SCHEDULING STATUS

S4

1 NAME OF MEDICINE

ISENTRESS® Tablets (400 mg)

ISENTRESS® CHEWABLE 25 mg and 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains raltegravir potassium equivalent to 400 mg of raltegravir.

Each chewable tablet contains raltegravir potassium equivalent to 25 mg or 100 mg of raltegravir.

3 PHARMCEUTICAL FORM

A.20.2.8 Antiviral agents

Raltegravir is an HIV integrase strand transfer inhibitor active against the Human Immunodeficiency Virus (HIV-1).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ISENTRESS is indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus (HIV-1) infection in patients 2 years of age and older.

4.2 Posology and method of administration

ISENTRESS is available as a 400 mg tablet formulation and as a chewable tablet formulation in 100 mg (scored) and 25 mg strengths.

Because the formulations are not bioequivalent, do not substitute chewable tablets for the 400 mg tablet. The maximum dose of the chewable tablet is 300 mg twice daily.

ISENTRESS can be administered with or without food.

ISENTRESS is to be given in a combination regimen with other antiretroviral medicines. For the treatment of patients with HIV-1 infection, the dosage of ISENTRESS is as follows:

Adults: One 400 mg tablet twice daily, orally.

Children and adolescents:

- At least 25 kg: One 400 mg tablet twice daily, orally
- 2 to less than 6 years of age:

  Chewable tablets: Weight based to maximum dose 300 mg, twice daily, as specified in **Table 1.**

Table 1: Recommended Dose* for ISENTRESS CHEWABLE Tablets in Paediatric Patients

Body Weight (kg)	Dose	Number of Chewable Tablets
7 to < 10	50 mg twice daily	0,5 x 100 mg† twice daily
10 to < 14	75 mg twice daily	3 x 25 mg twice daily
14 to < 20	100 mg twice daily	1 x 100 mg twice daily
20 to < 28	150 mg twice daily	1,5 x 100 mg† twice daily
28 to < 40	200 mg twice daily	2 x 100 mg twice daily

At least 40	300 mg twice daily	3 x 100 mg twice daily

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

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

Paediatric Use

The safety, tolerability, pharmacokinetic profile, and efficacy of ISENTRESS were evaluated in HIV-1 infected children and adolescents 2 through 18 years of age in an open-label, multi-centre clinical trial, IMPAACT P1066 (see **5.2 Pharmacokinetic properties, Characteristics in Patients**). The safety profile was comparable to that observed in adults (see 4.8). See 4.2 for dosing recommendations for children 2 years of age and older.

Safety and effectiveness of ISENTRESS in children below 2 years of age have not been established.

Use in the Elderly

Clinical studies of ISENTRESS did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. Dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other medicine therapy.

4.3 Contraindications

ISENTRESS is contraindicated in patients who are hypersensitive to any component of ISENTRESS.

ISENTRESS is contraindicated in mothers breastfeeding their babies (see 4.6).

4.4 Special warnings and precautions for use

Severe Skin and Hypersensitivity Reactions

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

Interactions

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

Caution should be used when co-administering ISENTRESS with strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 (e.g. rifampicin) due to reduced plasma concentrations of raltegravir (see 4.5).

Immune and Reconstitution Syndrome

During the initial phase of treatment, patients responding to antiretroviral therapy such as ISENTRESS may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jirovecii* pneumonia, and tuberculosis or reactivation of varicella zoster virus), which may necessitate further evaluation and treatment.

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

ISENTRESS contains lactose; ISENTRESS CHEWABLE Tablets contain fructose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take ISENTRESS/ISENTRESS CHEWABLE Tablets.

Lactose and fructose may have an effect on the glycaemic control of patients with diabetes mellitus.

ISENTRESS CHEWABLE Tablets also contain the following:
Aspartame, a component of which is phenylalanine. Phenylalanine can be harmful to patients with phenylketonuria.

Sorbitol and mannitol: Patients with the rare hereditary condition of sorbitol/mannitol intolerance should not take ISENTRESS CHEWABLE Tablets, and saccharin sodium and sucralose.

4.5 Interaction with other medicines and other forms of interaction

Co-administration of ISENTRESS with medicines that are potent inducers of UGT1A1, such as rifampicin (an inducer of numerous medicine metabolising enzymes), reduces plasma concentrations of ISENTRESS. Caution should be used when co-administering ISENTRESS with rifampicin or other strong inducers of UGT1A1 (see 4.4). The impact of other potent inducers of medicine metabolising enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown.

Co-administration of ISENTRESS 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 ISENTRESS administration significantly decreased raltegravir plasma levels. Therefore, co-administration of ISENTRESS with aluminium and/or magnesium containing antacids is not recommended.

Co-administration of ISENTRESS with a calcium carbonate antacid decreased raltegravir plasma levels however, this interaction is not considered clinically meaningful. Therefore, when ISENTRESS is co-administered with calcium carbonate containing antacids, no dose adjustment is recommended.

