9 (64.2%) ‡
15 to 18 days	3.0 mg/kg twice daily	23	14.3 (43.3%) §	558 (83.7%) §

*Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose.
†Geometric coefficient of variation.
‡ AUC0-24hr (N = 24); C24hr
§AUC0-12hr; C12hr

Elderly
There was no clinically meaningful effect of age on raltegravir pharmacokinetics in healthy subjects and patients with HIV-1 infection, over the age range studied (19 to 84 years, with few individuals over the age of 65).

Gender, race and BMI
There were no clinically important pharmacokinetic differences due to gender, race or body mass index (BMI) in adults.

Renal impairment
Renal clearance of unchanged medicinal product is a minor pathway of elimination. In adults, there were no clinically important pharmacokinetic differences between patients with severe renal insufficiency and healthy subjects (see section 4.2). Because the extent to which raltegravir may be dialysable is unknown, dosing before a dialysis session should be avoided.

Hepatic impairment
Raltegravir is eliminated primarily by glucuronidation in the liver. In adults, there were no clinically important pharmacokinetic differences between patients with moderate hepatic insufficiency and healthy subjects. The effect of severe hepatic insufficiency on the pharmacokinetics of raltegravir has not been studied (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Non-clinical toxicology studies, including conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, developmental toxicity and juvenile toxicity, have been conducted with raltegravir in mice, rats, dogs and rabbits. Effects at exposure levels sufficiently in excess of clinical exposure levels indicate no special hazard for humans.

Mutagenicity

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.

Carcinogenicity

A carcinogenicity study 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 similar to that at the clinical dose of 400 mg twice daily. In rats, tumours (squamous cell carcinoma) of the nose/nasopharynx were identified at 300 and 600 mg/kg/day in females and at 300 mg/kg/day in males. This neoplasia could result from local deposition and/or aspiration of drug on the mucosa of the nose/nasopharynx during oral gavage dosing and subsequent chronic irritation and inflammation; it is likely that it is of limited relevance for the intended clinical use. At the NOAEL, systemic exposure was similar to that at the clinical dose of 400 mg twice daily. Standard genotoxicity studies to evaluate mutagenicity and clastogenicity were negative.

Developmental toxicity

Raltegravir was not teratogenic in developmental toxicity studies in rats and rabbits. A slight increase in incidence of supernumerary ribs, a variant in the normal developmental process, was observed in rat foetuses of dams exposed to raltegravir at approximately 4.4-fold human exposure at 400 mg twice daily based on $AUC_{0\text{-}24\ hr}$. No development effects were seen at 3.4-fold human exposure at 400 mg twice daily based on $AUC_{0\text{-}24\ hr}$. Similar findings were not observed in rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Hydroxypropyl cellulose
- Sucralose
- Mannitol (E 421)
- Monoammonium glycyrrhizinate
- Sorbitol (E 420)
- Fructose
- Banana flavour
- Sucrose
- Crospovidone, TypeA
- Magnesium stearate
- Hypromellose 2910/6cP
- Macrogol/PEG 400
- Ethylcellulose 20 cP
- Ammonium hydroxide
- Medium chain triglycerides
- Oleic acid
- Microcrystalline cellulose
- Carmellose sodium

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years for unopened sachet.
After reconstitution: 30 minutes when stored at or below 30 °C.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

PET/aluminium/LLDPE sachets.
One carton contains 60 sachets, two 1 mL, two 3 mL and two 10 mL oral dosing syringes and 2 mixing cups.

6.6 Special precautions for disposal and other handling

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

Each single-use sachet contains 100 mg of raltegravir which is to be suspended in 10 mL of water giving a final concentration of 10 mg per mL.

After administration of the required volume, the remaining suspension in the mixing cup cannot be re-used and must be discarded.

Parents and/or caregivers should be instructed to read the instructions for use booklet before preparing and administering ISENTRESS granules for oral suspension to paediatric patients.

The dose should be administered orally within 30 minutes of mixing.

Complete details on preparation and administration of the suspension can be found in the instructions for use booklet that is included in the carton.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 December 2007
Date of latest renewal: 14 May 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for 400 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 400 mg film-coated tablets
raltegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 400 mg of raltegravir (as potassium).

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets
Multipack: 180 (3 bottles of 60) film-coated tablets

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not switch with other strengths or formulations of Isentress without first talking with your doctor, pharmacist or nurse.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/001
EU/1/07/436/002 180 film-coated tablets (3 bottles of 60)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ISENTRESS 400 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle for ISENTRESS 400 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 400 mg film-coated tablets
raltegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 400 mg of raltegravir (as potassium).

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not switch with other strengths or formulations of Isentress without first talking with your doctor, pharmacist or nurse.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MSD

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/001
EU/1/07/436/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for 600 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 600 mg film-coated tablets
raltegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 600 mg of raltegravir (as potassium).

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets
Multipack: 180 (3 bottles of 60) film-coated tablets

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Two tablets once a day

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not switch with other strengths or formulations of Isentress without first talking with your doctor, pharmacist or nurse.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/006
EU/1/07/436/007 180 film-coated tablets (3 bottles of 60)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ISENTRESS 600 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle for ISENTRESS 600 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 600 mg film-coated tablets
raltegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 600 mg of raltegravir (as potassium).

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Two tablets once a day

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not switch with other strengths or formulations of Isentress without first talking with your doctor, pharmacist or nurse.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MSD

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/006
EU/1/07/436/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for 100 mg chewable tablets

1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 100 mg chewable tablets
raltegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains fructose, sorbitol, sucrose and aspartame. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 chewable tablets

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not switch with other strengths or formulations of Isentress without first talking with your doctor, pharmacist or nurse.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ISENTRESS 100 mg chewable tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

ISENTRESS 100 mg – bottle labeling

1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 100 mg chewable tablets
raltegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains fructose, E 420, sucrose, and E 951. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 chewable tablets

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not switch with other strengths or formulations of Isentress without first talking with your doctor, pharmacist or nurse.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MSD

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for the 25 mg chewable tablets

1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 25 mg chewable tablets
raltegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains fructose, sorbitol, sucrose and aspartame. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 chewable tablets

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not switch with other strengths or formulations of Isentress without first talking with your doctor, pharmacist or nurse.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ISENTRESS 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

ISENTRESS 25 mg – bottle labeling

1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 25 mg chewable tablets
raltegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains fructose, E 420, sucrose and E 951. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 chewable tablets

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not switch with other strengths or formulations of Isentress without first talking with your doctor, pharmacist or nurse.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MSD

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for ISENTRESS 100 mg granules for oral suspension

1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 100 mg granules for oral suspension
raltegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 100 mg of raltegravir (as potassium). Following reconstitution the oral suspension has a concentration of 10 mg per mL.

3. LIST OF EXCIPIENTS

Contains fructose, sorbitol and sucrose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 sachets, two 1 mL, two 3 mL and two 10 mL oral dosing syringes and 2 mixing cups.

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet and booklet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not switch with other strengths or formulations of Isentress without first talking with your doctor, pharmacist or nurse.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ISENTRESS 100 mg granules for oral suspension

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Unit dose sachet for ISENTRESS 100 mg granules for oral suspension – foil sachet

1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 100 mg granules
Raltegravir
Oral use

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Isentress 400 mg film-coated tablets
raltegravir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
If you are the parent of a child taking Isentress, please read this information carefully with your child.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you or your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Isentress is and what it is used for

What Isentress is
Isentress contains the active substance raltegravir. Isentress is an antiviral medicine that works against the Human Immunodeficiency Virus (HIV). This is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

How Isentress works
The virus produces an enzyme called HIV integrase. This helps the virus to multiply in the cells in your body. Isentress stops this enzyme from working. When used with other medicines, Isentress may reduce the amount of HIV in your blood (this is called your "viral load") and increase your CD4-cell count (a type of white blood cells that plays an important role in maintaining a healthy immune system to help fight infection). Reducing the amount of HIV in the blood may improve the functioning of your immune system. This means your body may fight infection better.

When Isentress should be used
Isentress is used to treat those who are infected by HIV. Your doctor has prescribed Isentress to help control your HIV infection.

2. What you need to know before you take Isentress

Do not take Isentress:
- If you are allergic to raltegravir or to any of the other ingredients in this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Isentress.
Remember that Isentress is not a cure for HIV infection. This means that you may keep getting infections or other illnesses associated with HIV. You should keep seeing your doctor regularly while taking this medicine.

Mental health problems
Tell your doctor if you have a history of depression or psychiatric illness. Depression, including suicidal thoughts and behaviours, has been reported in some patients taking this medicine, particularly in patients with a prior history of depression or psychiatric illness.

Bone problems
Some patients taking combination anti-retroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination anti-retroviral therapy, corticosteroid use, alcohol consumption, severe reduction of the activity of the immune system, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms, please inform your doctor.

Liver problems
Tell your doctor, pharmacist or nurse if you have had problems with your liver before, including hepatitis B or C. Your doctor may evaluate how severe your liver disease is before deciding if you can take this medicine.

Infections
Tell your doctor, pharmacist or nurse immediately if you notice any symptoms of infection, such as fever, and/or feeling unwell. In some patients with advanced HIV infection and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

Muscle problems
Contact your doctor, pharmacist or nurse immediately if you experience unexplained muscle pain, tenderness, or weakness while taking this medicine.

Skin problems
Contact your doctor promptly if you develop a rash. Severe and life-threatening skin reactions and allergic reactions have been reported in some patients taking this medicine.

Other medicines and Isentress
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines with or without a prescription.

Isentress might interact with other medicines.

