SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Raltegravir 600 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (Tablet).

Yellow, oval-shaped, dimensions 19 mm x 9.3 mm, debossed with C30 on one side and 600 on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Raltegravir 600 mg film-coated tablets are indicated in combination with other antiretroviral 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

Raltegravir 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 raltegravir 400 mg twice daily.

Additional formulations and strengths available:

Raltegravir 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).

Raltegravir 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, Raltegravir 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, Raltegravir should be used with caution in patients with severe hepatic impairment (see sections 4.4 and 5.2).

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

Method of administration

Oral use.

Raltegravir 600 mg film-coated 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).

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.

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.
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).

calcium carbonate antacid (raltegravir 1,200 mg single dose)	raltegravir AUC ↓ 72% raltegravir $C_{24\ hr}$ ↓ 48% raltegravir C_{max} ↓ 74% 12 hours after raltegravir 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 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
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

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

Raltegravir 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 raltegravir 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, 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 Tlymphoid 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, 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)
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 noninferiority < 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)
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 $AUC_{0\text{-}24}$ 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.

<u>Distribution</u>

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 raltegravirglucuronide. Studies using isoform-selective chemical inhibitors and cDNA-expressed UDPglucuronosyltransferases (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†)* AUC0-12hr (μM●hr)	Geometric mean *(%CV†)* C12hr (nM)
≥ 25 kg	Film-coated tablet	400 mg twice daily	18	14.1 *(121 %)*	233 (*157 %*)
≥ 25 kg	Chewable tablet	Weight based dosing, see 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 (PH 105)
- Croscarmellose sodium
- Carbomers
- Magnesium stearate

Film-coating

- Macrogols (polyvinyl alcohol graft copolymer)
- Talc
- Titanium dioxide (E171)
- Glycerol monocaprylocaprate type 1
- Poly(vinyl alcohol) partly hydrolzed
- Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Keep the bottle tightly closed 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 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

Celix Pharma Ltd

12 Constance Street

London

United Kingdom, E16 2DQ

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 53835/0042

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/12/2025

10 DATE OF REVISION OF THE TEXT

03/12/2025