ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT
ISENTRESS 400 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 400 mg of raltegravir (as potassium).

Excipient with known effect:
Each tablet contains 26.06 mg lactose (as monohydrate).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.
Pink, oval tablet, marked with "227" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
ISENTRESS is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adults, adolescents, children, toddlers and infants from the age of 4 weeks (see sections 4.2, 4.4, 5.1 and 5.2).

4.2 Posology and method of administration
Therapy should be initiated by a physician experienced in the management of HIV infection.

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

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

Children and adolescents
If at least 25 kg, the recommended dosage is 400 mg (one tablet) twice daily. If unable to swallow a tablet, consider the chewable tablet.

ISENTRESS is also available in a chewable tablet formulation for children weighing at least 11 kg and in granules for oral suspension formulation for infants and toddlers from 4 weeks of age and weighing at least 3 kg to less than 20 kg. Refer to the chewable tablet and granules for oral suspension EU-SmPCs for additional dosing information.

The maximum dose of the chewable tablet is 300 mg twice daily. Because the formulations are not bioequivalent, neither the chewable tablets nor the granules for oral suspension should be substituted for the 400 mg tablet (see section 5.2). The chewable tablets and the granules for oral suspension have not been studied in HIV-infected adolescents (12 to 18 years) or adults.
Elderly
There is limited information regarding the use of raltegravir in the elderly (see section 5.2). Therefore, ISENTRESS should be used with caution in this population.

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

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

Paediatric population
Safety and efficacy of raltegravir in infants below 4 weeks of age have not yet been established. No data are available.

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

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

4.4 Special warnings and precautions for use
Patients should be advised that current anti-retroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV to others through blood contact. While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Overall, considerable inter- and intra-subject variability was observed in the pharmacokinetics of raltegravir (see sections 4.5 and 5.2).

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, ISENTRESS 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 etiology 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) have also been reported to occur in the setting of immune reactivation: however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

**Antacids**
Co-administration of 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 section 4.5).

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

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

**Severe skin and hypersensitivity reactions**
Severe, potentially life-threatening, and fatal skin reactions have been reported in patients taking ISENTRESS, 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 characterized by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure. Discontinue ISENTRESS 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 ISENTRESS 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 ISENTRESS and darunavir compared to patients receiving ISENTRESS without darunavir or darunavir without ISENTRESS (see section 4.8).

Lactose
ISENTRESS film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Although *in vitro* studies indicated that raltegravir is not an inhibitor of the UDP glucuronosyltransferases (UGTs) 1A1 and 2B7, one clinical study has suggested that some inhibition of UGT1A1 may occur *in vivo* based on effects observed on bilirubin glucuronidation. However, the magnitude of the effect seems unlikely to result in clinically important drug-drug interactions.

Considerable inter- and intra-individual variability was observed in the pharmacokinetics of raltegravir. The following drug interaction information is based on Geometric Mean values; the effect for an individual patient cannot be predicted precisely.

**Effect of raltegravir on the pharmacokinetics of other medicinal products**

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

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

**Effect of other agents on the pharmacokinetics of raltegravir**

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

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

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 required.

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

All interaction studies were performed in adults.

Table 1
Pharmacokinetic Interaction Data

<table>
<thead>
<tr>
<th>Medicinal products by therapeutic area</th>
<th>Interaction (mechanism, if known)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-RETROVIRAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease inhibitors (PI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 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 ISENTRESS. |
| 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 ISENTRESS. |
| 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 ISENTRESS. |
| 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 ISENTRESS or etravirine. |
### Medicinal products by therapeutic area

#### Nucleoside/tide reverse transcriptase inhibitors

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
</table>
| tenofovir  | raltegravir AUC ↑ 49%  
raltegravir C<sub>12hr</sub> ↑ 3%  
raltegravir C<sub>max</sub> ↑ 64%  
(mechanism of interaction unknown)  
tenofovir AUC ↓ 10%  
tenofovir C<sub>24hr</sub> ↓ 13%  
tenofovir C<sub>max</sub> ↓ 23% | No dose adjustment required for ISENTRESS or tenofovir disoproxil fumarate. |

#### CCR5 inhibitors

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
</table>
| maraviroc | raltegravir AUC ↓ 37%  
raltegravir C<sub>12hr</sub> ↓ 28%  
raltegravir C<sub>max</sub> ↓ 33%  
(mechanism of interaction unknown)  
maraviroc AUC ↓ 14%  
maraviroc C<sub>12hr</sub> ↓ 10%  
maraviroc C<sub>max</sub> ↓ 21% | No dose adjustment required for ISENTRESS or maraviroc. |

#### HCV ANTIVIRALS

**NS3/4A protease inhibitors (PI)**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
</table>
| boceprevir | raltegravir AUC ↑ 4%  
raltegravir C<sub>12hr</sub> ↓ 25%  
raltegravir C<sub>max</sub> ↑ 11%  
(mechanism of interaction unknown) | No dose adjustment required for ISENTRESS or boceprevir. |

#### ANTIMICROBIALS

**Antimycobacterial**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
</table>
| rifampicin | raltegravir AUC ↓ 40%  
raltegravir C<sub>12hr</sub> ↓ 61%  
raltegravir C<sub>max</sub> ↓ 38%  
(UGT1A1 induction) | Rifampicin reduces plasma levels of ISENTRESS. If co-administration with rifampicin is unavoidable, a doubling of the dose of ISENTRESS can be considered (see section 4.4). |

#### SEDATIVE

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
</table>
| midazolam  | midazolam AUC ↓ 8%  
midazolam C<sub>max</sub> ↑ 3% | No dosage adjustment required for ISENTRESS 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.
<table>
<thead>
<tr>
<th>Medicinal products by therapeutic area</th>
<th>Interaction (mechanism, if known)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>METAL CATION ANTACIDS</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| aluminium and magnesium hydroxide antacid (raltegravir 400 mg Twice Daily) | raltegravir AUC ↓ 49%  
raltegravir C<sub>12 hr</sub> ↓ 63%  
raltegravir C<sub>max</sub> ↓ 44%  
2 hours before raltegravir  
raltegravir AUC ↓ 51%  
raltegravir C<sub>12 hr</sub> ↓ 56%  
raltegravir C<sub>max</sub> ↓ 51%  
2 hours after raltegravir  
raltegravir AUC ↓ 30%  
raltegravir C<sub>12 hr</sub> ↓ 57%  
raltegravir C<sub>max</sub> ↓ 24%  
6 hours before raltegravir  
raltegravir AUC ↓ 13%  
raltegravir C<sub>12 hr</sub> ↓ 50%  
raltegravir C<sub>max</sub> ↓ 10%  
6 hours after raltegravir  
raltegravir AUC ↓ 11%  
raltegravir C<sub>12 hr</sub> ↓ 49%  
raltegravir C<sub>max</sub> ↓ 10%  |
| Calcium carbonate antacid (raltegravir 400 mg Twice Daily) | raltegravir AUC ↓ 55%  
raltegravir C<sub>12 hr</sub> ↓ 32%  
raltegravir C<sub>max</sub> ↓ 52%  |
| (chelation of metal cations)           |                                   |                                               |
| **H2 BLOCKERS AND PROTON PUMP INHIBITORS** |                                   |                                               |
| omeprazole (raltegravir 400 mg Twice Daily) | raltegravir AUC ↑ 37%  
raltegravir C<sub>12 hr</sub> ↑ 24%  
raltegravir C<sub>max</sub> ↑ 51%  |
| (increased solubility)                |                                   | No dose adjustment required for ISENTRESS.    |
| famotidine (raltegravir 400 mg Twice Daily) | raltegravir AUC ↑ 44%  
raltegravir C<sub>12 hr</sub> ↑ 6%  
raltegravir C<sub>max</sub> ↑ 60%  |
| (increased solubility)                |                                   | No dose adjustment required for ISENTRESS.    |
| **HORMONAL CONTRACEPTIVES**           |                                   |                                               |
| Ethinyl Estradiol Norelgestromin (raltegravir 400 mg Twice Daily) | Ethinyl Estradiol AUC ↓ 2%  
Ethinyl Estradiol C<sub>max</sub> ↑ 6%  
Norelgestromin AUC ↑ 14%  
Norelgestromin C<sub>max</sub> ↑ 29%  |
| No dosage adjustment required for ISENTRESS or hormonal contraceptives (estrogen- and/or progesterone-based). |
| **OPIOID ANALGESICS**                 |                                   |                                               |
| methadone (raltegravir 400 mg Twice Daily) | methadone AUC ↔  
methadone C<sub>max</sub> ↔ |
| No dose adjustment required for ISENTRESS or methadone. |
4.6 Pregnancy, pregnancy and lactation

Pregnancy
There are no adequate data from the use of raltegravir in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. ISENTRESS should not be used during pregnancy.