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take:
- antacids (an agent that counteracts or neutralises the acid in the stomach to relieve indigestion and heartburn). It is not recommended to take Isentress with certain antacids (those containing aluminium and/or magnesium). Talk to your doctor about other antacids you can take.
- iron salts (to treat and prevent iron deficiency or anemia). You should wait at least two hours between taking iron salts and taking Isentress, as these medicines may reduce Isentress efficacy.
- rifampicin (a medicine used to treat some infections such as tuberculosis), as it may decrease your levels of Isentress. Your doctor may consider increasing your dose of Isentress if you are taking rifampicin.

Taking Isentress with food and drink
See section 3.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- Breast-feeding is not recommended in women living with HIV because HIV infection can be passed on to the baby in breast milk.
- If you are breast-feeding, or thinking about breast-feeding, you should discuss it with your doctor as soon as possible.

Ask your doctor, pharmacist or nurse for advice before taking any medicine if you are pregnant or breast-feeding.

Driving and using machines
Do not operate machines, drive or cycle if you feel dizzy after taking this medicine.

Isentress contains lactose
This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Isentress contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. How to take Isentress

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. You should check with your doctor, pharmacist or nurse if you are not sure. Isentress must be used in combination with other medicines for HIV.

How much to take
Adults
The recommended dose is 1 tablet (400 mg) by mouth twice a day.

Use in children and adolescents
The recommended dose of Isentress is 400 mg by mouth, twice a day for adolescents and children weighing at least 25 kg.

Do not chew, crush or split the tablets because it may change the level of medicine in your body. This medicine can be taken with or without food or drink.

Isentress is also available in a 600 mg tablet, a chewable tablet and in granules for oral suspension. Do not switch between the 400 mg tablet, the 600 mg tablet, chewable tablet or granules for oral suspension without first talking with your doctor, pharmacist or nurse.

If you take more Isentress than you should
Do not take more tablets than the doctor recommends. If you do take too many tablets, contact your doctor.

If you forget to take Isentress
- If you forget to take a dose, take it as soon as you remember it.
- However, if it is time for your next dose, skip the missed dose and go back to your regular schedule.
- Do not take a double dose to make up for a forgotten dose.

If you stop taking Isentress
It is important that you take Isentress exactly as your doctor has instructed. Do not change the dose or stop taking this medicine without first talking with your doctor, pharmacist or nurse. Do not stop taking it because:
- It is very important to take all your HIV medicines as prescribed and at the right times of day. This can help your medicines work better. It also lowers the chance that your medicines will stop being able to fight HIV (also called "drug resistance").
- When your supply of Isentress starts to run low, get more from your doctor or pharmacy. This is because it is very important not to be without the medicine, even for a short time. During a short break in taking the medicine the amount of virus in your blood may increase. This may mean that the HIV virus will develop resistance to Isentress and become harder to treat.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects – these are uncommon (may affect up to 1 in 100 people)
See a doctor immediately, if you notice any of the following:
- herpes infections including shingles
- anaemia including due to low iron
- signs and symptoms of infection or inflammation
- mental disorder
- suicide intention or attempt
- stomach inflammation
- inflammation of liver
- liver failure
- allergic rash
- certain kinds of kidney problems
- drug ingestion in quantities greater than recommended

See a doctor immediately, if you notice any of the side effects above.

Common: the following may affect up to 1 in 10 people
- decreased appetite
- trouble sleeping; abnormal dreams; nightmare; abnormal behaviour; feelings of deep sadness and unworthiness
- feeling dizzy; headache
- spinning sensation
- bloating; abdominal pain; diarrhoea; excessive gas in the stomach or bowel; feeling sick; vomiting; indigestion; belching
- certain kinds of rash (more often when used in combination with darunavir)
- tiredness, unusual tiredness or weakness; fever

- increased liver blood tests; abnormal white blood cells; increased fat levels in blood; increased level of enzyme from salivary glands or pancreas

Uncommon: the following may affect up to 1 in 100 people
- infection of the hair roots; influenza; skin infection due to virus; vomiting or diarrhoea due to an infectious agent; upper respiratory tract infection; lymph node abscess
- wart
- lymph node pain; low count of white blood cells that fight infection; swollen glands in the neck, armpit and groin
- allergic reaction
- increased appetite; diabetes; increased blood cholesterol and lipids; high sugar levels in the blood; excessive thirst; severe weight loss; high levels of fat (such as cholesterol and triglycerides) in the blood; body fat disorder
- feeling anxious; feeling of confusion; depressed mood; mood changes; panic attack
- loss of memory; pain in the hand due to nerve compression; disturbance in attention; dizziness with rapid changes in posture; abnormal taste; increased sleepiness; lack of energy; forgetfulness; migraine headache; loss of feeling, numbness or weakness of the arms and/or legs; tingling; sleepiness; tension headache; tremors; poor quality sleep
- visual disturbance
- buzzing, hissing, whistling, ringing or other persistent noise in the ears
- palpitations; slow heart rates; fast or irregular heart beats
- hot flush; high blood pressure
- harsh, raspy, or strained voice; nosebleed; nasal congestion
- abdominal pain upper; rectal discomfort; constipation; dry mouth; heartburn; pain when swallowing; inflammation of the pancreas; ulcer or sore in stomach or upper intestine; bleeding at anus; stomach discomfort; inflammation of the gums; swollen, red sore tongue
- accumulation of fat in the liver
- acne; unusual hair loss or thinning; redness of skin; unusual distribution of fat on the body, this may include loss of fat from legs, arms, and face, and increase in abdomen fat; excessive sweating; night sweats; thickening and itching of the skin due to repeated scratching; skin lesion; dry skin
- joint pain; painful joint disease; back pain; pain in bone/muscle; muscle tenderness or weakness; neck pain; pain in arms or legs; inflammation of the tendons; decrease in the amount of minerals in the bone
- kidney stones; urination at night; kidney cyst
- erectile dysfunction; breast enlargement in men; menopausal symptoms
- chest discomfort; chills; swelling of face; feeling jittery; generally feeling unwell; neck mass; swelling of hands, ankles or feet; pain
- decreased white blood cell count; decreased count of platelets in blood (a kind of cell that helps blood clot); blood test showing reduced kidney function; high blood sugar level; increased muscle enzyme in blood; sugar present in urine; red blood cells present in urine; weight gain; increase in waist size; decreased blood protein (albumin); increase in time for blood to clot

Additional side effects in children and adolescents
- hyperactivity

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Isentress

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the bottle after EXP. The expiry date refers to the last day of that month.
- This product does not require any special storage conditions.
- Keep the bottle tightly closed, with the desiccant (drying agent) in order to protect from moisture. Do not swallow the desiccant.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Isentress contains
The active substance is raltegravir. Each film-coated tablet contains 400 mg of raltegravir (as potassium).

The other ingredients are: lactose monohydrate, microcrystalline cellulose, calcium phosphate dibasic anhydrous, hypromellose 2208, poloxamer 407, sodium stearyl fumarate, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, red iron oxide and black iron oxide.

What Isentress looks like and contents of the pack
The 400 mg film-coated tablet is oval-shaped, pink, marked with "227" on one side.
Two pack sizes are available: packs containing 1 bottle with 60 tablets, and multipacks comprising 3 bottles, each containing 60 tablets. The bottle contains desiccant.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
MSD Belgium
Tél/Tel: +32(0)27766211
dpoc_belux@msd.com

България
Мерк Шарп и Доум България ЕООД
Тел.: +359 2 819 3737
info-msdbg@msd.com

Česká republika
Merck Sharp & Dohme s.r.o.
Tel.: +420 277 050 000
dpoc_czechslovak@msd.com

Lietuva
UAB Merck Sharp & Dohme
Tel. +370 5 2780 247
dpoc_lithuania@msd.com

Luxembourg/Luxemburg
MSD Belgium
Tél/Tel: +32(0)27766211
dpoc_belux@msd.com

Magyarország
MSD Pharma Hungary Kft.
Tel.: +36 1 888 5300
hungary_msd@msd.com

Danmark
MSD Danmark ApS
Tlf.: +45 4482 4000
dkmail@msd.com

Deutschland
MSD Sharp & Dohme GmbH
Tel.: +49 (0) 89 20 300 4500
medinfo@msd.de

Eesti
Merck Sharp & Dohme OÜ
Tel: +372 614 4200
dpoc.estonia@msd.com

Ελλάδα
MSD Α.Φ.Ε.Ε.
Τηλ: +30 210 98 97 300
dpoc.greece@msd.com

España
Merck Sharp & Dohme de España, S.A.
Tel: +34 91 321 06 00
msd_info@msd.com

France
MSD France
Tél: +33 (0)1 80 46 40 40

Hrvatska
Merck Sharp & Dohme d.o.o.
Tel: +385 1 6611 333
dpoc.croatia@msd.com

Ireland
Merck Sharp & Dohme Ireland (Human Health) Limited
Tel: +353 (0)1 2998700
medinfo_ireland@msd.com

Ísland
Vistor ehf.
Sími: +354 535 7000

Italia
MSD Italia S.r.l.
Tel: 800 23 99 89 (+39 06 361911)
dpoc.italy@msd.com

Κύπρος
Merck Sharp & Dohme Cyprus Limited
Τηλ: 800 00 673 (+357 22866700)
dpoccyprus@msd.com

Malta
Merck Sharp & Dohme Cyprus Limited
Tel: 8007 4433 (+356 99917558)
dpoccyprus@msd.com

Nederland
Merck Sharp & Dohme B.V.
Tel: 0800 9999000
(+31 23 5153153)
medicalinfo.nl@msd.com

Norge
MSD (Norge) AS
Tlf: +47 32 20 73 00
medinfo.norway@msd.com

Österreich
Merck Sharp & Dohme Ges.m.b.H.
Tel: +43 (0) 1 26 044
dpoc_austria@msd.com