Raltegravir is not a substrate of cytochrome P450 (CYP) enzymes and does not inhibit (IC_{50} > 100 µM) CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A *in vitro*. Moreover, *in vitro*, raltegravir did not induce CYP3A4. An interaction study with midazolam confirmed the low propensity of raltegravir to alter the pharmacokinetics of medicines metabolised by CYP3A4 *in vivo*, by demonstrating a lack of meaningful effect of raltegravir on the pharmacokinetics of midazolam, a sensitive CYP3A4 substrate.

Similarly, raltegravir is not an inhibitor (IC_{50} > 50 µM) of the UDP-glucuronosyltransferases (UGTs) tested (UGT1A1, UGT2B7), and raltegravir does not inhibit P-glycoprotein-mediated transport. Based on these data, ISENTRESS is not expected to affect the pharmacokinetics of medicines that are substrates of these enzymes or P-glycoprotein. Based on *in vivo* and *in vitro* studies, raltegravir is eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway.

Co-administration of ISENTRESS with medicines that are known to be potent UGT1A1 inhibitors (e.g. atazanavir) increases plasma levels of ISENTRESS. However, the degree of increase is modest and combination therapy with these inhibitors was well tolerated in the clinical studies such that no dose adjustment is required.

Co-administration of ISENTRESS with medicines that are known to increase gastric pH (e.g. omeprazole), may increase ISENTRESS plasma levels based on increased solubility of ISENTRESS at higher pH. In subjects who received ISENTRESS in combination with proton pump inhibitors or H_2 blockers in Protocols 018 and 019, comparable safety profiles were observed in this subgroup relative to subjects not receiving proton pump inhibitors or H_2

blockers. Based on these data, proton pump inhibitors and H_2 blockers may be co-administered with ISENTRESS without dose adjustment.

Effect of Raltegravir on the Pharmacokinetics of Other Medicines

In interaction studies, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of the following: Hormonal contraceptives, methadone, tenofovir, midazolam, lamivudine, etravirine, and darunavir/ritonavir and boceprevir.

In a multiple-dose interaction study, ethinylestradiol and norelgestromin AUC values were 98 % and 114 %, respectively, when co-administered with raltegravir as compared to when administered without raltegravir.

In a multiple-dose interaction study, tenofovir AUC and trough concentrations when co-administered with raltegravir were 90 % and 87 % of values obtained with tenofovir monotherapy. In another interaction study, midazolam AUC from co-administration was 92 % of the value obtained with midazolam alone. In a Phase II study, lamivudine pharmacokinetics were similar in patients receiving combinations with raltegravir versus with efavirenz.

Effect of Other Medicines on the Pharmacokinetics of Raltegravir

In interaction studies, atazanavir, efavirenz, ritonavir, tenofovir and tipranavir/ritonavir did not have a clinically meaningful effect on the pharmacokinetics of raltegravir. Rifampicin, which is a strong inducer of medicine metabolising enzymes, caused a decrease in trough levels of raltegravir (see 4.4).

An aluminium and magnesium antacid significantly decreased raltegravir plasma levels. Co-administration of ISENTRESS with aluminium and/or magnesium containing antacids is not recommended.

All interaction studies were performed in adults. Interactions are further described below.

Table 2: Effect of Other Medicines on the Pharmacokinetics of Raltegravir in Adults

Co-administered medicine	Co-administered medicine Dose/Schedule	Raltegravir Dose/Schedule	Ratio (90 % Confidence Interval) of Raltegravir Pharmacokinetic Parameters with/without Co-administered medicine; No Effect = 1,00			
			n	C_{max}	AUC	C_{min}
Aluminium and magnesium hydroxide antacid	20 mL single dose given with raltegravir	400 mg twice daily	25	0,56 (0,42, 0,73)	0,51 (0,40, 0,65)	0,37 (0,29, 0,48)
	20 mL single dose given 2 hours before raltegravir		23	0,49 (0,33, 0,71)	0,49 (0,35, 0,67)	0,44 (0,34, 0,55)
	20 mL single dose given 2 hours after raltegravir		23	0,78 (0,53, 1,13)	0,70 (0,50, 0,96)	0,43 (0,34, 0,55)

