ISENTRESS® (raltegravir)

PRESCRIBING INFORMATION
Refer to Summary of Product Characteristics before prescribing

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to MSD, UK (Tel: 0208 1548000).
By clicking the above link you will leave the MSD website and be taken to the MHRA website.

PRESENTATION
400 mg film-coated tablet containing 400 mg of raltegravir (as potassium).
25 mg chewable tablet containing 25 mg of raltegravir (as potassium).
100 mg chewable tablet containing 100 mg of raltegravir (as potassium).
100 mg granules for oral suspension containing 100mg of raltegravir (as potassium).

USES
For use in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection.

DOSAGE AND ADMINISTRATION: Therapy to be initiated by a physician experienced in the management of HIV infection. *Film coated tablets:* Patients weighing at least 25 kg: 400 mg twice daily. *Chewable tablets*: Children weighing at least 11kg: weight-based dosing to a maximum dose of 300 mg twice daily. *Oral suspension*: Neonates, infants and toddlers from birth: weight-based dosing up to maxiumum of 100 mg twice daily. Refer to SmPC for full dosing information. *Elderly:* Use with caution. *Renal impairment*: No dosage adjustment required. *Hepatic impairment:* No dosage adjustment required for mild to moderate hepatic impairment. Use with caution in severe hepatic impairment.
Safety and efficacy: Not established in patients with severe underlying liver disorders. Do not substitute chewable tablets or granules for oral suspension for the 400 mg tablets as they are not bioequivalent. The granules for oral suspension and the chewable tablets have not been studied in adolescents (12-18 years) or adults.

CONTRA-INDICATIONS: Hypersensitivity to the active ingredients or excipients.

PRECAUTIONS: Use with caution in patients with a pre-existing history of depression or psychiatric illness.
Monitor patients with pre-existing liver dysfunction including chronic hepatitis. Consider interruption or discontinuation if evidence of worsening liver disease exists.
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 events.
Osteonecrosis has been reported. Advise patients to seek medical advice if they experience joint effects or difficulty in movement.
An inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise in HIV-infected patients with severe immune deficiency. Evaluate symptoms and institute treatment when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have been reported. These can occur many months after initiation of treatment.
Use with caution in patients with a history of myopathy and rhabdomyolysis or any risk factors associated with these conditions.
Severe, potentially life threatening and fatal skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported; in most cases other medications associated with these reactions were used concomitantly. Hypersensitivity reactions have been reported. Discontinue Isentress and other suspect agents immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop. Monitor clinical status including liver aminotransferase and initiate appropriate therapy.
Rash occurred more commonly in patients receiving ISENTRESS with darunavir compared to patients receiving either medicine alone.
Patients with rare hereditary problems of fructose intolerance glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take Isentress. **The chewable tablets and oral suspension contain** fructose and sucrose which may be harmful and damage teeth. Also contain, sorbitol which may affect the bioavailability of other oral use medicinal products. Patients who are lactose intolerant should not take Isentress tablets. Chewable tablets contain

aspartame, a source of phenylalanine which may be harmful for patients with phenylketonuria. All formulations contain less than 1 mmol sodium, which is essentially sodium-free. Raltegravir has a relatively low genetic barrier to resistance. When possible, administer raltegravir with two other active ARTs to minimise the potential for virological failure and the development of resistance.

Drug interactions*:* Refer to SmPC for full information on drug interactions. Raltegravir is metabolised primarily via UGT1A1, use caution when co-administering with strong inducers of UGT1A1 (e.g., rifampicin). If co-administration with rifampicin is unavoidable, consider doubling the dose of Isentress. The impact of other strong inducers of drug metabolising enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown. Less potent inducers (e.g., efavirenz, nevirapine, etravirine, rifabutin, glucocorticoids, St. John's wort, pioglitazone) may be used.
Co-administration with aluminium and magnesium antacids is not recommended. Co-administration with iron salts leads to reduced raltegravir plasma levels. Administering iron salts at least 2 hours from raltegravir may allow to limit this effect. All interactions studies were performed in adults.