Polska
MSD Polska Sp. z o.o.
Tel.: +48 22 549 51 00
msdpolska@msd.com

Portugal
Merck Sharp & Dohme, Lda
Tel.: +351 21 4465700
inform_pt@msd.com

România
Merck Sharp & Dohme Romania S.R.L.
Tel.: +40 21 529 29 00
msdromania@msd.com

Slovenija
Merck Sharp & Dohme, inovativna zdravila d.o.o.
Tel: +386 1 520 4201
msd.slovenia@msd.com

Slovenská republika
Merck Sharp & Dohme, s. r. o.
Tel.: +421 2 58282010
dpoc_czechslovak@msd.com

Suomi/Finland
MSD Finland Oy
Puh/Tel: +358 (0)9 804 650
info@msd.fi

Sverige
Merck Sharp & Dohme (Sweden) AB
Tel: +46 77 5700488
medicinskinfo@msd.com

Latvija
SIA Merck Sharp & Dohme Latvija
Tel.: +371 67025300
dpoc.latvia@msd.com

This leaflet was last revised in <{MM/YYYY}><{month YYYY}>.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Package leaflet: Information for the user

Isentress 600 mg film-coated tablets
raltegravir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
If you are the parent of a child taking Isentress, please read this information carefully with your child.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you or your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Isentress is and what it is used for

What Isentress is
Isentress contains the active substance raltegravir. Isentress is an antiviral medicine that works against the Human Immunodeficiency Virus (HIV). This is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

How Isentress works
The virus produces an enzyme called HIV integrase. This helps the virus to multiply in the cells in your body. Isentress stops this enzyme from working. When used with other medicines, Isentress may reduce the amount of HIV in your blood (this is called your "viral load") and increase your CD4-cell count (a type of white blood cells that plays an important role in maintaining a healthy immune system to help fight infection). Reducing the amount of HIV in the blood may improve the functioning of your immune system. This means your body may fight infection better.

When Isentress should be used
Isentress 600 mg film-coated tablets is used to treat adults and paediatric patients weighing at least 40 kg who are infected by HIV. Your doctor has prescribed Isentress to help control your HIV infection.

2. What you need to know before you take Isentress

Do not take Isentress:
- If you are allergic to raltegravir or to any of the other ingredients in this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Isentress.
Remember that Isentress is not a cure for HIV infection. This means that you may keep getting infections or other illnesses associated with HIV. You should keep seeing your doctor regularly while taking this medicine.

Mental health problems
Tell your doctor if you have a history of depression or psychiatric illness. Depression, including suicidal thoughts and behaviours, has been reported in some patients taking this medicine, particularly in patients with a prior history of depression or psychiatric illness.

Bone problems
Some patients taking combination anti-retroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination anti-retroviral therapy, corticosteroid use, alcohol consumption, severe reduction of the activity of the immune system, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms, please inform your doctor.

Liver problems
Tell your doctor, pharmacist or nurse if you have had problems with your liver before, including hepatitis B or C. Your doctor may evaluate how severe your liver disease is before deciding if you can take this medicine.

Infections
Tell your doctor, pharmacist or nurse immediately if you notice any symptoms of infection, such as fever, and/or feeling unwell. In some patients with advanced HIV infection and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

Muscle problems
Contact your doctor, pharmacist or nurse immediately if you experience unexplained muscle pain, tenderness, or weakness while taking this medicine.

Skin problems
Contact your doctor promptly if you develop a rash. Severe and life-threatening skin reactions and allergic reactions have been reported in some patients taking this medicine.

Other medicines and Isentress
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Isentress might interact with other medicines. Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take:

- antacids (an agent that counteracts or neutralises the acid in the stomach to relieve indigestion and heartburn)

- iron salts (to treat and prevent iron deficiency or anemia). You should wait at least two hours between taking iron salts and taking Isentress, as these medicines may reduce Isentress efficacy
- atazanavir (an antiretroviral medication)
- rifampicin (a medicine used to treat some infections such as tuberculosis)
- tipranavir/ritonavir (antiretroviral medicines)

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

Taking Isentress with food and drink
See section 3.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- Isentress 1,200 mg (two 600 mg tablets once daily) is not recommended in pregnancy because it has not been studied in pregnant women.
- Breast-feeding is not recommended in women living with HIV because HIV infection can be passed on to the baby in breast milk.
- If you are breast-feeding, or thinking about breast-feeding, you should discuss it with your doctor as soon as possible.

Ask your doctor, pharmacist or nurse for advice before taking any medicine if you are pregnant or breast-feeding.

Driving and using machines
Do not operate machines, drive or cycle if you feel dizzy after taking this medicine.

Isentress contains lactose
This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Isentress contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Isentress

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. You should check with your doctor, pharmacist or nurse if you are not sure. Isentress must be used in combination with other medicines for HIV.

How much to take
Adults, children and adolescents weighing at least 40 kg
The recommended dose is 1,200 mg taken as two 600 mg tablets taken by mouth once a day.

Do not chew, crush or split the tablets because it may change the level of medicine in your body. This medicine can be taken with or without food or drink.

Isentress is also available in a 400 mg tablet, a chewable tablet and in granules for oral suspension. Do not switch between the 600 mg tablet, 400 mg tablet, chewable tablet or granules for oral suspension without first talking with your doctor, pharmacist or nurse.

If you take more Isentress than you should
Do not take more tablets than the doctor recommends. If you do take too many tablets, contact your doctor.

If you forget to take Isentress
- If you forget to take a dose, take it as soon as you remember it.
- However, if it is time for your next dose, skip the missed dose and go back to your regular schedule.
- Do not take a double dose to make up for a forgotten dose.

If you stop taking Isentress
It is important that you take Isentress exactly as your doctor has instructed. Do not change the dose or stop taking this medicine without first talking with your doctor, pharmacist or nurse.
Do not stop taking it because:
- It is very important to take all your HIV medicines as prescribed and at the right times of day. This can help your medicines work better. It also lowers the chance that your medicines will stop being able to fight HIV (also called "drug resistance").
- When your supply of Isentress starts to run low, get more from your doctor or pharmacy. This is because it is very important not to be without the medicine, even for a short time. During a short break in taking the medicine the amount of virus in your blood may increase. This may mean that the HIV virus will develop resistance to Isentress and become harder to treat.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects – these are uncommon (may affect up to 1 in 100 people)
See a doctor immediately, if you notice any of the following:
- herpes infections including shingles
- anaemia including due to low iron
- signs and symptoms of infection or inflammation
- mental disorder
- suicide intention or attempt
- stomach inflammation
- inflammation of liver
- liver failure
- allergic rash
- certain kinds of kidney problems
- drug ingestion in quantities greater than recommended

See a doctor immediately, if you notice any of the side effects above.

Common: the following may affect up to 1 in 10 people
- decreased appetite
- trouble sleeping; abnormal dreams; nightmare; abnormal behaviour; feelings of deep sadness and unworthiness
- feeling dizzy; headache
- spinning sensation
- bloating; abdominal pain; diarrhoea; excessive gas in the stomach or bowel; feeling sick; vomiting; indigestion; belching
- certain kinds of rash (more often when used in combination with darunavir)
- tiredness, unusual tiredness or weakness; fever

- increased liver blood tests; abnormal white blood cells; increased fat levels in blood; increased level of enzyme from salivary glands or pancreas

Uncommon: the following may affect up to 1 in 100 people
- infection of the hair roots; influenza; skin infection due to virus; vomiting or diarrhoea due to an infectious agent; upper respiratory tract infection; lymph node abscess
- wart
- lymph node pain; low count of white blood cells that fight infection; swollen glands in the neck, armpit and groin
- allergic reaction
- increased appetite; diabetes; increased blood cholesterol and lipids; high sugar levels in the blood; excessive thirst; severe weight loss; high levels of fat (such as cholesterol and triglycerides) in the blood; body fat disorder
- feeling anxious; feeling of confusion; depressed mood; mood changes; panic attack
- loss of memory; pain in the hand due to nerve compression; disturbance in attention; dizziness with rapid changes in posture; abnormal taste; increased sleepiness; lack of energy; forgetfulness; migraine headache; loss of feeling, numbness or weakness of the arms and/or legs; tingling; sleepiness; tension headache; tremors; poor quality sleep
- visual disturbance
- buzzing, hissing, whistling, ringing or other persistent noise in the ears
- palpitations; slow heart rates; fast or irregular heart beats
- hot flush; high blood pressure
- harsh, raspy, or strained voice; nosebleed; nasal congestion
- abdominal pain upper; rectal discomfort; constipation; dry mouth; heartburn; pain when swallowing; inflammation of the pancreas; ulcer or sore in stomach or upper intestine; bleeding at anus; stomach discomfort; inflammation of the gums; swollen, red sore tongue
- accumulation of fat in the liver
- acne; unusual hair loss or thinning; redness of skin; unusual distribution of fat on the body, this may include loss of fat from legs, arms, and face, and increase in abdomen fat; excessive sweating; night sweats; thickening and itching of the skin due to repeated scratching; skin lesion; dry skin
- joint pain; painful joint disease; back pain; pain in bone/muscle; muscle tenderness or weakness; neck pain; pain in arms or legs; inflammation of the tendons; decrease in the amount of minerals in the bone
- kidney stones; urination at night; kidney cyst
- erectile dysfunction; breast enlargement in men; menopausal symptoms
- chest discomfort; chills; swelling of face; feeling jittery; generally feeling unwell; neck mass; swelling of hands, ankles or feet; pain
- decreased white blood cell count; decreased count of platelets in blood (a kind of cell that helps blood clot); blood test showing reduced kidney function; high blood sugar level; increased muscle enzyme in blood; sugar present in urine; red blood cells present in urine; weight gain; increase in waist size; decreased blood protein (albumin); increase in time for blood to clot

Additional side effects in children and adolescents
- hyperactivity

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Isentress

- Keep this medicine out of the sight and reach of children.