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

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

Breast-feeding
It is not known whether raltegravir is secreted in human milk. However, raltegravir is secreted in the milk of lactating rats. In rats, at a maternal dose of 600 mg/kg/day, mean active substance concentrations in milk were approximately 3-fold greater than in maternal plasma. Breastfeeding is not recommended while taking ISENTRESS. As a general rule, it is recommended that mothers infected by HIV do not breast-feed their babies in order to avoid transmission of HIV.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The safety profile of ISENTRESS was based on the pooled safety data from two Phase III clinical studies in treatment-experienced adult patients and one Phase III clinical study in treatment-naïve adult patients. The most frequently reported adverse reactions during treatment were headache and nausea, occurring at 5% or greater. The most frequently reported serious adverse reaction was immune reconstitution syndrome.

In treatment-experienced patients, the two randomised clinical studies used the recommended dose of 400 mg twice daily in combination with optimised background therapy (OBT) in 462 patients, in comparison to 237 patients taking placebo in combination with OBT. During double-blind treatment, the total follow-up was 708 patient-years in the group receiving ISENTRESS 400 mg twice daily, and 244 patient-years in the group receiving placebo.

In treatment-naïve patients, the multi-centre, randomised, double-blind, active-controlled clinical study used the recommended dose of 400 mg twice daily in combination with a fixed dose of emtricitabine 200 mg (+) tenofovir 245 mg in 281 patients, in comparison to 282 patients taking efavirenz (EFV) 600 mg (at bedtime) in combination with emtricitabine (+) tenofovir. During double-blind treatment, the total follow-up was 1104 patient-years in the group receiving ISENTRESS 400 mg twice daily, and 1036 patient-years in the group receiving efavirenz 600 mg at bedtime.

In the pooled analysis of treatment-experienced patients, the rates of discontinuation of therapy due to adverse reactions were 3.9 % in patients receiving ISENTRESS + OBT and 4.6 % in patients receiving...
placebo + OBT. The rates of discontinuation of therapy in naïve patients due to adverse reactions were 5.0% in patients receiving ISENTRESS + emtricitabine (+) tenofovir and 10.0% in patients receiving efavirenz + emtricitabine (+) tenofovir.

**Tabulated summary of adverse reactions**

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).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse reactions ISENTRESS (alone or in combination with other ART)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Uncommon</td>
<td>genital herpes, folliculitis, gastroenteritis, herpes simplex, herpes virus infection, herpes zoster, influenza, lymph node abscess, molluscum contagiosum, nasopharyngitis, upper respiratory tract infection</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (including cysts and polyps)</td>
<td>Uncommon</td>
<td>skin papilloma</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Uncommon</td>
<td>anaemia, iron deficiency anaemia, lymph node pain, lymphadenopathy, neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Uncommon</td>
<td>immune reconstitution syndrome, drug hypersensitivity, hypersensitivity</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>decreased appetite</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>cachexia, diabetes mellitus, dyslipidaemia, hypercholesterolaemia, hyperglycaemia, hyperlipidaemia, hyperphagia, increased appetite, polydipsia, body fat disorder</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>common</td>
<td>abnormal dreams, insomnia, nightmare, abnormal behaviour, depression</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>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)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>common</td>
<td>dizziness, headache, psychomotor hyperactivity</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>amnesia, carpal tunnel syndrome, cognitive disorder, disturbance in attention, dizziness postural, dysgeusia, hypersonnia, hypoaesthesia, lethargy, memory impairment, migraine, neuropathy peripheral, paraesthesia, somnolence, tension headache, tremor, poor quality sleep</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Uncommon</td>
<td>visual impairment</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>common</td>
<td>vertigo</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>tinnitus</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency</td>
<td>Adverse reactions</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
<td>-----------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ISENTRESS (alone or in combination with other ART)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>palpitations, sinus bradycardia, ventricular extrasystoles</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon</td>
<td>hot flush, hypertension</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Uncommon</td>
<td>dysphonia, epistaxis, nasal congestion</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>common</td>
<td>abdominal distention, abdominal pain, diarrhoea, flatulence, nausea, vomiting, dyspepsia</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>gastritis, abdominal discomfort, abdominal pain upper, abdominal tenderness, anorectal discomfort, constipation, dry mouth, epigastric discomfort, erosive duodenitis, eructation, gastrooesophageal reflux disease, gingivitis, glossitis, odynophagia, pancreatitis acute, peptic ulcer, rectal haemorrhage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hepatitis, hepatic steatosis, hepatitis alcoholic, hepatic failure</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>common</td>
<td>rash</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>acne, alopecia, dermatitis acneiforme, dry skin, erythema, facial wasting, hyperhidrosis, lipoatrophy, lipodystrophy acquired, lipohypertrophy, night sweats, prurigo, pruritus, pruritus generalised, rash macular, rash maculopapular, rash pruritic, skin lesion, urticaria, xeroderma, Stevens Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Uncommon</td>
<td>arthralgia, arthritis, back pain, flank pain, musculoskeletal pain, myalgia, neck pain, osteopenia, pain in extremity, tendonitis, rhabdomyolysis</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Uncommon</td>
<td>renal failure, nephritis, nephrolithiasis, nocturia, renal cyst, renal impairment, tubulointerstitial nephritis</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Uncommon</td>
<td>erectile dysfunction, gynaecomastia, menopausal symptoms</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>common</td>
<td>asthenia, fatigue, pyrexia</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>chest discomfort, chills, face oedema, fat tissue increased, feeling jittery, malaise, submandibular mass, oedema peripheral, pain</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency</td>
<td>Adverse reactions</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ISENTRESS (alone or in combination with other ART)</td>
</tr>
<tr>
<td>Investigations</td>
<td>common</td>
<td>alanine aminotransferase increased, atypical lymphocytes, aspartate aminotransferase increased, blood triglycerides increased, lipase increased, blood pancreatic amylase increased</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>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</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Uncommon</td>
<td>accidental overdose</td>
</tr>
</tbody>
</table>

**Description of selected adverse reactions**

Cancers were reported in treatment-experienced and treatment-naïve patients who initiated ISENTRESS 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 ISENTRESS and in the groups receiving comparators.

Grade 2-4 creatine kinase laboratory abnormalities were observed in subjects treated with ISENTRESS. 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) 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 ISENTRESS and darunavir compared to those containing ISENTRESS without darunavir or darunavir without ISENTRESS. 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 Phase III studies, treatment-experienced patients (N = 114/699 or 16%; HBV=6 %, HCV=9 %, HBV+HCV=1 %) and treatment-naïve patients (N = 34/563 or 6 %; HBV=4%, HCV=2%, HBV+HCV=0.2 %) 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 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 with hepatitis B and/or hepatitis C virus co-infection for both treatment groups. 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 subjects treated with ISENTRESS as compared to 11 %, 10 % and 9 % of all other subjects treated with ISENTRESS. 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 subjects treated with ISENTRESS as compared to 13 %, 13 % and 5 % of all other subjects treated with ISENTRESS.

The following adverse reactions were identified through post-marketing surveillance but not reported as drug-related in randomised controlled Phase III clinical trials (Protocols 018, 019, and 021): thrombocytopenia, suicidal ideation, suicidal behaviour (particularly in patients with a pre-existing history of psychiatric illness), hepatic failure, Stevens Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rhabdomyolysis.

