SUMMARY OF PRODUCT CHARACTERISTICS

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 (<2000 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 10mL 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 halves.		

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. While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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.

Medicinal products by therapeutic area	**Interaction** (mechanism, if known)	**Recommendations concerning co-administration**
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.
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).

Medicinal products by therapeutic area	**Interaction** (mechanism, if known)	**Recommendations concerning co-administration**
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 moderate amount of data on pregnant women (between 300 – 1,000 pregnancy outcomes from first trimester exposure) indicate no malformative or feto/neonatal toxicity of raltegravir 400 mg film-coated tablets twice daily. Animal studies have shown reproductive toxicity (see section 5.3). Raltegravir granules for oral suspension should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus. 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

It is unknown whether raltegravir/metabolites are excreted in human milk. 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.

Raltegravir should not be used during breast-feeding. As a general rule, it is recommended that mothers infected by HIV do not breast-feed their babies 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

System Organ Class	Frequency	Adverse reactions Raltegravir (alone or in combination with other ART)
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
Eye disorders	Uncommon	visual impairment
Ear and labyrinth disorders	Common	vertigo
	Uncommon	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	abdominal distention, abdominal pain, diarrhoea, flatulence, nausea, vomiting, dyspepsia
	Uncommon	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	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 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.

<u>Paediatric population</u>

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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, other antivirals, ATC code: J05AX08.

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 IC50 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 (E421)
- Monoammonium glycyrrhizinate
- Sorbitol (E420)
- Fructose
- Banana flavour
- Sucrose
- Crospovidone, Type A
- 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

2 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

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 (UK) Limited
120 Moorgate
London
EC2M 6UR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 53095/0030

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

01/01/2021