- Do not use this medicine after the expiry date which is stated on the bottle after EXP. The expiry date refers to the last day of that month.
- Keep the bottle tightly closed, with the desiccant (drying agent) in order to protect from moisture. Do not swallow the desiccant.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Isentress contains
The active substance is raltegravir. Each film-coated tablet contains 600 mg of raltegravir (as potassium).

The other ingredients are: microcrystalline cellulose, hypromellose 2910, croscarmellose sodium and magnesium stearate. In addition, the film coating contains the following inactive ingredients: lactose monohydrate, hypromellose 2910, titanium dioxide, triacetin, iron oxide yellow and black iron oxide. The tablet may also contain trace amount of carnauba wax.

What Isentress looks like and contents of the pack
The 600 mg film-coated tablet is oval-shaped, yellow, marked with MSD corporate logo and "242" on one side and plain on the other side.
Two pack sizes are available: packs containing 1 bottle with 60 tablets, and multipacks comprising 3 bottles, each containing 60 tablets. The bottle contains desiccant.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
MSD Belgium
Tél/Tel: +32(0)27766211
dpoc_belux@msd.com

България
Мерк Шарп и Доум България ЕООД
Тел.: +359 2 819 3737
info-msdbg@msd.com

Česká republika
Merck Sharp & Dohme s.r.o.
Tel.: +420 277 050 000
dpoc_czechslovak@msd.com

Lietuva
UAB Merck Sharp & Dohme
Tel. +370 5 2780 247
dpoc_lithuania@msd.com

Luxembourg/Luxemburg
MSD Belgium
Tél/Tel: +32(0)27766211
dpoc_belux@msd.com

Magyarország
MSD Pharma Hungary Kft.
Tel.: +36 1 888 5300
hungary_msd@msd.com

Danmark
MSD Danmark ApS
Tlf.: +45 4482 4000
dkmail@msd.com

Deutschland
MSD Sharp & Dohme GmbH
Tel.: +49 (0) 89 20 300 4500
medinfo@msd.de

Eesti
Merck Sharp & Dohme OÜ
Tel: +372 614 4200
dpoc.estonia@msd.com

Ελλάδα
MSD Α.Φ.Ε.Ε.
Τηλ: +30 210 98 97 300
dpoc.greece@msd.com

España
Merck Sharp & Dohme de España, S.A.
Tel: +34 91 321 06 00
msd_info@msd.com

France
MSD France
Tél: +33 (0)1 80 46 40 40

Hrvatska
Merck Sharp & Dohme d.o.o.
Tel: +385 1 6611 333
dpoc.croatia@msd.com

Ireland
Merck Sharp & Dohme Ireland (Human Health) Limited
Tel: +353 (0)1 2998700
medinfo_ireland@msd.com

Ísland
Vistor ehf.
Sími: +354 535 7000

Italia
MSD Italia S.r.l.
Tel: 800 23 99 89 (+39 06 361911)
dpoc.italy@msd.com

Κύπρος
Merck Sharp & Dohme Cyprus Limited
Τηλ: 800 00 673 (+357 22866700)
dpoccyprus@msd.com

Malta
Merck Sharp & Dohme Cyprus Limited
Tel: 8007 4433 (+356 99917558)
dpoccyprus@msd.com

Nederland
Merck Sharp & Dohme B.V.
Tel: 0800 9999000
(+31 23 5153153)
medicalinfo.nl@msd.com

Norge
MSD (Norge) AS
Tlf: +47 32 20 73 00
medinfo.norway@msd.com

Österreich
Merck Sharp & Dohme Ges.m.b.H.
Tel: +43 (0) 1 26 044
dpoc_austria@msd.com

Polska
MSD Polska Sp. z o.o.
Tel.: +48 22 549 51 00
msdpolska@msd.com

Portugal
Merck Sharp & Dohme, Lda
Tel.: +351 21 4465700
inform_pt@msd.com

România
Merck Sharp & Dohme Romania S.R.L.
Tel.: +40 21 529 29 00
msdromania@msd.com

Slovenija
Merck Sharp & Dohme, inovativna zdravila d.o.o.
Tel: +386 1 520 4201
msd.slovenia@msd.com

Slovenská republika
Merck Sharp & Dohme, s. r. o.
Tel.: +421 2 58282010
dpoc_czechslovak@msd.com

Suomi/Finland
MSD Finland Oy
Puh/Tel: +358 (0)9 804 650
info@msd.fi

Sverige
Merck Sharp & Dohme (Sweden) AB
Tel: +46 77 5700488
medicinskinfo@msd.com

Latvija
SIA Merck Sharp & Dohme Latvija
Tel.: +371 67025300
dpoc.latvia@msd.com

This leaflet was last revised in <{MM/YYYY}><{month YYYY}>.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Package leaflet: Information for the user

Isentress 25 mg chewable tablets
Isentress 100 mg chewable tablets
raltegravir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
If you are the parent of a child taking Isentress, please read this information carefully with your child.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you or your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Isentress is and what it is used for

What Isentress is
Isentress contains the active substance raltegravir. Isentress is an antiviral medicine that works against the Human Immunodeficiency Virus (HIV). This is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

How Isentress works
The virus produces an enzyme called HIV integrase. This helps the virus to multiply in the cells in your body. Isentress stops this enzyme from working. When used with other medicines, Isentress may reduce the amount of HIV in your blood (this is called your "viral load") and increase your CD4-cell count (a type of white blood cells that plays an important role in maintaining a healthy immune system to help fight infection). Reducing the amount of HIV in the blood may improve the functioning of your immune system. This means your body may fight infection better.

When Isentress should be used
Isentress is used to treat those who are infected by HIV. Your doctor has prescribed Isentress to help control your HIV infection.

2. What you need to know before you take Isentress

Do not take Isentress
- If you are allergic to raltegravir or to any of the other ingredients in this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Isentress.
Remember that Isentress is not a cure for HIV infection. This means that you may keep getting infections or other illnesses associated with HIV. You should keep seeing your doctor regularly while taking this medicine.

Mental health problems
Tell your doctor if you have a history of depression or psychiatric illness. Depression, including suicidal thoughts and behaviours, has been reported in some patients taking this medicine, particularly in patients with a prior history of depression or psychiatric illness.

Bone problems
Some patients taking combination anti-retroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination anti-retroviral therapy, corticosteroid use, alcohol consumption, severe reduction of the activity of the immune system, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms, please inform your doctor.

Liver problems
Tell your doctor, pharmacist or nurse if you have had problems with your liver before, including hepatitis B or C. Your doctor may evaluate how severe your liver disease is before deciding if you can take this medicine.

Infections
Tell your doctor, pharmacist or nurse immediately if you notice any symptoms of infection, such as fever, and/or feeling unwell. In some patients with advanced HIV infection and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

Muscle problems
Contact your doctor, pharmacist or nurse immediately if you experience unexplained muscle pain, tenderness, or weakness while taking this medicine.

Skin problems
Contact your doctor promptly if you develop a rash. Severe and life-threatening skin reactions and allergic reactions have been reported in some patients taking this medicine.

Other medicines and Isentress
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines with or without a prescription.

Isentress might interact with other medicines.

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take:
- antacids (an agent that counteracts or neutralises the acid in the stomach to relieve indigestion and heartburn). It is not recommended to take Isentress with certain antacids (those containing aluminium and/or magnesium). Talk to your doctor about other antacids you can take.
- iron salts (to treat and prevent iron deficiency or anemia). You should wait at least two hours between taking iron salts and taking Isentress, as these medicines may reduce Isentress efficacy.
- rifampicin (a medicine used to treat some infections such as tuberculosis), as it may decrease your levels of Isentress. Your doctor may consider increasing your dose of Isentress if you are taking rifampicin.

Taking Isentress with food and drink
See section 3.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- Isentress chewable tablets are not recommended in pregnancy because they have not been studied in pregnant women.
- Breast-feeding is not recommended in women living with HIV because HIV infection can be passed on to the baby in breast milk.
- If you are breast-feeding, or thinking about breast-feeding, you should discuss it with your doctor as soon as possible.

Ask your doctor, pharmacist or nurse for advice before taking any medicine if you are pregnant or breast-feeding.

Driving and using machines
Do not operate machines, drive or cycle if you feel dizzy after taking this medicine.

Isentress 25 mg chewable tablet

Isentress 25 mg chewable tablet contains fructose
This medicine contains fructose up to 0.54 mg in each tablet.
Fructose may damage teeth.

Isentress 25 mg chewable tablet contains sorbitol
This medicine contains sorbitol (E 420) up to 1.5 mg in each tablet.

Isentress 25 mg chewable tablet contains sucrose
This medicine contains up to 3.5 mg of sucrose in each 25 mg chewable tablet.
Sucrose may be harmful to the teeth.

If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

Isentress 25 mg chewable tablet contains aspartame
This medicine contains up to 0.47 mg aspartame (E 951) in each 25 mg chewable tablet which is equivalent to up to 0.05 mg phenylalanine. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Isentress 25 mg chewable tablet contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Isentress 100 mg chewable tablet

Isentress 100 mg chewable tablet contains fructose
This medicine contains fructose up to 1.07 mg in each tablet.
Fructose may damage teeth.

Isentress 100 mg chewable tablet contains sorbitol
This medicine contains sorbitol (E 420) up to 2.9 mg in each tablet.

Isentress 100 mg chewable tablet contains sucrose
This medicine contains up to 7 mg of sucrose in each 100 mg chewable tablet.
Sucrose may be harmful to the teeth.