Paediatric population

Children and adolescents 2 to 18 years of age

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

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

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

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

Infants and toddlers 4 weeks to less than 2 years of age

Raltegravir has also been studied in 26 HIV-1 infected infants and toddlers 4 weeks to less than 2 years of age, in combination with other antiretroviral agents in IMPAACT P1066 (see sections 5.1 and 5.2).

In these 26 infants and toddlers, the frequency, type and severity of drug related adverse reactions through Week 48 were comparable to those observed in adults.

One patient experienced a Grade 3 serious drug related allergic rash that resulted in treatment discontinuation.

Reporting of suspected adverse reactions

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

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

In the event of an overdose, it is reasonable to employ the standard supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required. It should be taken into account that raltegravir is presented for clinical use as the potassium salt. The extent to which raltegravir may be dialysable is unknown.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, other antivirals, ATC code: J05AX08.

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

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

Resistance
Most viruses isolated from patients failing raltegravir had high-level raltegravir resistance resulting from the appearance of two or more mutations. 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 ISENTRESS was based on the analyses of 96-week data from two randomised, double-blind, placebo-controlled trials, (BENCHMRK 1 and BENCHMRK 2, Protocols 018 and 019) in antiretroviral treatment-experienced HIV-1 infected adult patients and the analysis of 240-week data from randomised, double-blind, active-control trial, (STARTMRK, Protocol 021) in antiretroviral treatment-naive HIV-1 infected adult patients.

Efficacy
Treatment-experienced adult patients
BENCHMRK 1 and BENCHMRK 2 (multi-centre, randomised, double-blind, placebo-controlled trials) evaluated the safety and anti-retroviral activity of ISENTRESS 400 mg twice daily vs. placebo in a combination with optimized 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 randomization, 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 ISENTRESS 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 ISENTRESS 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>48 Weeks</th>
<th>Placebo + OBT (N = 237)</th>
<th>96 Weeks</th>
<th>Placebo + OBT (N = 237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent HIV-RNA &lt; 400 copies/ml (95 % CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>72 (68, 76)</td>
<td>37 (31, 44)</td>
<td>62 (57, 66)</td>
<td>28 (23, 34)</td>
</tr>
<tr>
<td>Baseline Characteristic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml</td>
<td>62 (53, 69)</td>
<td>17 (9, 27)</td>
<td>53 (45, 61)</td>
<td>15 (8, 25)</td>
</tr>
<tr>
<td>≤ 100,000 copies/ml</td>
<td>82 (77, 86)</td>
<td>49 (41, 58)</td>
<td>74 (69, 79)</td>
<td>39 (31, 47)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm³</td>
<td>61 (53, 69)</td>
<td>21 (13, 32)</td>
<td>51 (42, 60)</td>
<td>14 (7, 24)</td>
</tr>
<tr>
<td>&gt; 50 and ≤ 200 cells/mm³</td>
<td>80 (73, 85)</td>
<td>44 (33, 55)</td>
<td>70 (62, 77)</td>
<td>36 (25, 48)</td>
</tr>
<tr>
<td>&gt; 200 cells/mm³</td>
<td>83 (76, 89)</td>
<td>51 (39, 63)</td>
<td>78 (70, 85)</td>
<td>42 (30, 55)</td>
</tr>
<tr>
<td>Sensitivity score (GSS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>52 (42, 61)</td>
<td>8 (3, 17)</td>
<td>46 (36, 56)</td>
<td>5 (1, 13)</td>
</tr>
<tr>
<td>1</td>
<td>81 (75, 87)</td>
<td>40 (30, 51)</td>
<td>76 (69, 83)</td>
<td>31 (22, 42)</td>
</tr>
<tr>
<td>2 and above</td>
<td>84 (77, 89)</td>
<td>65 (52, 76)</td>
<td>71 (63, 78)</td>
<td>56 (43, 69)</td>
</tr>
<tr>
<td>Percent HIV-RNA &lt; 50 copies/ml (95 % CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>62 (57, 67)</td>
<td>33 (27, 39)</td>
<td>57 (52, 62)</td>
<td>26 (21, 32)</td>
</tr>
<tr>
<td>Baseline Characteristic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml</td>
<td>48 (40, 56)</td>
<td>16 (8, 26)</td>
<td>47 (39, 55)</td>
<td>13 (7, 23)</td>
</tr>
<tr>
<td>≤ 100,000 copies/ml</td>
<td>73 (68, 78)</td>
<td>43 (35, 52)</td>
<td>70 (64, 75)</td>
<td>36 (28, 45)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm³</td>
<td>50 (41, 58)</td>
<td>20 (12, 31)</td>
<td>50 (41, 58)</td>
<td>13 (6, 22)</td>
</tr>
<tr>
<td>&gt; 50 and ≤ 200 cells/mm³</td>
<td>67 (59, 74)</td>
<td>39 (28, 50)</td>
<td>65 (57, 72)</td>
<td>32 (22, 44)</td>
</tr>
<tr>
<td>&gt; 200 cells/mm³</td>
<td>76 (68, 83)</td>
<td>44 (32, 56)</td>
<td>71 (62, 78)</td>
<td>41 (29, 53)</td>
</tr>
<tr>
<td>Sensitivity score (GSS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>45 (35, 54)</td>
<td>3 (0, 11)</td>
<td>41 (32, 51)</td>
<td>5 (1, 13)</td>
</tr>
<tr>
<td>1</td>
<td>67 (59, 74)</td>
<td>37 (27, 48)</td>
<td>72 (64, 79)</td>
<td>28 (19, 39)</td>
</tr>
<tr>
<td>2 and above</td>
<td>75 (68, 82)</td>
<td>59 (46, 71)</td>
<td>65 (56, 72)</td>
<td>53 (40, 66)</td>
</tr>
</tbody>
</table>
### BENCHMRK 1 and 2 Pooled

<table>
<thead>
<tr>
<th>Parameter</th>
<th>48 Weeks</th>
<th>96 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISENTRESS 400 mg twice daily + OBT (N = 462)</td>
<td>Placebo + OBT (N = 237)</td>
<td>ISENTRESS 400 mg twice daily + OBT (N = 462)</td>
</tr>
<tr>
<td>Mean CD4 Cell Change (95% CI), cells/mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients²</td>
<td>109 (98, 121)</td>
<td>45 (32, 57)</td>
</tr>
<tr>
<td>Baseline Characteristic²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml</td>
<td>126 (107, 144)</td>
<td>36 (17, 55)</td>
</tr>
<tr>
<td>HIV-RNA ≤ 100,000 copies/ml</td>
<td>100 (86, 115)</td>
<td>49 (33, 65)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm³³</td>
<td>121 (100, 142)</td>
<td>33 (18, 48)</td>
</tr>
<tr>
<td>CD4-count &gt; 50 and ≤ 200 cells/mm³³</td>
<td>104 (88, 119)</td>
<td>47 (28, 66)</td>
</tr>
<tr>
<td>CD4-count &gt; 200 cells/mm³³</td>
<td>104 (80, 129)</td>
<td>54 (24, 84)</td>
</tr>
<tr>
<td>Sensitivity score (GSS) ³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>81 (55, 106)</td>
<td>11 (4, 26)</td>
</tr>
<tr>
<td>1</td>
<td>113 (96, 130)</td>
<td>44 (24, 63)</td>
</tr>
<tr>
<td>2 and above</td>
<td>125 (105, 144)</td>
<td>76 (48, 103)</td>
</tr>
</tbody>
</table>

¹ 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.
² 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.
³ The Genotypic Sensitivity Score (GSS) was defined as the total oral ARTs in the optimized background therapy (OBT) to which a patient's viral isolate showed genotypic sensitivity based upon genotypic resistance test. Enfuvirtide use in OBT in enfuvirtide-naïve patients was counted as one active drug in OBT. Similarly, darunavir use in OBT in darunavir-naïve patients was counted as one active drug in OBT.