	20 mL single dose given 6 hours before raltegravir		16	0,90 (0,58, 1,40)	0,87 (0,64, 1,18)	0,50 (0,39, 0,65)
	20 mL single dose given 6 hours after raltegravir		16	0,90 (0,58, 1,41)	0,89 (0,64, 1,22)	0,51 (0,40, 0,64)
Atazanavir	400 mg daily	100 mg single dose	10	1,53 (1,11, 2,12)	1,72 (1,47, 2,02)	1,95 (1,30, 2,92)
Atazanavir/Ritonavir	300 mg/100 mg daily	400 mg twice daily	10	1,24 (0,87, 1,77)	1,41 (1,12, 1,78)	1,77 (1,39, 2,25)
Boceprevir	800 mg three times daily	400 mg twice daily	22	1,11 (0,91, 1,136)	1,04 (0,88, 1,22)	0,75 (0,45, 1,23)
Calcium carbonate antacid	3 000 mg single dose	400 mg twice daily	24	0,48 (0,36, 0,63)	0,45 (0,35, 0,57)	0,68 (0,53, 0,87)
Darunavir/Ritonavir	600 mg/100 mg twice daily	400 mg twice daily	6	0,67 (0,33 - 1,37)	0,71 (0,38 - 1,33)	1,38 (0,16 - 12,12)

Efavirenz	600 mg daily	400 mg single dose	9	0,64 (0,41, 0,98)	0,64 (0,52, 0,80)	0,79 (0,49, 1,28)
Etravirine	200 mg twice daily	400 mg twice daily	19	0,89 (0,68, 1,15)	0,90 (0,68, 1,18)	0,66 (0,34, 1,26)
Omeprazole	20 mg daily	400 mg single dose	14 (10 for AUC)	4,15 (2,82, 6,10)	3,12 (2,13, 4,56)	1,46 (1,10, 1,93)
Rifampicin	600 mg daily	400 mg single dose	9	0,62 (0,37, 1,04)	0,60 (0,39, 0,91)	0,39 (0,30, 0,51)
Rifampicin	600 mg daily	800 mg twice daily	14	1,62* (1,12, 2,33)	1,27* (0,94, 1,71)	0,47* (0,36, 0,61)
Ritonavir	100 mg twice daily	400 mg single dose	10	0,76 (0,55, 1,04)	0,84 (0,70, 1,01)	0,99 (0,70, 1,40)
Tenofovir	300 mg daily	400 mg twice daily	9	1,64 (1,16, 2,32)	1,49 (1,15, 1,94)	1,03 (0,73, 1,45)

Tipranavir/Ritonavir	500 mg/200 mg twice daily	400 mg twice daily	15 (14 for C_{min})	0,82 (0,46, 1,46)	0,76 (0,49, 1,19)	0,45 (0,31, 0,66)

*Compared to 400 mg twice daily administered alone

4.6 Fertility, pregnancy and lactation

Pregnancy

Limited data on the use of raltegravir at recommended doses, covering the periconception period, first trimester and other trimesters of pregnancy did not result in an increase of neural tube defects or other congenital malformations. After due consideration of treatment options in pregnancy, the use of raltegravir can be considered if an integrase strand transfer inhibitor is deemed indicated to be a component of antiretroviral therapy in pregnancy. Mother and embryo/foetal wellbeing should be frequently monitored/assessed by appropriate methods.

Animal studies suggested minor congenital abnormalities (supernumerary ribs in rats). Toxicokinetic studies demonstrated placental transfer of raltegravir medicine in both animal species evaluated.

In vivo human studies confirmed that raltegravir readily crosses the human placenta.

Lactation

Safety of breastfeeding of babies born to women on treatment with ISENTRESS has not been established. Women on treatment with ISENTRESS should not breastfeed their babies (see 4.3).

It is not known whether raltegravir is secreted in human milk. However, ISENTRESS is secreted in the milk of lactating rats. In rats at a maternal dose of 600 mg/kg/day, mean medicine concentrations in milk were approximately 3-fold greater than in maternal plasma.

In addition, HIV-infected mothers should not breastfeed their infants, to avoid risking post-natal transmission of HIV.

4.7 Effects on ability to drive and use machines

Fatigue and drowsiness have been reported with ISENTRESS and may affect some patient's ability to drive or operate machinery. Individual responses to ISENTRESS may vary (see 4.8).

4.8 Undesirable effects

Adults

The safety assessment of ISENTRESS is based on the pooled safety data from randomised clinical studies, using the recommended dose of ISENTRESS 400 mg twice daily in combination with optimised background therapy (OBT) in 462 patients. During double-blind treatment, the total follow-up was 1 051 patient-years in the group receiving ISENTRESS 400 mg twice daily.

For patients receiving ISENTRESS 400 mg twice daily + OBT in the pooled analysis for studies P018 and P019, the most commonly reported clinical adverse experiences (> 10 % in either group) of all intensities and regardless of causality were:

- diarrhoea in 26,6 % and 24,9 %
- nausea in 13,6 % and 16,0 %

- headache in 12,1 % and 13,5 %
- nasopharyngitis in 14,3 % and 8,9 %
- fatigue in 12,1 % and 5,9 %
- upper respiratory tract infection in 15,8 % and 10,1 %
- bronchitis in 12,1 % and 6,8 %
- pyrexia in 9,7 % and 13,9 %
- vomiting in 8,9 % and 11,0 % of patients, respectively.