If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

Isentress 100 mg chewable tablet contains aspartame
This medicine contains up to 0.93 mg aspartame (E 951) in each 100 mg chewable tablet which is equivalent to up to 0.10 mg phenylalanine. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Isentress 100 mg chewable tablet contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Isentress

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. You should check with your doctor, pharmacist or nurse if you are not sure. Isentress must be used in combination with other medicines for HIV.

The 100 mg chewable tablet can be split into equal halves. However, breaking the tablets should be avoided whenever possible.

How much to take
Dose for children of 2 through 11 years of age
The doctor will work out the right dose of the chewable tablet based on the age and weight of the child. This dose must not exceed 300 mg twice a day. The doctor will tell you how many chewable tablets the child must take.

Isentress is also available in a 400 mg tablet, a 600 mg tablet and in granules for oral suspension. Do not switch between the chewable tablet, granules for oral suspension, 600 mg tablet or 400 mg tablet without first talking with your doctor, pharmacist or nurse.

Children should keep scheduled doctor's visits because their Isentress dosage should be adjusted as they get older, grow or gain weight. Their doctor may also want to prescribe the 400 mg tablet when they are able to swallow a tablet.

You can take this medicine with or without food or drink.

If you take more Isentress than you should
Do not take more tablets than the doctor recommends. If you do take too many tablets, contact your doctor.

If you forget to take Isentress
- If you forget to take a dose, take it as soon as you remember it.
- However, if it is time for your next dose, skip the missed dose and go back to your regular schedule.
- Do not take a double dose to make up for a forgotten dose.

If you stop taking Isentress
It is important that you take Isentress exactly as your doctor has instructed. Do not change the dose or stop taking this medicine without first talking with your doctor, pharmacist or nurse. Do not stop taking it because:
- It is very important to take all your HIV medicines as prescribed and at the right times of day. This can help your medicines work better. It also lowers the chance that your medicines will stop being able to fight HIV (also called "drug resistance").
- When your supply of Isentress starts to run low, get more from your doctor or pharmacy. This is because it is very important not to be without the medicine, even for a short time. During a short break in taking the medicine the amount of virus in your blood may increase. This may mean that the HIV virus will develop resistance to Isentress and become harder to treat.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects – these are uncommon (may affect up to 1 in 100 people)
See a doctor immediately, if you notice any of the following:
- herpes infections including shingles
- anaemia including due to low iron
- signs and symptoms of infection or inflammation
- mental disorder
- suicide intention or attempt
- stomach inflammation
- inflammation of liver
- liver failure
- allergic rash
- certain kinds of kidney problems
- drug ingestion in quantities greater than recommended

See a doctor immediately, if you notice any of the side effects above.

Common: the following may affect up to 1 in 10 people
- decreased appetite
- trouble sleeping; abnormal dreams; nightmare; abnormal behaviour; feelings of deep sadness and unworthiness
- feeling dizzy; headache
- spinning sensation
- bloating; abdominal pain; diarrhoea; excessive gas in the stomach or bowel; feeling sick; vomiting; indigestion; belching
- certain kinds of rash (more often when used in combination with darunavir)
- tiredness, unusual tiredness or weakness; fever

- increased liver blood tests; abnormal white blood cells; increased fat levels in blood; increased level of enzyme from salivary glands or pancreas

Uncommon: the following may affect up to 1 in 100 people
- infection of the hair roots; influenza; skin infection due to virus; vomiting or diarrhoea due to an infectious agent; upper respiratory tract infection; lymph node abscess
- wart
- lymph node pain; low count of white blood cells that fight infection; swollen glands in the neck, armpit and groin
- allergic reaction
- increased appetite; diabetes; increased blood cholesterol and lipids; high sugar levels in the blood; excessive thirst; severe weight loss; high levels of fat (such as cholesterol and triglycerides) in the blood; body fat disorder
- feeling anxious; feeling of confusion; depressed mood; mood changes; panic attack
- loss of memory; pain in the hand due to nerve compression; disturbance in attention; dizziness with rapid changes in posture; abnormal taste; increased sleepiness; lack of energy; forgetfulness; migraine headache; loss of feeling, numbness or weakness of the arms and/or legs; tingling; sleepiness; tension headache; tremors; poor quality sleep
- visual disturbance
- buzzing, hissing, whistling, ringing or other persistent noise in the ears
- palpitations; slow heart rates; fast or irregular heart beats
- hot flush; high blood pressure
- harsh, raspy, or strained voice; nosebleed; nasal congestion
- abdominal pain upper; rectal discomfort; constipation; dry mouth; heartburn; pain when swallowing; inflammation of the pancreas; ulcer or sore in stomach or upper intestine; bleeding at anus; stomach discomfort; inflammation of the gums; swollen, red sore tongue
- accumulation of fat in the liver
- acne; unusual hair loss or thinning; redness of skin; unusual distribution of fat on the body, this may include loss of fat from legs, arms, and face, and increase in abdomen fat; excessive sweating; night sweats; thickening and itching of the skin due to repeated scratching; skin lesion; dry skin
- joint pain; painful joint disease; back pain; pain in bone/muscle; muscle tenderness or weakness; neck pain; pain in arms or legs; inflammation of the tendons; decrease in the amount of minerals in the bone
- kidney stones; urination at night; kidney cyst
- erectile dysfunction; breast enlargement in men; menopausal symptoms
- chest discomfort; chills; swelling of face; feeling jittery; generally feeling unwell; neck mass; swelling of hands, ankles or feet; pain
- decreased white blood cell count; decreased count of platelets in blood (a kind of cell that helps blood clot); blood test showing reduced kidney function; high blood sugar level; increased muscle enzyme in blood; sugar present in urine; red blood cells present in urine; weight gain; increase in waist size; decreased blood protein (albumin); increase in time for blood to clot

Additional side effects in children and adolescents
- hyperactivity

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Isentress

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the bottle after EXP. The expiry date refers to the last day of that month.
- Keep the bottle tightly closed, with the desiccant (drying agent) in order to protect from moisture. Do not swallow the desiccant.
- Prior to breaking the seal, this product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Isentress contains
The active substance is raltegravir.

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

The other ingredients are: hydroxypropyl cellulose, sucralose, saccharin sodium, sodium citrate dihydrate, mannitol (E 421), yellow iron oxide, monoammonium glycyrrhizinate, sorbitol (E 420), fructose, natural and artificial flavours (orange, banana, and masking), aspartame (E 951), sucrose, crospovidone Type A, magnesium stearate, sodium stearyl fumarate, ethylcellulose 20 cP, ammonium hydroxide, medium chain triglycerides, oleic acid, hypromellose 2910/6cP and macrogol/PEG 400.

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

The other ingredients are: hydroxypropyl cellulose, sucralose, saccharin sodium , sodium citrate dihydrate, mannitol (E 421), red iron oxide, yellow iron oxide, monoammonium glycyrrhizinate, sorbitol (E 420), fructose, natural and artificial flavours (orange, banana, and masking), aspartame (E 951), sucrose, crospovidone Type A, magnesium stearate, sodium stearyl fumarate, ethylcellulose 20 cP, ammonium hydroxide, medium chain triglycerides, oleic acid, hypromellose 2910/6cP, and macrogol/PEG 400.

What Isentress looks like and contents of the pack

Isentress 25 mg chewable tablets:
The orange-banana flavoured chewable tablet is round and pale yellow, marked with the MSD corporate logo on one side and “473” on the other side.
One pack size is available: 1 bottle with 60 tablets. The bottle contains desiccant.

Isentress 100 mg chewable tablets:
The orange-banana flavoured chewable tablet is oval-shaped, pale orange coloured, scored on both sides with the MSD corporate logo and "477" on one side and without inscription on the other side.
One pack size is available: 1 bottle with 60 tablets. The bottle contains desiccant.

Marketing Authorisation Holder and Manufacturer

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
MSD Belgium
Tél/Tel: +32(0)27766211
dpoc_belux@msd.com

България
Мерк Шарп и Доум България ЕООД
Тел.: +359 2 819 3737
info-msdbg@msd.com

Česká republika
Merck Sharp & Dohme s.r.o.
Tel.: +420 277 050 000
dpoc_czechslovak@msd.com

Danmark
MSD Danmark ApS
Tlf.: +45 4482 4000
dkmail@msd.com

Deutschland
MSD Sharp & Dohme GmbH
Tel.: +49 (0) 89 20 300 4500
medinfo@msd.de

Eesti
Merck Sharp & Dohme OÜ
Tel: +372 614 4200
dpoc.estonia@msd.com

Ελλάδα
MSD Α.Φ.Ε.Ε.
Τηλ: +30 210 98 97 300
dpoc.greece@msd.com

España
Merck Sharp & Dohme de España, S.A.
Tel: +34 91 321 06 00
msd_info@msd.com

France
MSD France
Tél: +33 (0)1 80 46 40 40

Hrvatska
Merck Sharp & Dohme d.o.o.
Tel: +385 1 6611 333
dpoc.croatia@msd.com

Lietuva
UAB Merck Sharp & Dohme
Tel. +370 5 2780 247
dpoc_lithuania@msd.com

Luxembourg/Luxemburg
MSD Belgium
Tél/Tel: +32(0)27766211
dpoc_belux@msd.com

Magyarország
MSD Pharma Hungary Kft.
Tel.: +36 1 888 5300
hungary_msd@msd.com

Malta
Merck Sharp & Dohme Cyprus Limited
Tel: 8007 4433 (+356 99917558)
dpoccyprus@msd.com

Nederland
Merck Sharp & Dohme B.V.
Tel: 0800 9999000
(+31 23 5153153)
medicalinfo.nl@msd.com