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

### Switch to raltegravir

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

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

### Treatment-naïve adult patients

STARTMRK (multi-centre, randomised, double-blind, active-control trial) evaluated the safety and anti-retroviral activity of ISENTRESS 400 mg twice daily vs. efavirenz 600 mg at bedtime, in a combination with emtricitabine (+) tenofovir, in treatment-naïve HIV-infected patients with HIV RNA > 5,000 copies/ml. Randomization 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 ISENTRESS 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 ISENTRESS and 230/281 (81.9 %) in the group receiving efavirenz. The treatment difference (ISENTRESS – efavirenz) was 4.2 % with an associated 95 % CI of (-1.9, 10.3) establishing that ISENTRESS is non-inferior to efavirenz (p-value for non-inferiority < 0.001). At Week 240, the treatment difference (ISENTRESS – 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 ISENTRESS 400 mg twice daily from STARTMRK are shown in Table 3.

**Table 3  Efficacy Outcome at Weeks 48 and 240**

<table>
<thead>
<tr>
<th>STARTMRK Study</th>
<th>48 Weeks</th>
<th>240 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ISENTRESS 400 mg twice daily (N = 281)</td>
<td>Efavirenz 600 mg at bedtime (N = 282)</td>
</tr>
<tr>
<td>Percent HIV-RNA &lt; 50 copies/ml (95 % CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients†</td>
<td>86 (81, 90)</td>
<td>82 (77, 86)</td>
</tr>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml</td>
<td>91 (85, 95)</td>
<td>89 (83, 94)</td>
</tr>
<tr>
<td>HIV-RNA ≤ 100,000 copies/ml</td>
<td>93 (86, 97)</td>
<td>89 (82, 94)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm³</td>
<td>84 (64, 95)</td>
<td>86 (67, 96)</td>
</tr>
<tr>
<td>&gt; 50 and ≤ 200 cells/mm³</td>
<td>89 (81, 95)</td>
<td>86 (77, 92)</td>
</tr>
<tr>
<td>&gt; 200 cells/mm³</td>
<td>94 (89, 98)</td>
<td>92 (87, 96)</td>
</tr>
<tr>
<td>Viral Subtype Clade B</td>
<td>90 (85, 94)</td>
<td>89 (83, 93)</td>
</tr>
<tr>
<td>Non-Clade B</td>
<td>96 (87, 100)</td>
<td>91 (78, 97)</td>
</tr>
<tr>
<td>Mean CD4 Cell Change (95 % CI), cells/mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients‡</td>
<td>189 (174, 204)</td>
<td>163 (148, 178)</td>
</tr>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml</td>
<td>196 (174, 219)</td>
<td>192 (169, 214)</td>
</tr>
<tr>
<td>HIV-RNA ≤ 100,000 copies/ml</td>
<td>180 (160, 200)</td>
<td>134 (115, 153)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm³</td>
<td>170 (122, 218)</td>
<td>152 (123, 180)</td>
</tr>
<tr>
<td>&gt; 50 and ≤ 200 cells/mm³</td>
<td>193 (169, 217)</td>
<td>175 (151, 198)</td>
</tr>
<tr>
<td>&gt; 200 cells/mm³</td>
<td>190 (168, 212)</td>
<td>157 (134, 181)</td>
</tr>
<tr>
<td>Viral Subtype Clade B</td>
<td>187 (170, 204)</td>
<td>164 (147, 181)</td>
</tr>
<tr>
<td>Non-Clade B</td>
<td>189 (153, 225)</td>
<td>156 (121, 190)</td>
</tr>
</tbody>
</table>

† 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.

ISENTRESS and efavirenz were administered with emtricitabine (+) tenofovir.
Paediatric population

Children and adolescents 2 to 18 years of age
IMPAACT P1066 is a Phase I/II open label multicenter trial to evaluate the pharmacokinetic profile, safety, tolerability, and efficacy of raltegravir in HIV infected children. This study enrolled 126 treatment experienced children and adolescents 2 to 18 years of age. Patients were stratified by age, enrolling adolescents first and then successively younger children. Patients received either the 400 mg tablet formulation (6 to 18 years of age) or the chewable tablet formulation (2 to less than 12 years of age). Raltegravir was administered with an optimized background regimen.

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

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

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

Infants and toddlers 4 weeks to less than 2 years of age
IMPAACT P1066 also enrolled HIV-infected, infants and toddlers 4 weeks to less than 2 years of age who had received prior antiretroviral therapy either as prophylaxis for prevention of mother to child transmission (PMTCT) and/or as combination antiretroviral therapy for treatment of HIV infection. Raltegravir was administered as granules for oral suspension formulation without regard to food in combination with an optimized background regimen that included lopinavir plus ritonavir in two-thirds of patients.
Table 5
Baseline Characteristics and Efficacy Outcomes at Weeks 24 and 48 from IMPAACT P1066
(4 weeks to less than 2 years of age)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N=26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age (weeks), median [range]</td>
<td>28 [4 - 100]</td>
</tr>
<tr>
<td>Male Gender</td>
<td>65 %</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>8 %</td>
</tr>
<tr>
<td>Black</td>
<td>85 %</td>
</tr>
<tr>
<td>Baseline Characteristics</td>
<td></td>
</tr>
<tr>
<td>Plasma HIV-1 RNA (log10 copies/ml), mean [range]</td>
<td>5.7 [3.1 - 7]</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm3), median [range]</td>
<td>1400 [131 - 3648]</td>
</tr>
<tr>
<td>CD4 percent, median [range]</td>
<td>18.6 % [3.3 – 39.3]</td>
</tr>
<tr>
<td>HIV-1 RNA &gt;100,000 copies/ml</td>
<td>69 %</td>
</tr>
<tr>
<td>CDC HIV category B or C</td>
<td>23 %</td>
</tr>
<tr>
<td>Prior ART Use by Class</td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>73 %</td>
</tr>
<tr>
<td>NRTI</td>
<td>46 %</td>
</tr>
<tr>
<td>PI</td>
<td>19 %</td>
</tr>
<tr>
<td>Response</td>
<td>Week 24</td>
</tr>
<tr>
<td>Achieved ≥1 log10 HIV RNA drop from baseline or &lt;400 copies/ml</td>
<td>91 %</td>
</tr>
<tr>
<td>Achieved HIV RNA &lt;50 copies/ml</td>
<td>43 %</td>
</tr>
<tr>
<td>Mean CD4 cell count (%) increase from baseline</td>
<td>500 cells/mm3 (7.5 %)</td>
</tr>
<tr>
<td>Virologic failure</td>
<td>Week 24</td>
</tr>
<tr>
<td>Non-responder</td>
<td>0</td>
</tr>
<tr>
<td>Rebounder</td>
<td>0</td>
</tr>
<tr>
<td>Number with genotype available*</td>
<td>0</td>
</tr>
</tbody>
</table>

*One patient had a mutation at the 155 position.

The European Medicines Agency has deferred the obligation to submit the results of studies with ISENTRESS in one or more subsets of the paediatric population in Human Immunodeficiency virus infection (see section 4.2 for information on paediatric use).

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 tmax of approximately 3 hours postdose. Raltegravir AUC and Cmax increase dose proportionally over the dose range 100 mg to 1,600 mg. Raltegravir C12 hr increases dose proportionally over the dose range of 100 to 800 mg and increases slightly less than dose proportionally over the dose range 100 mg to 1,600 mg. Dose proportionality has not been established in patients.

With twice-daily dosing, pharmacokinetic steady state is achieved rapidly, within approximately the first 2 days of dosing. There is little to no accumulation in AUC and Cmax and evidence of slight accumulation in C12 hr. The absolute bioavailability of raltegravir has not been established.