The rates of discontinuation of therapy due to adverse experiences (clinical and laboratory) were 4,5 % in patients receiving ISENTRESS + OBT.

Serious Events

Medicine-Related

The following serious medicine-related clinical adverse experiences were reported in the clinical studies: gastritis, hepatitis, renal failure, genital herpes, accidental overdose.

Adverse reactions considered by investigators to be causally related to ISENTRESS (alone or in combination with other ART) 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 ISENTRESS (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, medicine 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	Abnormal dreams, insomnia, nightmares, depression
	Uncommon	Mental disorders, attempted suicide, suicidal ideation, suicidal behaviour (particularly in patients with a pre-existing history of psychiatric illness), anxiety, confusional state, depressed mood, major depression, middle insomnia, altered mood, panic attacks, sleep disorder
Nervous system disorders	Common	Dizziness, headache
	Uncommon	Amnesia, carpal tunnel syndrome, cognitive disorder, disturbance in attention, postural dizziness, dysgeusia, hypersomnia, hypoaesthesia, lethargy, memory impairment, migraine, peripheral neuropathy, 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 flushes, hypertension
Respiratory, thoracic and mediastinal disorders	Uncommon	Dysphonia, epistaxis, nasal congestion
Gastrointestinal disorders	Common	Abdominal distension, abdominal pain, diarrhoea, flatulence, nausea, vomiting, dyspepsia
	Uncommon	Gastritis, abdominal discomfort, upper abdominal pain, abdominal tenderness, anorectal discomfort, constipation, dry mouth, epigastric discomfort, erosive duodenitis, eructation, gastro-oesophageal reflux disease, gingivitis, glossitis, odynophagia, acute pancreatitis, peptic ulcer, rectal haemorrhage
Hepatobiliary disorders	Uncommon	Hepatitis, hepatic steatosis, alcoholic hepatitis, hepatic failure
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Acne, alopecia, acneiform dermatitis, dry skin, erythema, facial wasting, hyperhidrosis, lipoatrophy, acquired lipodystrophy, lipohypertrophy, night

		sweats, prurigo, pruritus, generalised pruritus, macular rash, maculopapular rash, pruritic rash, skin lesions, 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 extremities, tendonitis, rhabdomyolysis
Renal and urinary disorders	Uncommon	Renal failure, nephritis, nephrolithiasis, nocturia, renal cysts, renal impairment, tubulo-interstitial nephritis
Reproductive system and breast disorders	Uncommon	Erectile dysfunction, gynaecomastia
General disorders and administration site conditions	Common Uncommon	Asthenia, fatigue, pyrexia Chest discomfort, chills, facial oedema, increased fat tissue, feeling jittery, malaise, submandibular mass, peripheral oedema, pain

Investigations	Common	Increased alanine aminotransferase (ALT), atypical lymphocytes, increased aspartate aminotransferase (AST), increased blood triglycerides, increased lipase, increased blood pancreatic amylase
	Uncommon	Decreased absolute neutrophil count, increased alkaline phosphatase, decreased blood albumin, increased blood amylase, increased blood bilirubin, increased blood cholesterol, increased blood creatinine, increased blood glucose, increased blood urea, increased creatine phosphokinase, increased fasting blood glucose, glucose present in urine, increased lipoprotein, increased international normalised ratio (INR), increased low-density lipoprotein, decreased platelet count, positive test for red blood cells in urine, increased waist circumference, increased weight, decreased white blood cell count

Serious Events

Public disclosed

Medicine-related

The following serious medicine-related adverse experiences were reported: anaemia, immune reconstitution syndrome, mental disorders, suicide attempts, depression.

Selected Adverse Experiences

Cancers were observed in patients who initiated ISENTRESS; several were recurrent. The types and rates of specific cancers were those expected in a highly immunodeficient population (many had CD4+ counts below 50 cells/mm^3 and most had prior AIDS diagnoses). The cancers included Kaposi's sarcoma, lymphoma, squamous cell carcinoma, hepatocellular carcinoma and anal cancer. Most patients had other risk factors for cancer including tobacco use, papillomavirus and active hepatitis B virus infection. It is unknown if these cancers diagnoses were related to ISENTRESS use.

Grades 2 to 4 creatine kinase laboratory abnormalities were observed in subjects treated with ISENTRESS. Myopathy and rhabdomyolysis have been reported. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medicines known to cause these conditions.

Rash and skin reactions

Severe, potentially life-threatening and fatal skin reactions have been reported in patients taking ISENTRESS (see 4.4).