Norge
MSD (Norge) AS
Tlf: +47 32 20 73 00
medinfo.norway@msd.com

Österreich
Merck Sharp & Dohme Ges.m.b.H.
Tel: +43 (0) 1 26 044
dpoc_austria@msd.com

Polska
MSD Polska Sp. z o.o.
Tel.: +48 22 549 51 00
msdpolska@msd.com

Portugal
Merck Sharp & Dohme, Lda
Tel.: +351 21 4465700
inform_pt@msd.com

România
Merck Sharp & Dohme Romania S.R.L.
Tel.: +40 21 529 29 00
msdromania@msd.com

Ireland
Merck Sharp & Dohme Ireland (Human Health) Limited
Tel: +353 (0)1 2998700
medinfo_ireland@msd.com

Ísland
Vistor ehf.
Sími: +354 535 7000

Italia
MSD Italia S.r.l.
Tel: 800 23 99 89 (+39 06 361911)
dpoc.italy@msd.com

Κύπρος
Merck Sharp & Dohme Cyprus Limited
Τηλ: 800 00 673 (+357 22866700)
dpoccyprus@msd.com

Latvija
SIA Merck Sharp & Dohme Latvija
Tel.: +371 67025300
dpoc.latvia@msd.com

Slovenija
Merck Sharp & Dohme, inovativna zdravila d.o.o.
Tel: +386 1 520 4201
msd.slovenia@msd.com

Slovenská republika
Merck Sharp & Dohme, s. r. o.
Tel.: +421 2 58282010
dpoc_czechslovak@msd.com

Suomi/Finland
MSD Finland Oy
Puh/Tel: +358 (0)9 804 650
info@msd.fi

Sverige
Merck Sharp & Dohme (Sweden) AB
Tel: +46 77 5700488
medicinskinfo@msd.com

This leaflet was last revised in <{MM/YYYY}><{month YYYY}>.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Package leaflet: Information for the user

Isentress 100 mg granules for oral suspension
raltegravir

If you are the parent or carer of a child taking Isentress, please read this information carefully. Read all of this leaflet carefully before you start giving this medicine to your child because it contains important information.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Isentress is and what it is used for

What Isentress is
Isentress contains the active substance raltegravir. Isentress is an antiviral medicine that works against the Human Immunodeficiency Virus (HIV). This is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

How Isentress works
The virus produces an enzyme called HIV integrase. This helps the virus to multiply in the cells in your body. Isentress stops this enzyme from working. When used with other medicines, Isentress may reduce the amount of HIV in your blood (this is called your "viral load") and increase your CD4-cell count (a type of white blood cells that plays an important role in maintaining a healthy immune system to help fight infection). Reducing the amount of HIV in the blood may improve the functioning of your immune system. This means your body may fight infection better.

When Isentress should be used
Isentress is used to treat adults, adolescents, children, toddlers and infants who are infected by HIV and to treat newborn babies exposed to HIV-1 infection from the mother. Your doctor has prescribed Isentress to help control your HIV infection.

2. What you need to know before you take Isentress

Do not take Isentress
- If you are allergic to raltegravir or to any of the other ingredients in this medicine (listed in section 6.).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Isentress.
Remember that Isentress is not a cure for HIV infection. This means that you may keep getting infections or other illnesses associated with HIV. You should keep seeing your doctor regularly while taking this medicine.

Mental health problems
Tell your doctor if you have a history of depression or psychiatric illness. Depression, including suicidal thoughts and behaviours, has been reported in some patients taking this medicine, particularly in patients with a prior history of depression or psychiatric illness.

Bone problems
Some patients taking combination anti-retroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination anti-retroviral therapy, corticosteroid use, alcohol consumption, severe reduction of the activity of the immune system, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms, please inform your doctor.

Liver problems
Tell your doctor, pharmacist or nurse if you have had problems with your liver before, including hepatitis B or C. Your doctor may evaluate how severe your liver disease is before deciding if you can take this medicine.

Infections
Tell your doctor, pharmacist or nurse immediately if you notice any symptoms of infection, such as fever, and/or feeling unwell. In some patients with advanced HIV infection and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

Muscle problems
Contact your doctor, pharmacist or nurse immediately if you experience unexplained muscle pain, tenderness, or weakness while taking this medicine.

Skin problems
Contact your doctor promptly if you develop a rash. Severe and life-threatening skin reactions and allergic reactions have been reported in some patients taking this medicine.

Other medicines and Isentress
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines with or without a prescription.

Isentress might interact with other medicines.

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take:
- antacids (an agent that counteracts or neutralises the acid in the stomach to relieve indigestion and heartburn). It is not recommended to take Isentress with certain antacids (those containing aluminium and/or magnesium). Talk to your doctor about other antacids you can take.
- iron salts (to treat and prevent iron deficiency or anemia). You should wait at least two hours between taking iron salts and taking Isentress, as these medicines may reduce Isentress efficacy.
- rifampicin (a medicine used to treat some infections such as tuberculosis), as it may decrease your levels of Isentress. Your doctor may consider increasing your dose of Isentress if you are taking rifampicin.

Taking Isentress with food and drink
See section 3.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- Isentress granules for oral suspension are not recommended in pregnancy because they have not been studied in pregnant women.
- Breast-feeding is not recommended in women living with HIV because HIV infection can be passed on to the baby in breast milk.
- If you are breast-feeding, or thinking about breast-feeding, you should discuss it with your doctor as soon as possible.

Ask your doctor, pharmacist or nurse for advice before taking any medicine if you are pregnant or breast-feeding.

Driving and using machines
Do not operate machines, drive or cycle if you feel dizzy after taking this medicine.

Isentress 100 mg granules for oral suspension contain fructose
This medicine contains fructose up to 0.5 mg in each sachet.
Fructose may damage teeth.

Isentress 100 mg granules for suspension contain sorbitol
This medicine contains sorbitol (E 420) up to 1.5 mg in each sachet.

Isentress 100 mg granules for suspension contain sucrose
This medicine contains up to 4.7 mg of sucrose in each sachet.
Sucrose may be harmful to the teeth.

If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

Isentress 100 mg granules for suspension contain sodium
This medicine contains less than 1 mmol sodium (23 mg) per sachet, that is to say essentially 'sodium-free'.

3. How to take Isentress

Always give this medicine to your child exactly as their doctor, pharmacist or nurse has told you. You should check with your child's doctor, pharmacist or nurse if you are not sure. Isentress must be used in combination with other medicines for HIV.
- See the instructions for use in the booklet for how to prepare and give a dose of Isentress. Keep the booklet and follow it each time you prepare the medicine. Bring this booklet to your child's appointments.

- Make sure the doctor, pharmacist or nurse explains how to mix and give the right dose to your child.
- The granules need to be mixed with water before use. You must give to your child within 30 minutes of mixing.
- The dose will change over time. Make sure to follow the instructions of your doctor. The doctor will tell you if and when to stop giving Isentress to your baby.

How much to take
The doctor will work out the right dose of granules for oral suspension based on the age and weight of the infant or toddler. The doctor will tell you how much of the oral suspension the infant or toddler must take.
Your child can take this medicine with or without food or drink.

Isentress is also available in a 400 mg tablet, a 600 mg tablet and in a chewable tablet.
Do not switch between the granules for oral suspension, chewable tablet, 600 mg tablet or 400 mg tablet without first talking to your child's doctor, pharmacist or nurse.

Children should keep scheduled doctor's visits because their Isentress dosage should be adjusted as they get older, grow or gain weight. Their doctor may also want to prescribe the chewable tablet when they are able to chew a tablet.

If you take more Isentress than you should
Do not take more Isentress than the doctor recommends. If you do take more than you should, contact your doctor.

If you forget to take Isentress
- If you forget to take a dose, take it as soon as you remember it.
- However, if it is time for your next dose, skip the missed dose and go back to your regular schedule.
- Do not take a double dose to make up for a forgotten dose.

If you stop taking Isentress
It is important that you take Isentress exactly as your doctor has instructed. Do not change the dose or stop taking this medicine without first talking with your doctor, pharmacist or nurse. Do not stop taking it because:
- It is very important to take all your HIV medicines as prescribed and at the right times of day. This can help your medicines work better. It also lowers the chance that your medicines will stop being able to fight HIV (also called "drug resistance").
- When your supply of Isentress starts to run low, get more from your doctor or pharmacy. This is because it is very important not to be without the medicine, even for a short time. During a short break in taking the medicine the amount of virus in your blood may increase. This may mean that the HIV virus will develop resistance to Isentress and become harder to treat.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects – these are uncommon (may affect up to 1 in 100 people)
See a doctor immediately, if you notice any of the following:
- herpes infections including shingles
- anaemia including due to low iron
- signs and symptoms of infection or inflammation
- mental disorder

- suicide intention or attempt
- stomach inflammation
- inflammation of liver
- liver failure
- allergic rash
- certain kinds of kidney problems
- drug ingestion in quantities greater than recommended

See a doctor immediately, if you notice any of the side effects above.