ISENTRESS 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 C12 hr was 66 % higher and Cmax was 5 % higher following a moderate-fat meal compared to fasting. Administration of raltegravir following a high-fat meal increased AUC and Cmax by approximately 2-fold and increased C12 hr by 4.1-fold. Administration of raltegravir following a low-fat meal decreased AUC and Cmax by 46 % and
52 %, respectively; C$_{12\,hr}$ was essentially unchanged. Food appears to increase pharmacokinetic variability relative to fasting.

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

**Distribution**

Raltegravir is approximately 83 % bound to human plasma protein over the concentration range of 2 to 10 µM.

Raltegravir readily crossed the placenta in rats, but did not penetrate the brain to any appreciable extent.

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

**Biotransformation and excretion**

The apparent terminal half-life of raltegravir is approximately 9 hours, with a shorter α-phase half-life (~1 hour) accounting for much of the AUC. Following administration of an oral dose of radiolabeled raltegravir, approximately 51 and 32 % of the dose was excreted in faeces and urine, respectively. In faeces, only raltegravir was present, most of which is likely to be derived from hydrolysis of raltegravir-glucuronide secreted in bile as observed in preclinical species. Two components, namely raltegravir and raltegravir-glucuronide, were detected in urine and accounted for approximately 9 and 23 % of the dose, respectively. The major circulating entity was raltegravir and represented approximately 70 % of the total radioactivity; the remaining radioactivity in plasma was accounted for by raltegravir-glucuronide. Studies using isoform-selective chemical inhibitors and cDNA-expressed UDP-glucuronosyltransferases (UGT) show that UGT1A1 is the main enzyme responsible for the formation of raltegravir-glucuronide. Thus the data indicate that the major mechanism of clearance of raltegravir in humans is UGT1A1-mediated glucuronidation.

**UGT1A1 Polymorphism**

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

**Special populations**

**Paediatric population**

Based on a formulation comparison study in healthy adult volunteers, the chewable tablet and granules for oral suspension have higher oral bioavailability compared to the 400 mg tablet. In this study, administration of the chewable tablet with a high fat meal led to an average 6 % decrease in AUC, 62 % decrease in C$_{\text{max}}$ 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 6 displays pharmacokinetic parameters in the 400 mg tablet, the chewable tablet), and the granules for oral suspension, by body weight.
Table 6
Raltegravir Pharmacokinetic Parameters IMPAACT P1066 Following Administration of Doses in Section 4.2

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Formulation</th>
<th>Dose</th>
<th>N*</th>
<th>Geometric mean (%CV)</th>
<th>Geometric mean (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AUC$_{0-12hr}$ (μM•hr)</td>
<td>C$_{12hr}$ (nM)</td>
</tr>
<tr>
<td>≥25 kg</td>
<td>Film-coated tablet</td>
<td>400 mg twice daily</td>
<td>18</td>
<td>14.1 (121 %)</td>
<td>233 (157 %)</td>
</tr>
<tr>
<td>≥25 kg</td>
<td>Chewable tablet</td>
<td>Weight based dosing, see</td>
<td>9</td>
<td>22.1 (36 %)</td>
<td>113 (80 %)</td>
</tr>
<tr>
<td>11 to less</td>
<td>Chewable tablet</td>
<td>dosing tables for the</td>
<td>13</td>
<td>18.6 (68 %)</td>
<td>82 (123 %)</td>
</tr>
<tr>
<td>25 kg</td>
<td></td>
<td>chewable tablet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 to less</td>
<td>Oral suspension</td>
<td>Weight based dosing, see</td>
<td>19</td>
<td>24.5 (43 %)</td>
<td>113 (69 %)</td>
</tr>
<tr>
<td>than</td>
<td></td>
<td>dosing tables for granules</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 kg</td>
<td></td>
<td>for oral suspension</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

†Geometric coefficient of variation.

The pharmacokinetics of raltegravir in infants under 4 weeks of age has not been established.

**Elderly**
There was no clinically meaningful effect of age on raltegravir pharmacokinetics over the age range studied (19 to 71 years, with few (8) subjects over the age of 65).

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

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

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

### 5.3 Preclinical safety data

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

**Mutagenicity**
No evidence of mutagenicity or genotoxicity was observed in *in vitro* microbial mutagenesis (Ames) tests, *in vitro* alkaline elution assays for DNA breakage and *in vitro* and *in vivo* chromosomal aberration studies.

**Carcinogenicity**
A carcinogenicity study of raltegravir in mice did not show any carcinogenic potential. At the highest dose levels, 400 mg/kg/day in females and 250 mg/kg/day in males, systemic exposure was similar to
that at the clinical dose of 400 mg twice daily. In rats, tumours (squamous cell carcinoma) of the nose/nasopharynx were identified at 300 and 600 mg/kg/day in females and at 300 mg/kg/day in males. These 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 they are of limited relevance for the intended clinical use. At the NOAEL, systemic exposure was similar to that at the clinical dose of 400 mg twice daily. Standard genotoxicity studies to evaluate mutagenicity and clastogenicity were negative.

Developmental toxicity
Raltegravir was not teratogenic in developmental toxicity studies in rats and rabbits. A slight increase in incidence of supernumerary ribs was observed in rat pups of dams exposed to raltegravir at approximately 4.4-fold human exposure at 400 mg twice daily based on AUC$_{0-24\ hr}$. No development effects were seen at 3.4-fold human exposure at 400 mg twice daily based on AUC$_{0-24\ hr}$ (see section 4.6). Similar findings were not observed in rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a child-resistant polypropylene closure. Two pack sizes are available: 1 bottle with 60 tablets, and 3 bottles of 60 tablets.

Not all pack sizes may be marketed.
6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.emea.europa.eu.
1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 100 mg chewable tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:
Each chewable tablet contains approximately 0.93 mg fructose, approximately 0.10 mg phenylalanine (as a component of aspartame) and approximately 2.8 mg sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ISENTRESS is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adults, adolescents, children, toddlers and infants from the age of 4 weeks (see sections 4.2, 4.4, 5.1 and 5.2).

4.2 Posology and method of administration

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

Posology
ISENTRESS should be used in combination with other active anti-retroviral therapies (ARTs) (see sections 4.4 and 5.1).
The maximum dose of the chewable tablet is 300 mg twice daily.
Because the formulations are not bioequivalent, neither the chewable tablets nor the granules for oral suspension should be substituted for the 400 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.

Children
Children at least 11 kg: weight based dose of the chewable tablet to a maximum dose of 300 mg, twice daily as specified in Tables 1 and 2. The chewable tablets are available in 25 mg and scored 100 mg strengths.
See section 5.2 regarding the limited data on which these dose recommendations are based.
Table 1
**Recommended Dose* for ISENTRESS Chewable Tablets for Paediatric Patients Weighing at Least 25 kg**

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Dose</th>
<th>Number of chewable tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 to less than 28</td>
<td>150 mg twice daily</td>
<td>1.5 x 100 mg† twice daily</td>
</tr>
<tr>
<td>28 to less than 40</td>
<td>200 mg twice daily</td>
<td>2 x 100 mg twice daily</td>
</tr>
<tr>
<td>At least 40</td>
<td>300 mg twice daily</td>
<td>3 x 100 mg twice daily</td>
</tr>
</tbody>
</table>

*The weight-based dosing recommendation for the chewable tablet is based on approximately 6 mg/kg/dose twice daily (see section 5.2).
†The 100 mg chewable tablet can be divided into equal 50 mg doses. However, breaking the tablets should be avoided whenever possible.

If at least 4 weeks of age and weighing at least 3 kg to less than 25 kg: Weight based dosing, as specified in Table 2.

For patients weighing between 11 and 20 kg, either the chewable tablet or oral suspension can be used, as specified in Table 2. Patients can remain on the oral suspension as long as their weight is below 20 kg. Refer to Table 2 for appropriate dosing (see section 5.1).