Patients with Co-Existing Conditions

Patients co-infected with hepatitis B and/or hepatitis C virus

In Phase III studies, treatment-experienced adult patients (n=114/699 or 16 %) and treatment-naïve patients (n=34/563 or 6 %) with chronic (but not acute) active hepatitis B and/or hepatitis C co-infection were permitted to enrol, provided that baseline liver function tests did not exceed 5 times the upper limit of normal. In general, the safety profile of ISENTRESS in patients with hepatitis B and or hepatitis C co-infection, was similar to that in patients without hepatitis B and/or hepatitis C co-infection, although the rates of AST (aspartate aminotransferase) and ALT (alanine aminotransferase) abnormalities were somewhat higher in the subgroup with hepatitis B and/or hepatitis C co-infection for both treatment groups.

Paediatric Adverse Experiences

ISENTRESS 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 medicines in IMPAACT P1066 (see **5.2 Pharmacokinetic properties, Characteristics in Patients, Paediatrics**). Of the 126 patients, 96 received the recommended dose of ISENTRESS.

In these 96 children and adolescents, the frequency, type and severity of medicine related adverse reactions through Week 24 were comparable to those observed in adults.

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

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

Laboratory Test Findings

Laboratory Abnormalities

The percentages of adult patients treated with ISENTRESS 400 mg twice daily with selected Grades 2 to 4 laboratory abnormalities that represent a worsening from baseline are presented in the following table.

Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Experienced Patients		
Laboratory Parameter Preferred Term (Unit)	**Limit**	**ISENTRESS 400 mg twice daily + OBT (n=462)**
Blood chemistry		
Fasting (non-random) serum glucose test (mmol/L)		
Grade 2	7,0 to 13,9	11,3 %
Grade 3	13,9 to 27,8	2,9 %
Grade 4	27,8	0,0 %
Total serum bilirubin (µmol/L)		
Grade 2	1,6 to 2,5 x ULN	5,6 %
Grade 3	2,6 to 5,0 x ULN	3,0 %
Grade 4	> 5,0 x ULN	0,9 %
Serum aspartate aminotransferase (IU (aminot.)/L)		
Grade 2	2,6 to 5,0 x ULN	9,5 %

Grade 3 Grade 4	5,1 to 10,0 x ULN > 10,0 x ULN	4,3 % 0,7 %
Serum alanine aminotransferase (IU (aminot.)/L)		
Grade 2 Grade 3 Grade 4	2,6 to 5,0 x ULN 5,1 to 10,0 x ULN > 10,0 x ULN	10,8 % 4,8 % 1,3 %
Serum alkaline phosphatase (IU (alk phos)/L)		
Grade 2 Grade 3 Grade 4	2,6 to 5,0 x ULN 5,1 to 10,0 x ULN > 10,0 x ULN	2,2 % 0,4 % 0,7 %
Serum creatine kinase		
Grade 2 Grade 3 Grade 4	6,0 to 9,9 x ULN 10,0 to 19,9 x ULN ≥ 20,0 x ULN	2,6 % 4,1 % 3,0 %
ULN = Upper limit of normal range		

The percentages of treatment-naïve adult patients receiving either ISENTRESS 400 mg twice daily or efavirenz (both with emtricitabine (+) tenofovir), [in P021] with selected Grade 2 to 4 laboratory abnormalities that represent a worsening Grade from baseline are presented in the following table.

Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Naïve Patients		
Laboratory Parameter Preferred Term (Unit)	**Limit**	**ISENTRESS 400 mg twice daily +**

		Emtricitabine (+) Tenofovir (n=281)
Blood chemistry		
Fasting (non-random) serum glucose test (mmol/L)		
Grade 2	7,0 to 13,9	6,6 %
Grade 3	13,9 to 27,8	1,8 %
Grade 4	27,8	0,0 %
Total serum bilirubin µmol/L		
Grade 2	1,6 to 2,5 x ULN	4,6 %
Grade 3	2,6 to 5,0 x ULN	0,7 %
Grade 4	> 5,0 x ULN	0,4 %
Serum aspartate aminotransferase (IU (aminot.)/L)		
Grade 2	2,6 to 5,0 x ULN	7,5 %
Grade 3	5,1 to 10,0 x ULN	4,6 %
Grade 4	> 10,0 x ULN	1,1 %
Serum alanine aminotransferase (IU (aminot.)/L)		
Grade 2	2,6 to 5,0 x ULN	11,0 %
Grade 3	5,1 to 10,0 x ULN	1,8 %
Grade 4	> 10,0 x ULN	1,8 %
Serum alkaline phosphatase (IU (alk phos)/L)		
Grade 2	2,6 to 5,0 x ULN	1,1 %
Grade 3	5,1 to 10,0 x ULN	0,0 %
Grade 4	> 10,0 x ULN	0,4 %