Common: the following may affect up to 1 in 10 people
- decreased appetite
- trouble sleeping; abnormal dreams; nightmare; abnormal behaviour; feelings of deep sadness and unworthiness
- feeling dizzy; headache
- spinning sensation
- bloating; abdominal pain; diarrhoea; excessive gas in the stomach or bowel; feeling sick; vomiting; indigestion; belching
- certain kinds of rash (more often when used in combination with darunavir)
- tiredness, unusual tiredness or weakness; fever
- increased liver blood tests; abnormal white blood cells; increased fat levels in blood; increased level of enzyme from salivary glands or pancreas

Uncommon: the following may affect up to 1 in 100 people
- infection of the hair roots; influenza; skin infection due to virus; vomiting or diarrhoea due to an infectious agent; upper respiratory tract infection; lymph node abscess
- wart
- lymph node pain; low count of white blood cells that fight infection; swollen glands in the neck, armpit and groin
- allergic reaction
- increased appetite; diabetes; increased blood cholesterol and lipids; high sugar levels in the blood; excessive thirst; severe weight loss; high levels of fat (such as cholesterol and triglycerides) in the blood; body fat disorder
- feeling anxious; feeling of confusion; depressed mood; mood changes; panic attack
- loss of memory; pain in the hand due to nerve compression; disturbance in attention; dizziness with rapid changes in posture; abnormal taste; increased sleepiness; lack of energy; forgetfulness; migraine headache; loss of feeling, numbness or weakness of the arms and/or legs; tingling; sleepiness; tension headache; tremors; poor quality sleep
- visual disturbance
- buzzing, hissing, whistling, ringing or other persistent noise in the ears
- palpitations; slow heart rates; fast or irregular heart beats
- hot flush; high blood pressure
- harsh, raspy, or strained voice; nosebleed; nasal congestion
- abdominal pain upper; rectal discomfort; constipation; dry mouth; heartburn; pain when swallowing; inflammation of the pancreas; ulcer or sore in stomach or upper intestine; bleeding at anus; stomach discomfort; inflammation of the gums; swollen, red sore tongue
- accumulation of fat in the liver
- acne; unusual hair loss or thinning; redness of skin; unusual distribution of fat on the body, this may include loss of fat from legs, arms, and face, and increase in abdomen fat; excessive sweating; night sweats; thickening and itching of the skin due to repeated scratching; skin lesion; dry skin
- joint pain; painful joint disease; back pain; pain in bone/muscle; muscle tenderness or weakness; neck pain; pain in arms or legs; inflammation of the tendons; decrease in the amount of minerals in the bone
- kidney stones; urination at night; kidney cyst

- erectile dysfunction; breast enlargement in men; menopausal symptoms
- chest discomfort; chills; swelling of face; feeling jittery; generally feeling unwell; neck mass; swelling of hands, ankles or feet; pain
- decreased white blood cell count; decreased count of platelets in blood (a kind of cell that helps blood clot); blood test showing reduced kidney function; high blood sugar level; increased muscle enzyme in blood; sugar present in urine; red blood cells present in urine; weight gain; increase in waist size; decreased blood protein (albumin); increase in time for blood to clot

Additional side effects in children and adolescents
- hyperactivity

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Isentress

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and sachet after EXP. The expiry date refers to the last day of that month.
- Granules for oral suspension should be given to the patient within 30 minutes of mixing.
- Store in the original package in order to protect from moisture.
- This product does not require any special storage conditions. Do not open the Isentress sachets until ready to prepare a dose.

See the instructions for use booklet for the right way to dispose of your leftover medicine.

6. Contents of the pack and other information

What Isentress contains
The active substance is raltegravir. Each single-use sachet of granules for oral suspension contains 100 mg of raltegravir (as potassium).

The other ingredients are: hydroxypropyl cellulose, sucralose, mannitol (E 421), monoammonium glycyrrhizinate, sorbitol (E 420), fructose, banana flavour, sucrose, crospovidone Type A, magnesium stearate, ethylcellulose 20 cP, ammonium hydroxide, medium chain triglycerides, oleic acid, hypromellose 2910/6cP, macrogol/PEG 400, microcrystalline cellulose and carmellose sodium.

What Isentress looks like and contents of the pack
The banana flavoured granules for oral suspension is a white to off-white powder that may contain yellow or beige to tan particles in a single-use sachet.
One pack size is available: 1 carton with 60 sachets, two 10 mL syringes, two 3 mL syringes, two 1 mL syringes, two mixing cups, this package leaflet and booklet with instructions for use. Each single-use sachet contains 100 mg of raltegravir which is to be suspended in 10 mL of water giving a final concentration of 10 mg per mL.

Marketing Authorisation Holder and Manufacturer

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
MSD Belgium
Tél/Tel: +32(0)27766211
dpoc_belux@msd.com

България
Мерк Шарп и Доум България ЕООД
Тел.: +359 2 819 3737
info-msdbg@msd.com

Česká republika
Merck Sharp & Dohme s.r.o.
Tel.: +420 277 050 000
dpoc_czechslovak@msd.com

Danmark
MSD Danmark ApS
Tlf.: +45 4482 4000
dkmail@msd.com

Deutschland
MSD Sharp & Dohme GmbH
Tel.: +49 (0) 89 20 300 4500
medinfo@msd.de

Eesti
Merck Sharp & Dohme OÜ
Tel: +372 614 4200
dpoc.estonia@msd.com

Ελλάδα
MSD Α.Φ.Ε.Ε.
Τηλ: +30 210 98 97 300
dpoc.greece@msd.com

España
Merck Sharp & Dohme de España, S.A.
Tel: +34 91 321 06 00
msd_info@msd.com

France
MSD France
Tél: +33 (0)1 80 46 40 40

Hrvatska
Merck Sharp & Dohme d.o.o.
Tel: +385 1 6611 333
dpoc.croatia@msd.com

Lietuva
UAB Merck Sharp & Dohme
Tel. +370 5 2780 247
dpoc_lithuania@msd.com

Luxembourg/Luxemburg
MSD Belgium
Tél/Tel: +32(0)27766211
dpoc_belux@msd.com

Magyarország
MSD Pharma Hungary Kft.
Tel.: +36 1 888 5300
hungary_msd@msd.com

Malta
Merck Sharp & Dohme Cyprus Limited
Tel: 8007 4433 (+356 99917558)
dpoccyprus@msd.com

Nederland
Merck Sharp & Dohme B.V.
Tel: 0800 9999000
(+31 23 5153153)
medicalinfo.nl@msd.com

Norge
MSD (Norge) AS
Tlf: +47 32 20 73 00
medinfo.norway@msd.com

Österreich
Merck Sharp & Dohme Ges.m.b.H.
Tel: +43 (0) 1 26 044
dpoc_austria@msd.com

Polska
MSD Polska Sp. z o.o.
Tel.: +48 22 549 51 00
msdpolska@msd.com

Portugal
Merck Sharp & Dohme, Lda
Tel.: +351 21 4465700
inform_pt@msd.com

România
Merck Sharp & Dohme Romania S.R.L.
Tel.: +40 21 529 29 00
msdromania@msd.com

Ireland
Merck Sharp & Dohme Ireland (Human Health) Limited
Tel: +353 (0)1 2998700
medinfo_ireland@msd.com

Ísland
Vistor ehf.
Sími: +354 535 7000

Italia
MSD Italia S.r.l.
Tel: 800 23 99 89 (+39 06 361911)
dpoc.italy@msd.com

Κύπρος
Merck Sharp & Dohme Cyprus Limited
Τηλ: 800 00 673 (+357 22866700)
dpoccyprus@msd.com

Latvija
SIA Merck Sharp & Dohme Latvija
Tel.: +371 67025300
dpoc.latvia@msd.com

Slovenija
Merck Sharp & Dohme, inovativna zdravila d.o.o.
Tel: +386 1 520 4201
msd.slovenia@msd.com

Slovenská republika
Merck Sharp & Dohme, s. r. o.
Tel.: +421 2 58282010
dpoc_czechslovak@msd.com

Suomi/Finland
MSD Finland Oy
Puh/Tel: +358 (0)9 804 650
info@msd.fi

Sverige
Merck Sharp & Dohme (Sweden) AB
Tel: +46 77 5700488
medicinskinfo@msd.com

This leaflet was last revised in <{MM/YYYY}><{month YYYY}>.

Detailed information on this medicine is available on the European Medicines Agency web site:https://www.ema.europa.eu.

Instructions for Use
Bring this booklet to your child's appointments.

Isentress 100 mg granules for oral suspension
raltegravir

Instructions for Use
for babies

Be sure you read and understand these instructions for use.

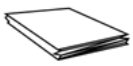
Before You Start

Note: Make sure your doctor shows you how to prepare and give Isentress for oral suspension.

- Be sure you understand these instructions before you start. If you are not sure, call your doctor.
- It is very important that you measure the water and Isentress carefully using the correct syringe.
- Before you give Isentress to your child, check the expiration date. The expiry date is printed on the carton and the Isentress sachets.
- The amount of Isentress depends on your child's age and weight, so it will change over time. Your doctor will tell you the right dose at each check-up after weighing your child. Be sure to keep your doctor's appointments so you get new dosing information as your child grows.
  During your child's first week of life, you will give Isentress 1 time a day. After that, you will give it 2 times a day.

- This booklet tells you how to:
  - Mix Isentress into a liquid form
  - Measure the right dose using a syringe
  - Give Isentress to your child
  - Clean up

Kit Contents

- Outer carton 
- Instructions (this booklet) 
- Prescribing leaflet
- 2 mixing cups 
- 60 sachets of Isentress granules 
- 6 syringes

2 **blue** (10 mL) syringes

2 **green** (3 mL) syringes

2 **white** (1 mL) syringes

The kit has an extra cup and set of syringes in case one is lost or damaged. Do not use any damaged cups or syringes.