Pregnancy and Lactation: **400 mg Film-coated Tablets:** A moderate amount of data on pregnant women (between 300 – 1,000 pregnancy outcomes from first trimester exposure) indicate no malformative or feto/neonatal toxicity of raltegravir 400 mg twice daily.
25 &100 mg Chewable Tablets and Oral suspension: There are no data for the use of raltegravir chewable tablets or oral suspension in pregnant women.
Raltegravir 400 mg film-coated tablets, chewable tablets and granules for oral suspension should only used if the expected benefit justifies the potential risk to the foetus (see SmPC for full details). An Anti-retroviral Pregnancy Registry has been established which physicians are encouraged to use. Breastfeeding is not recommended.

SIDE EFFECTS
Refer to Summary of Product Characteristics for complete information on side-effects

Frequencies of adverse reactions are defined as common (≥1/100 to <1/10) and uncommon (≥1/1,000 to <1/100).

Common: decreased appetite, abnormal dreams, insomnia, nightmare, abnormal behaviour, depression, dizziness, headache, psychomotor hyperactivity vertigo, abdominal distention, abdominal pain, flatulence, diarrhoea, nausea, vomiting, dyspepsia, rash, fatigue, asthenia, pyrexia, ALT increased, atypical lymphocytes, AST increased, blood triglycerides increased, lipase increased, blood pancreatic amylase increased.

Uncommon and Serious: neutropenia, thrombocytopenia, immune reconstitution syndrome, drug hypersensitivity, major depression, suicidal ideation, suicidal behaviour (particularly in patients with a pre-existing history of psychiatric illness), cognitive disorder, neuropathy peripheral, ventricular extrasystoles, pancreatitis acute, peptic ulcer, rectal haemorrhage, hepatitis, hepatic steatosis, hepatic failure, Stevens Johnson syndrome, rhabdomyolysis, renal failure, nephritis, drug rash with eosinophilia, systemic symptoms (DRESS). For a full list, please refer to the SmPC.

Cancers were reported. 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 Isentress and in the groups receiving comparators.

Grade 2-4 creatine kinase laboratory abnormalities were observed in subjects treated with Isentress

Patients co-infected with hepatitis B and/or hepatitis C virus: The safety profile of Isentress in patients with hepatitis B and/or hepatitis C virus co-infection was similar to that in uninfected patients although the rates of AST and ALT abnormalities were somewhat higher in the subgroup co-infected with hepatitis B and/or hepatitis C virus.

Paediatric population: Raltegravir has been studied in 126 antiretroviral treatment-experienced HIV-1 infected children and adolescents aged 2 to 18 years and 26 infants and toddlers aged 4 weeks to < 2 years, in combination with other antiretroviral agents. The safety profile was comparable to that in adults. In a paediatric clinical study, eligible infants were at least 37 weeks gestation and at least 2 kg in weight. Sixteen (16) neonates received 2 doses of ISENTRESS in first 2 weeks of life, and 26 neonates received 6 weeks of daily dosing; all were followed for 24 weeks. There were no drug-related clinical

adverse experiences and three drug-related laboratory adverse experiences considered non-serious and not requiring specific therapy.

PACKAGE QUANTITIES AND BASIC NHS COST
Bottles of 60 tablets:
400 mg film coated tablets- £471.41
25 mg chewable tablets- £29.46,
100 mg chewable tablets- £117.85
100 mg granules for oral suspension- 60 sachets- £213.02

Marketing Authorisation number
Great Britain:
100 mg Chewable Tablets: PLGB 53095/0029
100 mg Granules for Oral Suspension: PLGB 53095/0030
25 mg Chewable Tablets: PLGB 53095/0031
400 mg Film-Coated Tablets: PLGB 53095/0032

UK (Northern Ireland):
400 mg tablets: EU/1/07/436/001
25 mg chewable tablets: EU/1/07/436/003
100 mg chewable tablets: EU/1/07/436/004
100 mg granules for oral suspension: EU/1/07/436/005

Marketing Authorisation holder
Great Britain:
Merck Sharp & Dohme (UK) Limited
120 Moorgate
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EC2M 6UR
UK

UK (Northern Ireland):
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Legal Category: POM

Date of review of prescribing information: September 2021

PI.IST.21.GB-NI.7840.PSUSA-202009.RCN020148