ULN = Upper limit of normal range

Lipids, Change from Baseline

Lipid Values, Change from baseline in Serum Lipids at Week 240			
Laboratory Parameter Preferred Term (Unit)	**ISENTRESS 400 mg twice daily (n=207)**		**Comparator**
		Change from Baseline at Week 240	
	Baseline Mean	**Mean Change (95 % CI)†**	**Baseline Mean**
Total Cholesterol (mg/dL)‡	158,8	16,0 (11,5, 20,6)	157,1
HDL-Cholesterol (mg/dL)‡	37,9	5,7 (4,3, 6,9)	38,4
LDL-Cholesterol (mg/dL)‡	96,2	9,92 (6,1, 13,8)	92,5
Triglyceride (mg/dL)‡	128,3	1,5 (-9,9, 13,0)	140,6
Total: HDL-C ratio	4,4	-0,2 (-0,4, -0,1)	4,4
Non-HDL-C (mg/dL)	121,0	10,3 (6,13, 14,6)	118,7

† Within group 95 % CIS were based on t-distribution

‡Fasting (non-random) laboratory tests at Week 240

Post-Marketing Experience

The following additional adverse experiences have been reported in post-marketing experience without regard to causality:

Blood and lymphatic system disorders

Thrombocytopenia

Hepatobiliary disorders

Hepatic failure (with or without associated hypersensitivity) in patients with underlying liver disease and/or concomitant medicines

Musculoskeletal and connective tissue disorders

Rhabdomyolysis

Nervous system disorders

Cerebellar ataxia

Psychiatric disorders

Suicidal ideation and behaviour

Depression (particularly in patients with a pre-existing history of psychiatric illness)

Skin and subcutaneous tissue disorders

Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS).

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose, side effects may be exacerbated and exaggerated (see 4.8).

In the event of overdose, standard supportive measures should be employed, e.g. removing unabsorbed material from the gastrointestinal tract by administering activated charcoal, clinical monitoring (including obtaining an electrocardiogram) and institute supportive therapy if required. The extent to which ISENTRESS may be dialysable is unknown.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Raltegravir inhibits the catalytic activity of HIV 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 during the early phase of infection. HIV genomes that fail to integrate cannot direct the production of new infectious viral particles, so inhibiting integration prevents propagation of the viral infection. Raltegravir did not significantly inhibit human phosphoryl transferases including DNA polymerases α, β and γ.

Raltegravir at concentrations of 31 ± 20 nM resulted in 95 % inhibition (IC_{95}) of viral spread (relative to an untreated virus-infected culture) in human T-lymphoid cell cultures infected with the cell-line adapted HIV-1 variant H9IIIB.

In addition, raltegravir at concentrations of 6 to 50 nM resulted in 95 % inhibition of viral spread in cultures of mitogen-activated human peripheral blood mononuclear cells infected with diverse, primary clinical isolates of HIV-1, including isolates from 5 non-B subtypes, and isolates resistant to reverse transcriptase inhibitors and protease inhibitors. In a single-cycle infection assay, raltegravir inhibited infection of 23 HIV isolates representing 5 non-B

subtypes and 5 circulating recombinant forms with IC_{50} values ranging from 5 to 12 nM. Raltegravir also inhibited replication of an HIV-2 isolate when tested in CEM x 174 cells (IC_{95}=6 nM). Additive to synergistic antiretroviral activity was observed when human T-lymphoid cells infected with the H9IIIB variant of HIV-1 were incubated with raltegravir in combination with nucleoside analogue reverse transcriptase inhibitors (zidovudine, zalcitabine, stavudine, abacavir, tenofovir, didanosine or lamivudine), non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine or delavirdine), protease inhibitors (indinavir, saquinavir, ritonavir, amprenavir, lopinavir, nelfinavir or atazanavir) or the entry inhibitor enfuvirtide.

Medicine Resistance

The mutations observed in HIV-1 integrase that contributed to raltegravir resistance (evolved either *in vitro* or in patients treated with raltegravir), included a substitution at either Y143 (changed to C, H or R) or Q148 (changed to H, K or R) or N155 (changed to H), plus one or more additional mutations (e.g. L74I/M, E92Q, E138A/K, G140A/S or V151I). Amino acid substitution at Y143C/H/R is another pathway to raltegravir resistance.

Recombinant viruses containing a single primary mutation (Q148H, K or R, or N155H) displayed decreased replication capacity and reduced susceptibility to raltegravir *in vitro*. Secondary mutations generally increased viral replication capacity and/or further decreased susceptibility to raltegravir and sometimes acted as compensatory mutations for viral replication capacity.

Mutations conferring resistance to raltegravir generally also confer resistance to the integrase strand 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.

Treatment-Naïve Subjects: By Week 48 in the STARTMRK trial, the primary raltegravir resistance-associated substitutions were observed in 4 (2 with Y143HR and 2 with Q148H/R) of the 10 virologic failure subjects, with evaluable paired genotypic data from paired baseline and raltegravir treatment-failure isolates.