Table 2
**Recommended Dose* for ISENTRESS Granules For Oral Suspension and Chewable Tablets in Paediatric Patients Weighing Less than 25 kg**

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Volume (dose) of suspension to be administered</th>
<th>Number of chewable tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 to less than 4</td>
<td>1 ml (20 mg) twice daily</td>
<td></td>
</tr>
<tr>
<td>4 to less than 6</td>
<td>1.5 ml (30 mg) twice daily</td>
<td></td>
</tr>
<tr>
<td>6 to less than 8</td>
<td>2 ml (40 mg) twice daily</td>
<td></td>
</tr>
<tr>
<td>8 to less than 11</td>
<td>3 ml (60 mg) twice daily</td>
<td></td>
</tr>
<tr>
<td>11 to less than 14†</td>
<td>4 ml (80 mg) twice daily</td>
<td>3 x 25 mg twice daily</td>
</tr>
<tr>
<td>14 to less than 20†</td>
<td>5 ml (100 mg) twice daily</td>
<td>1 x 100 mg twice daily</td>
</tr>
<tr>
<td>20 to less than 25</td>
<td></td>
<td>1.5 x 100 mg‡ twice daily</td>
</tr>
</tbody>
</table>

*The weight-based dosing recommendation for the chewable tablet and oral suspension is based on approximately 6 mg/kg/dose twice daily (see section 5.2).
†For weight between 11 and 20 kg either formulation can be used.
‡The 100 mg chewable tablet can be divided into equal 50 mg doses. However, breaking the tablets should be avoided whenever possible.

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

ISENTRESS is also available in a 400 mg tablet for use in adults, adolescents and children weighing at least 25 kg and able to swallow a tablet; and as granules for oral suspension for use in infants and toddlers from 4 weeks of age and weighing at least 3 kg to less than 20 kg. Refer to the 400 mg tablet and granules for oral suspension EU-SmPCs for additional dosing information.

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

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

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

Paediatric population
Safety and efficacy of raltegravir in infants below 4 weeks of age have not yet been established. No data are available.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Patients should be advised that current anti-retroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV to others through blood contact. While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Overall, considerable inter- and intra-subject variability was observed in the pharmacokinetics of raltegravir (see sections 4.5 and 5.2).

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, ISENTRESS 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 etiology 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) have also been reported to occur in the setting of immune reactivation: however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

**Antacids**

Co-administration of 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 section 4.5).

**Rifampicin**

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

**Myopathy and rhabdomyolysis**

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

**Severe skin and hypersensitivity reactions**

Severe, potentially life-threatening, and fatal skin reactions have been reported in patients taking ISENTRESS, 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 characterized by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure. Discontinue ISENTRESS 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 ISENTRESS 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 ISENTRESS and darunavir compared to patients receiving ISENTRESS without darunavir or darunavir without ISENTRESS (see section 4.8).

**Fructose**

ISENTRESS chewable tablets contain fructose and sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.
4.5 Interaction with other medicinal products and other forms of interaction

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

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

Although in vitro studies indicated that raltegravir is not an inhibitor of the UDP glucuronosyltransferases (UGTs) 1A1 and 2B7, one clinical study has suggested that some inhibition of UGT1A1 may occur in vivo based on effects observed on bilirubin glucuronidation. However, the magnitude of the effect seems unlikely to result in clinically important drug-drug interactions.

Considerable inter- and intra-individual variability was observed in the pharmacokinetics of raltegravir. The following drug interaction information is based on Geometric Mean values; the effect for an individual patient cannot be predicted precisely.

**Effect of raltegravir on the pharmacokinetics of other medicinal products**

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

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

**Effect of other agents on the pharmacokinetics of raltegravir**

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

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

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

All interaction studies have been performed in adults.

### Table 3
Pharmacokinetic Interaction Data in Adults

<table>
<thead>
<tr>
<th>Medicinal products by therapeutic area</th>
<th>Interaction (mechanism, if known)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-RETROVIRAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease inhibitors (PI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 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 ISENTRESS. |
| 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 ISENTRESS. |
| 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 ISENTRESS. |
| 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 ISENTRESS or etravirine. |
| Nucleoside/tide reverse transcriptase inhibitors |                                   |                                               |
| tenofovir (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 ISENTRESS or tenofovir disoproxil fumarate. |
<table>
<thead>
<tr>
<th>Medicinal products by therapeutic area</th>
<th>Interaction (mechanism, if known)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCR5 inhibitors</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| maraviroc (raltegravir 400 mg Twice Daily) | raltegravir AUC ↓ 37%  
raltegravir C\textsubscript{12hr} ↓ 28%  
raltegravir C\textsubscript{max} ↓ 33%  
(mechanism of interaction unknown)  
maraviroc AUC ↓ 14%  
maraviroc C\textsubscript{12hr} ↓ 10%  
maraviroc C\textsubscript{max} ↓ 21% | No dose adjustment required for ISENTRESS or maraviroc. |
| **HCV ANTIVIRALS**                   |                                   |                                               |
| *NS3/4A protease inhibitors (PI)*    |                                   |                                               |
| boceprevir (raltegravir 400 mg Single Dose) | raltegravir AUC ↑ 4%  
raltegravir C\textsubscript{12hr} ↓ 25%  
raltegravir C\textsubscript{max} ↑ 11%  
(mechanism of interaction unknown) | No dose adjustment required for ISENTRESS or boceprevir. |
| **ANTIMICROBIALS**                   |                                   |                                               |
| *Antimycobacterial*                  |                                   |                                               |
| rifampicin (raltegravir 400 mg Single Dose) | raltegravir AUC ↓ 40%  
raltegravir C\textsubscript{12hr} ↓ 61%  
raltegravir C\textsubscript{max} ↓ 38%  
(UGT1A1 induction) | Rifampicin reduces plasma levels of ISENTRESS. If co-administration with rifampicin is unavoidable, a doubling of the dose of ISENTRESS can be considered (see section 4.4). |
| **SEDATIVE**                         |                                   |                                               |
| midazolam (raltegravir 400 mg Twice Daily) | midazolam AUC ↓ 8%  
midazolam C\textsubscript{max} ↑ 3% | No dosage adjustment required for ISENTRESS 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. |
<table>
<thead>
<tr>
<th>Medicinal products by therapeutic area</th>
<th>Interaction (mechanism, if known)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>METAL CATION ANTACIDS</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| aluminium and magnesium hydroxide antacid (raltegravir 400 mg Twice Daily) | raltegravir AUC ↓ 49 %  
raltegravir C$_{12hr}$ ↓ 63 %  
raltegravir C$_{max}$ ↓ 44 %  
2 hours before raltegravir  
raltegravir AUC ↓ 51 %  
raltegravir C$_{12hr}$ ↓ 56 %  
raltegravir C$_{max}$ ↓ 51 %  
2 hours after raltegravir  
raltegravir AUC ↓ 30 %  
raltegravir C$_{12hr}$ ↓ 57 %  
raltegravir C$_{max}$ ↓ 24 %  
6 hours before raltegravir  
raltegravir AUC ↓ 13 %  
raltegravir C$_{12hr}$ ↓ 50 %  
raltegravir C$_{max}$ ↓ 10 %  
6 hours after raltegravir  
raltegravir AUC ↓ 11 %  
raltegravir C$_{12hr}$ ↓ 49 %  
raltegravir C$_{max}$ ↓ 10 %  
(chelation of metal cations) | Aluminium and magnesium containing antacids reduce raltegravir plasma levels. Co-administration of ISENTRESS with aluminium and/or magnesium containing antacids is not recommended. |
| calcium carbonate antacid (raltegravir 400 mg Twice Daily) | raltegravir AUC ↓ 55 %  
raltegravir C$_{12hr}$ ↓ 32 %  
raltegravir C$_{max}$ ↓ 52 %  
(chelation of metal cations) | No dose adjustment required for ISENTRESS. |
| **H2 BLOCKERS AND PROTON PUMP INHIBITORS** |                                   |                                               |
| omeprazole (raltegravir 400 mg Twice Daily) | raltegravir AUC ↑ 37 %  
raltegravir C$_{12hr}$ ↑ 24 %  
raltegravir C$_{max}$ ↑ 51 %  
(increased solubility) | No dose adjustment required for ISENTRESS. |
| famotidine (raltegravir 400 mg Twice Daily) | raltegravir AUC ↑ 44 %  
raltegravir C$_{12hr}$ ↑ 6 %  
raltegravir C$_{max}$ ↑ 60 %  
(increased solubility) | No dose adjustment required for ISENTRESS. |
| **HORMONAL CONTRACEPTIVES** | Ethinyl Estradiol AUC ↓ 2 %  
Ethinyl Estradiol C$_{max}$ ↑ 6 %  
Norelgestromin AUC ↑ 14 %  
Norelgestromin C$_{max}$ ↑ 29 %  | No dosage adjustment required for ISENTRESS or hormonal contraceptives (estrogen- and/or progesterone-based). |
| Ethinyl Estradiol Norelgestromin (raltegravir 400 mg Twice Daily) |                                   |                                               |
| **OPIOID ANALGESICS**               |                                   |                                               |
| methadone (raltegravir 400 mg Twice Daily) | methadone AUC ↔  
methadone C$_{max}$ ↔ | No dose adjustment required for ISENTRESS or methadone. |
4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of raltegravir in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. ISENTRESS should not be used during pregnancy.