Step 1. Get ready

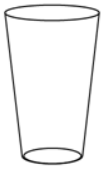
- Put your child in a safe place. You will need both hands to prepare Isentress.
- Wash your hands with soap and water.
- Take out what you need to make 1 dose and place on a clean surface:

1 mixing cup

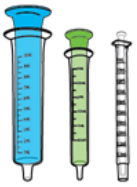
(Using the tab on the mixing cup,

pull open the lid)

1 sachet of Isentress granules



a clean glass

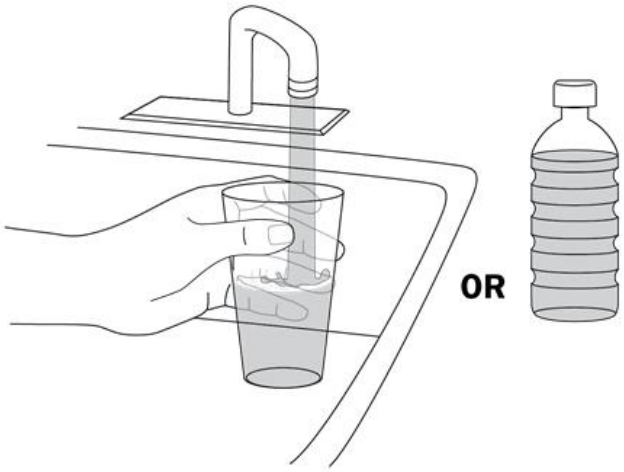


3 syringes

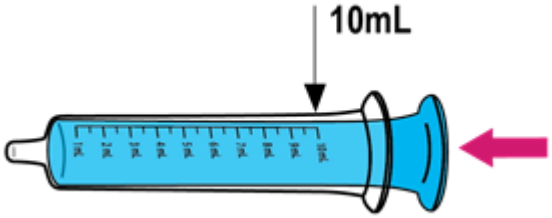
(Have one of each size ready, but you only need 1 or 2, depending on the size of the dose)

Step 2. Fill a glass with water

Fill the clean glass with room-temperature drinking water from your tap or using bottled still water.

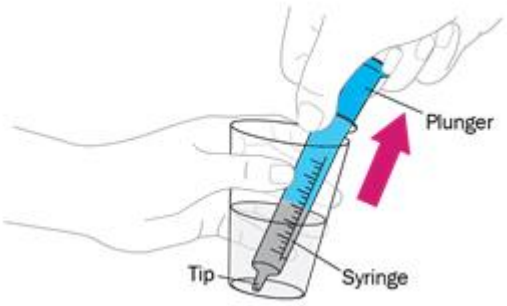


Step 3. Fill the blue syringe with water



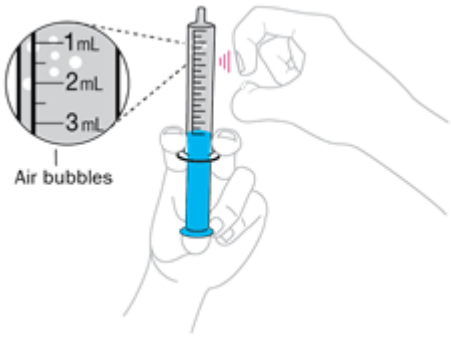
Push the plunger of the **blue** syringe into the syringe as far as it goes.

Put the tip of the syringe into the glass of water.
Pull back the plunger.
Stop when you get to the 10 mL mark.

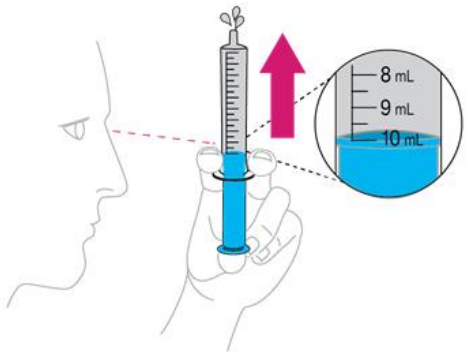


Step 4. Check for air bubbles

Hold the syringe with tip up.
Tap it with your finger to move any air bubbles up.



Slowly push up on the plunger to make the air come out.

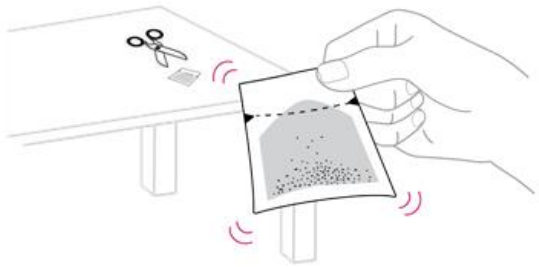


Re-check the amount of water in the syringe. If it is less than 10 mL, put the tip back into the water and pull back on the plunger until you get to the 10 mL mark.

Step 5. Add the 10 mL of water to the mixing cup

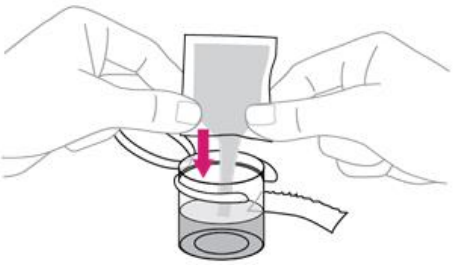
Step 6. Add Isentress to the cup

Note before adding Isentress:
Make sure you and your child are ready! After mixing Isentress, use it within 30 minutes. Throw away any leftover Isentress after you have given the dose to your child.



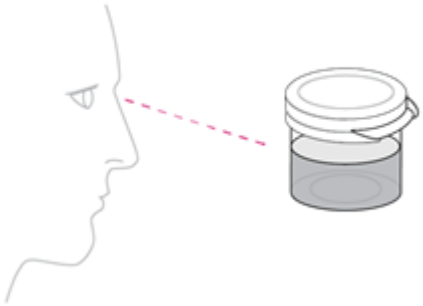
Tear or cut open the sachet and add all of the granules to the water in the mixing cup. Make sure the sachet is completely empty.

Take 1 sachet of ISENTRESS and shake the granules to the bottom of the sachet.



Step 7. Mix Isentress and water

Snap the lid of the mixing cup shut. Gently swirl the mixing cup for 45 seconds in a circular motion to mix the granules and water. Use a clock or timer to time for 45 seconds. **DO NOT SHAKE** the mixture



Check to make sure the granules are mixed.
If it is not mixed, swirl it some more.
The mixture should look cloudy.

Step 8. Check your prescription

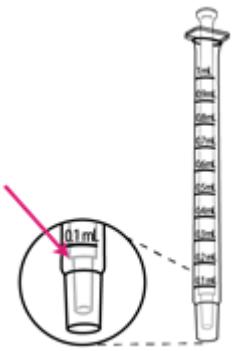
Use the dose amount in 'mL' prescribed by the doctor.

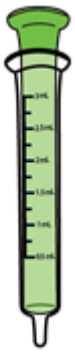
Remember that the dose may change each time you go to the doctor, so make sure you have all the recent information. Be sure to go to all of your doctor's appointments so your child gets the right dose!

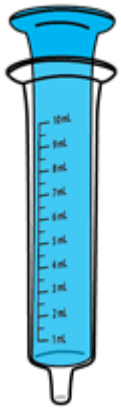
Step 9. Choose the syringe you need

Choose the correct syringe for your child's dose:

WHITE	GREEN	BLUE
(1 mL)	(3 mL)	(10 mL)
for 1 mL or less	for 1.5 mL to 3 mL	for 3.5 mL to 10 mL







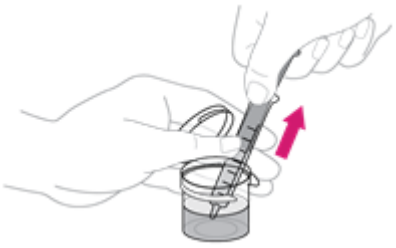
Move this part of
the plunger
to the correct mark
on the syringe

Then find the mL mark on the syringe barrel that matches your child's dose.

Step 10. Measure Isentress

Push the plunger into the barrel
of the syringe as far as it goes.

Put the tip of the syringe into
the cup of the prepared Isentress and pull back
on the plunger.



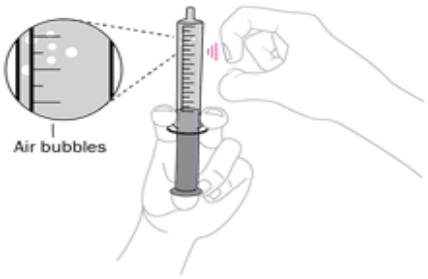
Stop when you get to the line
that matches your child's
prescribed dose.

IMPORTANT:

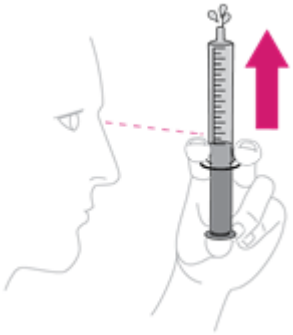
- Your child's dose may be different from the one shown in this figure.
- There will usually be some leftover, prepared Isentress in the mixing cup.

Step 11. Check for air bubbles

Hold the syringe with tip up.
Tap it with your finger
to move any air bubbles up.



Slowly push the plunger to make the air come out.



Re-check the amount of Isentress in the syringe.
If it is less than the prescribed dose, put the tip back into the cup of prepared Isentress and pull back on the plunger until you get to the right dose mark.

Step 12. Give Isentress to your baby

Place the tip of the syringe
inside your child's mouth so
that it touches either the right
or left cheek.

Slowly push in the plunger to give the prepared Isentress. If your child fusses, take the tip of the syringe out of the mouth and try again. It is important that your child takes all of the prescribed dose (a little left in the syringe tip is OK).

IMPORTANT: If your child does not take all of the prescribed dose or spits some of it out, call your doctor to find out what to do.

Step 13. Clean up

Pour the leftover prepared Isentress into the rubbish.
Do not pour it into the sink.

Pull the plungers out of any syringes you used.

Hand wash the syringes, plungers, and mixing cup with warm water and dishwashing soap.
Do not wash in the dishwasher.

Rinse with water and air dry.
Put everything in a clean, dry place.

How should I store Isentress?

Store in the original package in order to protect from moisture.
Do not open the Isentress sachets until you are ready to prepare a dose.

Be sure to keep your doctor's appointments so you always know how much Isentress to give.