Treatment-Experienced Subjects: By Week 48 in the BENCHMRK trials, at least one of the 3 primary raltegravir resistance-associated substitutions was observed in 63 (64,3 %) of the 98 virologic failure subjects out of 462 patients, treated with evaluable genotypic data from paired baseline and raltegravir treatment-failure isolates. The emergence of the primary raltegravir resistance-associated substitutions was observed cumulatively in 70 subjects by Week 48 and 78 subjects by Week 96, 15,2 % and 17 % of the raltegravir recipients, respectively. Some (n=58) of those HIV-1 isolates harbouring one or more of the 3 primary raltegravir resistance-associated substitutions were evaluated for raltegravir susceptibility yielding a median decrease of 26,3-fold (mean 48,9 ± 44,8-fold decrease, ranging from 0,8- to 159-fold) compared to the wild-type reference.

Cardiac Electrophysiology

In a randomised, placebo-controlled, crossover study, 31 healthy subjects were administered a single oral supra-therapeutic dose of raltegravir 1 600 mg and placebo. There was no effect on the QTc interval. Peak raltegravir plasma concentrations were approximately 4-fold higher than the peak concentrations following a 400 mg dose.

After baseline and placebo adjustment, the mean maximum QTc increase was -0,41 msec (1-sided 95 % upper; CI:3,1 msec).

5.2 Pharmacokinetic properties

Absorption – Adults

Raltegravir is absorbed with a T_{max} of approximately 3 hours post-dose in the fasted state. Raltegravir AUC and C_{max} increase dose proportionally over the dose range 100 mg to 1 600 mg. With twice-daily dosing, pharmacokinetic steady-state is achieved, within approximately the first 2 days of dosing. There is little to no accumulation in AUC and C_{max} and evidence of slight accumulation in C_{12h}. The absolute bioavailability of raltegravir has not been established.

In patients on 400 mg twice daily monotherapy, raltegravir medicine exposures were characterised by a geometric mean $AUC_{0\text{-}12h}$ of 14,3 µM●hr and C_{12h} of 142 nM.

Effect of Food on Oral Absorption

Raltegravir was administered without regard to food in the pivotal safety and efficacy studies in HIV positive patients. The effect of consumption of low-, moderate- and high-fat meals on steady-state raltegravir pharmacokinetics was assessed in healthy volunteers. Administration of multiple doses of raltegravir following a moderate-fat meal (600 kCal/2 500 kJ, 21 g fat) did not affect raltegravir AUC to a clinically meaningful degree with an increase of 13 % relative to fasting. Raltegravir C_{12h} 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 (825 kCal, 52 g fat) increased AUC and C_{max} by approximately 2-fold and

increased C_{12h} by 4,1-fold. Administration of raltegravir following a low-fat meal (300 kCal, 2,5 g fat) decreased AUC and C_{max} by 46 % and 52 %, respectively; C_{12h} was essentially unchanged. Food appears to increase pharmacokinetic variability relative to fasting.

Distribution - Adults

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 and rabbits; there was also substantial excretion into rat milk. It was also detectable in brain tissue of rats.

Metabolism and Excretion - Adults

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 radio-labelled 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 derived from hydrolysis of raltegravir-glucuronide secreted in bile as observed in pre-clinical 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 radio-activity; the remaining radio-activity 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.

Characteristics in Patients

Age

There is no clinically meaningful effect of age on raltegravir pharmacokinetics in adults. There is limited information on pharmacokinetics in elderly patients (see 4.2). No dosage adjustment is necessary.

Paediatrics

Based on a formulation comparison study in healthy adult volunteers, the chewable tablet has 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_{12h} 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 doses recommended for HIV-infected children and adolescents 2 to 18 years of age (see 4.4) resulted in a pharmacokinetic profile of raltegravir similar to that observed in adults receiving 400 mg twice daily. **Table 2** displays pharmacokinetic parameters in the 400 mg tablet (6 to 18 years of age) and the chewable tablet (2 to < 12 years of age).

Table 2: Raltegravir Pharmacokinetic Parameters IMPAACT P1066 Following Administration of Doses in DOSAGE AND ADMINISTRATION

Age	Formulation	Dose	n*	Geometric Mean *(% CV†)* AUC_{0-12h} (µM•hr)	Geometric Mean *(% CV†)* C_{12h} (nM)
12 to 18 years	400 mg tablet	400 mg twice daily regardless of weight	11	15,7 (98 %)	333 (78 %)
6 to < 12 years	400 mg tablet	400 mg twice daily, for patients ≥ 25 kg	11	15,8 (120 %)	246 (221 %)
6 to < 12 years	Chewable tablet	Weight based dosing, see Table 1	10	22,6 (34 %)	130 (88 %)
2 to < 6 years	Chewable tablet	Weight based dosing, see Table 1	12	18,0 (59 %)	71 (55 %)

*Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose

†Coefficient of variation

Patients in this age group received approximately 8 mg/kg dose at time of intensive PK which met PK and safety targets. Based on review of the individual profiles and receipt of a mean dose of 390 mg, 400 mg twice daily was selected as the recommended dose for this age group.