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

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

Breast-feeding
It is not known whether raltegravir is secreted in human milk. However, raltegravir is secreted in the milk of lactating rats. In rats, at a maternal dose of 600 mg/kg/day, mean active substance concentrations in milk were approximately 3-fold greater than in maternal plasma. Breastfeeding is not recommended while taking ISENTRESS. As a general rule, it is recommended that mothers infected by HIV do not breast-feed their babies in order to avoid transmission of HIV.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The safety profile of ISENTRESS was based on the pooled safety data from two Phase III clinical studies in treatment-experienced adult patients and one Phase III clinical study in treatment-naïve adult patients. The most frequently reported adverse reactions during treatment were headache and nausea, occurring at 5% or greater. The most frequently reported serious adverse reaction was immune reconstitution syndrome.

In treatment-experienced patients, the two randomised clinical studies used the recommended dose of 400 mg twice daily in combination with optimised background therapy (OBT) in 462 patients, in comparison to 237 patients taking placebo in combination with OBT. During double-blind treatment, the total follow-up was 708 patient-years in the group receiving ISENTRESS 400 mg twice daily, and 244 patient-years in the group receiving placebo.

In treatment-naïve patients, the multi-centre, randomised, double-blind, active-controlled clinical study used the recommended dose of 400 mg twice daily in combination with a fixed dose of emtricitabine 200 mg (+) tenofovir 245 mg in 281 patients, in comparison to 282 patients taking efavirenz (EFV) 600 mg (at bedtime) in combination with emtricitabine (+) tenofovir. During double-blind treatment, the total follow-up was 1104 patient-years in the group receiving ISENTRESS 400 mg twice daily, and 1036 patient-years in the group receiving efavirenz 600 mg at bedtime.

In the pooled analysis of treatment-experienced patients, the rates of discontinuation of therapy due to adverse reactions were 3.9 % in patients receiving ISENTRESS + OBT and 4.6 % in patients receiving
placebo + OBT. The rates of discontinuation of therapy in naïve patients due to adverse reactions were 5.0% in patients receiving ISENTRESS + emtricitabine (+) tenofovir and 10.0% in patients receiving efavirenz + emtricitabine (+) tenofovir.

Tabulated summary of adverse reactions

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).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse reactions (ISENTRESS (alone or in combination with other ART))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Uncommon</td>
<td>genital herpes, folliculitis, gastroenteritis, herpes simplex, herpes virus infection, herpes zoster, influenza, lymph node abscess, molluscum contagiosum, nasopharyngitis, upper respiratory tract infection</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (including cysts and polyps)</td>
<td>Uncommon</td>
<td>skin papilloma</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Uncommon</td>
<td>anaemia, iron deficiency anaemia, lymph node pain, lymphadenopathy, neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Uncommon</td>
<td>immune reconstitution syndrome, drug hypersensitivity, hypersensitivity</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>decreased appetite</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>cachexia, diabetes mellitus, dyslipidaemia, hypercholesterolaemia, hyperglycaemia, hyperlipidaemia, hyperphagia, increased appetite, polydipsia, body fat disorder</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>common</td>
<td>abnormal dreams, insomnia, nightmare, abnormal behaviour, depression</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>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)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>common</td>
<td>dizziness, headache, psychomotor hyperactivity</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>amnesia, carpal tunnel syndrome, cognitive disorder, disturbance in attention, dizziness postural, dyseusia, hypersomnia, hypoesthesia, lethargy, memory impairment, migraine, neuropathy peripheral, paraesthesia, somnolence, tension headache, tremor, poor quality sleep</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Uncommon</td>
<td>visual impairment</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>common</td>
<td>vertigo</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>tinnitus</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency</td>
<td>Adverse reactions ISENTRESS (alone or in combination with other ART)</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>------------</td>
<td>---------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>palpitations, sinus bradycardia, ventricular extrasystoles</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon</td>
<td>hot flush, hypertension</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Uncommon</td>
<td>dysphonia, epistaxis, nasal congestion</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>common</td>
<td>abdominal distention, abdominal pain, diarrhoea, flatulence, nausea, vomiting, dyspepsia</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>gastritis, abdominal discomfort, abdominal pain upper, abdominal tenderness, anorectal discomfort, constipation, dry mouth, epigastric discomfort, erosive duodenitis, eructation, gastrooesophageal reflux disease, gingivitis, glossitis, odynophagia, pancreatitis acute, peptic ulcer, rectal haemorrhage</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Uncommon</td>
<td>hepatitis, hepatic steatosis, hepatitis alcoholic, hepatic failure</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>common</td>
<td>rash</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>acne, alopecia, dermatitis acniforme, dry skin, erythema, facial wasting, hyperhidrosis, lipoatrophy, lipodystrophy acquired, lipo hypertrophy, night sweats, prurigo, pruritus, pruritus generalised, rash macular, rash maculopapular, rash pruritic, skin lesion, urticaria, xeroderma, Stevens Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Uncommon</td>
<td>arthralgia, arthritis, back pain, flank pain, musculoskeletal pain, myalgia, neck pain, osteopenia, pain in extremity, tendonitis, rhabdomyolysis</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Uncommon</td>
<td>renal failure, nephritis, nephrolithiasis, nocturia, renal cyst, renal impairment, tubulointerstitial nephritis</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Uncommon</td>
<td>erectile dysfunction, gynaecomastia, menopausal symptoms</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>common</td>
<td>asthenia, fatigue, pyrexia</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>chest discomfort, chills, face oedema, fat tissue increased, feeling jittery, malaise, submandibular mass, oedema peripheral, pain</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency</td>
<td>Adverse reactions ISENTRESS (alone or in combination with other ART)</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Investigations</td>
<td>common</td>
<td>alanine aminotransferase increased, atypical lymphocytes, aspartate aminotransferase increased, blood triglycerides increased, lipase increased, blood pancreatic amylase increased</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>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</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Uncommon</td>
<td>accidental overdose</td>
</tr>
</tbody>
</table>

Description of selected adverse reactions
Cancers were reported in treatment-experienced and treatment-naïve patients who initiated ISENTRESS 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 ISENTRESS and in the groups receiving comparators.

Grade 2-4 creatine kinase laboratory abnormalities were observed in subjects treated with ISENTRESS. 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) 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 ISENTRESS and darunavir compared to those containing ISENTRESS without darunavir or darunavir without ISENTRESS. 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 Phase III studies, treatment-experienced patients (N = 114/699 or 16%; HBV=6 %, HCV=9 %, HBV+HCV=1 %) and treatment-naïve patients (N = 34/563 or 6 %; HBV=4%, HCV=2%, HBV+HCV=0.2 %) 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 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 with hepatitis B and/or hepatitis C virus co-infection for both treatment groups. 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 subjects treated with ISENTRESS as compared to 11 %, 10 % and 9 % of all other subjects treated with ISENTRESS. 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 subjects treated with ISENTRESS as compared to 13 %, 13 % and 5 % of all other subjects treated with ISENTRESS.