The pharmacokinetics of raltegravir in children < 2 years of age has not been established.

Hepatic Insufficiency

Raltegravir is eliminated primarily by glucuronidation in the liver. A study of the pharmacokinetics of raltegravir was performed in adult patients with moderate hepatic insufficiency. Additionally, hepatic insufficiency was evaluated in the composite pharmacokinetic analysis. There were no clinically important pharmacokinetic differences between patients with moderate hepatic insufficiency and healthy subjects. No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency. The effect of severe hepatic insufficiency on the pharmacokinetics of raltegravir has not been studied.

Renal Insufficiency

Renal clearance of unchanged medicine is a minor pathway of elimination. A study of the pharmacokinetics of raltegravir was performed in adult patients with severe renal insufficiency. Additionally, renal insufficiency was evaluated in the composite pharmacokinetic analysis. There were no clinically important pharmacokinetic differences between patients with severe renal insufficiency and healthy subjects. No dosage adjustment is necessary. Because the extent to which raltegravir may be dialysable is unknown, dosing before a dialysis session should be avoided.

UGT1A1 Polymorphism

There is no evidence that common UGT1A1 polymorphisms alter raltegravir pharmacokinetics to a clinically meaningful extent. In a comparison of 30 adult subjects with *28/*28 genotype (associated with reduced activity of UGT1A1) to 27 adult subjects with wild-type genotype, the geometric mean ratio (90 % CI) of AUC was 1,41 (0,96, 2,09).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each film-coated 400 mg ISENTRESS Tablet also contains: microcrystalline cellulose, lactose monohydrate, calcium phosphate dibasic anhydrous, hypromellose 2208, poloxamer 407 (contains 0,01 % butylated hydroxytoluene as antioxidant), sodium stearyl fumarate, magnesium stearate. The film coating contains polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc and black iron oxide.
Contains sugar (lactose monohydrate).

Each 25 mg and 100 mg ISENTRESS CHEWABLE Tablet also contains: hydroxypropyl cellulose, sucralose, saccharin sodium, sodium citrate dihydrate, mannitol, monoammonium glycyrrhizinate, sorbitol, fructose, natural and artificial flavours (orange, banana, and masking that contains aspartame), crospovidone, magnesium stearate, sodium stearyl fumarate, ethylcellulose 20 cP, ammonium hydroxide, medium chain triglycerides, oleic acid, hypromellose 2910/6cP, macrogol/PEG 400. In addition, the 25 mg tablet contains yellow iron oxide and the 100 mg tablet contains yellow iron oxide and red iron oxide.
Contains aspartame.
Contains sugar (mannitol, sorbitol, and fructose).
Contains sucralose, saccharin sodium.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Not applicable.

6.4 Special precautions for storage

Store at or below 30 °C.

Do not remove the silica gel desiccant canister from the bottle. Keep container well closed.

The tablet should not be removed from its original packaging until required for use.

Keep out of reach of children

6.5 Nature and contents of container

ISENTRESS Tablets (400 mg): Grey, oval, biconvex film-coated tablets debossed with 227 and Corporate logo on one side and plain on the other.

ISENTRESS CHEWABLE 25 mg Tablets: Pale yellow, round flat faced, bevelled edge tablets debossed with the Corporate logo on one side and 473 on the other.

ISENTRESS CHEWABLE 100 mg Tablets: Pale orange, oval shaped scored tablets, debossed with the Corporate logo on one side of the score and 477 on the other, and scored on the other side of the tablet.

ISENTRESS Tablets (400 mg): Round, white opaque HDPE bottles with white child-resistant closures containing 60 tablets as well as a 1 g silica gel desiccant canister. Each bottle is packed in a printed cardboard carton.

ISENTRESS CHEWABLE 25 mg Tablets: Round, white opaque HDPE bottles with white child-resistant polypropylene closures, with a foil induction seal containing 60 tablets as well as a 4 g silica gel desiccant. Each bottle is packed in a printed cardboard carton.
ISENTRESS CHEWABLE 100 mg Tablets: Round, white opaque HDPE bottles with white child-resistant polypropylene closures, with a foil induction seal containing 60 tablets as well as a 4 g silica gel desiccant. Each bottle is packed in a printed cardboard carton.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

MSD (Pty) Ltd

117 16th Road

Halfway House

1685

South Africa

8 REGISTRATION NUMBERS

ISENTRESS Tablets (400 mg): 42/20.2.8/0687

ISENTRESS CHEWABLE 25 mg Tablets: 46/20.2.8/0863

ISENTRESS CHEWABLE 100 mg Tablets: 46/20.2.8/0864

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

ISENTRESS Tablets (400 mg): 04 March 2011

ISENTRESS CHEWABLE 25 mg Tablets: 06 March 2014

ISENTRESS CHEWABLE 100 mg Tablets: 06 March 2014

10 DATE OF REVISION OF THE TEXT

21 November 2023