The following adverse reactions were identified through post-marketing surveillance but not reported as drug-related in randomised controlled Phase III clinical trials (Protocols 018, 019, and 021): thrombocytopenia, suicidal ideation, suicidal behaviour (particularly in patients with a pre-existing history of psychiatric illness), hepatic failure, Stevens Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rhabdomyolysis.

Paediatric population

Children and adolescents 2 to 18 years of age

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

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

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

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

Infants and toddlers 4 weeks to less than 2 years of age

Raltegravir has also been studied in 26 HIV-1 infected infants and toddlers 4 weeks to less than 2 years of age, in combination with other antiretroviral agents in IMPAACT P1066 (see sections 5.1 and 5.2).

In these 26 infants and toddlers, the frequency, type and severity of drug related adverse reactions through Week 48 were comparable to those observed in adults.

One patient experienced a Grade 3 serious drug related allergic rash that resulted in treatment discontinuation.

Reporting of suspected adverse reactions

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

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

In the event of an overdose, it is reasonable to employ the standard supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required. It should be taken into account that raltegravir is presented for clinical use as the potassium salt. The extent to which raltegravir may be dialysable is unknown.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, other antivirals, ATC code: J05AX08.

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

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

Resistance
Most viruses isolated from patients failing raltegravir had high-level raltegravir resistance resulting from the appearance of two or more mutations. 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 ISSENTRESS was based on the analyses of 96-week data from two randomised, double-blind, placebo-controlled trials, (BENCHMRK 1 and BENCHMRK 2, Protocols 018 and 019) in antiretroviral treatment-experienced HIV-1 infected adult patients and the analysis of 240-week data from a randomised, double-blind, active-control trial, (STARTMRK, Protocol 021) in antiretroviral treatment-naïve HIV-1 infected adult patients.

Efficacy
Treatment-experienced adult patients
BENCHMRK 1 and BENCHMRK 2 (multi-centre, randomised, double-blind, placebo-controlled trials) evaluated the safety and anti-retroviral activity of ISSENTRESS 400 mg twice daily vs. placebo in a combination with optimized 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 randomization, 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 ISSENTRESS 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 ISSENTRESS 400 mg twice daily from the pooled studies BENCHMRK 1 and BENCHMRK 2 are shown in Table 4.

Table 4
Efficacy Outcome at Weeks 48 and 96

<table>
<thead>
<tr>
<th>Parameter</th>
<th>48 Weeks</th>
<th>96 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ISSENTRESS 400 mg twice daily + OBT (N = 462)</td>
<td>Placebo + OBT (N = 237)</td>
</tr>
<tr>
<td>Percent HIV-RNA &lt; 400 copies/ml (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>72 (68, 76)</td>
<td>37 (31, 44)</td>
</tr>
<tr>
<td>Baseline Characteristic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml</td>
<td>62 (53, 69)</td>
<td>17 (9, 27)</td>
</tr>
<tr>
<td>≤ 100,000 copies/ml</td>
<td>82 (77, 86)</td>
<td>49 (41, 58)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm³</td>
<td>61 (53, 69)</td>
<td>21 (13, 32)</td>
</tr>
<tr>
<td>&gt; 50 and ≤ 200 cells/mm³</td>
<td>80 (73, 85)</td>
<td>44 (33, 55)</td>
</tr>
<tr>
<td>&gt; 200 cells/mm³</td>
<td>83 (76, 89)</td>
<td>51 (39, 63)</td>
</tr>
<tr>
<td>Sensitivity score (GSS) §</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>52 (42, 61)</td>
<td>8 (3, 17)</td>
</tr>
<tr>
<td>1</td>
<td>81 (75, 87)</td>
<td>40 (30, 51)</td>
</tr>
<tr>
<td>2 and above</td>
<td>84 (77, 89)</td>
<td>65 (52, 76)</td>
</tr>
<tr>
<td>Percent HIV-RNA &lt; 50 copies/ml (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>62 (57, 67)</td>
<td>33 (27, 39)</td>
</tr>
<tr>
<td>Baseline Characteristic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml</td>
<td>48 (40, 56)</td>
<td>16 (8, 26)</td>
</tr>
<tr>
<td>≤ 100,000 copies/ml</td>
<td>73 (68, 78)</td>
<td>43 (35, 52)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm³</td>
<td>50 (41, 58)</td>
<td>20 (12, 31)</td>
</tr>
<tr>
<td>&gt; 50 and ≤ 200 cells/mm³</td>
<td>67 (59, 74)</td>
<td>39 (28, 50)</td>
</tr>
<tr>
<td>&gt; 200 cells/mm³</td>
<td>76 (68, 83)</td>
<td>44 (32, 56)</td>
</tr>
<tr>
<td>Sensitivity score (GSS) §</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>45 (35, 54)</td>
<td>3 (0, 11)</td>
</tr>
<tr>
<td>1</td>
<td>67 (59, 74)</td>
<td>37 (27, 48)</td>
</tr>
<tr>
<td>2 and above</td>
<td>75 (68, 82)</td>
<td>59 (46, 71)</td>
</tr>
</tbody>
</table>
### BENCHMRK 1 and 2 Pooled

<table>
<thead>
<tr>
<th>Parameter</th>
<th>48 Weeks</th>
<th>96 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean CD4 Cell Change (95 % CI), cells/mm³</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Characteristic</td>
<td>109 (98, 121)</td>
<td>123 (110, 137)</td>
</tr>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml</td>
<td>126 (107, 144)</td>
<td>140 (115, 165)</td>
</tr>
<tr>
<td>≤ 100,000 copies/ml</td>
<td>100 (86, 115)</td>
<td>114 (98, 131)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm³</td>
<td>121 (100, 142)</td>
<td>130 (104, 156)</td>
</tr>
<tr>
<td>&gt; 50 and ≤ 200 cells/mm³</td>
<td>104 (88, 119)</td>
<td>123 (103, 144)</td>
</tr>
<tr>
<td>&gt; 200 cells/mm³</td>
<td>104 (80, 129)</td>
<td>117 (90, 143)</td>
</tr>
<tr>
<td>Sensitivity score (GSS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>81 (55, 106)</td>
<td>97 (70, 124)</td>
</tr>
<tr>
<td>1</td>
<td>113 (96, 130)</td>
<td>132 (111, 154)</td>
</tr>
<tr>
<td>2 and above</td>
<td>125 (105, 144)</td>
<td>134 (108, 159)</td>
</tr>
</tbody>
</table>

† Non-completer is failure imputation: patients who discontinued prematurely are imputed as failure thereafter. Percent of patients with response and associated 95 % confidence interval (CI) are reported.
‡ For analysis by prognostic factors, virologic failures were carried forward for percent < 400 and 50 copies/ml. For mean CD4 changes, baseline-carry-forward was used for virologic failures.
§ The Genotypic Sensitivity Score (GSS) was defined as the total oral ARTs in the optimised background therapy (OBT) to which a patient's viral isolate showed genotypic sensitivity based upon genotypic resistance test. Enfuvirtide use in OBT in enfuvirtide-naïve patients was counted as one active drug in OBT. Similarly, darunavir use in OBT in darunavir-naïve patients was counted as one active drug in OBT.

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

**Switch to raltegravir**

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

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

**Treatment-naïve adult patients**

STARTMRK (multi-centre, randomised, double-blind, active-control trial) evaluated the safety and anti-retroviral activity of ISENTRESS 400 mg twice daily vs. efavirenz 600 mg at bedtime, in a combination with emtricitabine (+) tenofovir, in treatment-naïve HIV-infected patients with HIV RNA > 5,000 copies/ml. Randomization 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 ISENTRESS 400 mg twice daily and the group receiving efavirenz 600 mg at bedtime.
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 ISENTRESS and 230/281 (81.9 %) in the group receiving efavirenz. The treatment difference (ISENTRESS – efavirenz) was 4.2 % with an associated 95 % CI of (-1.9, 10.3) establishing that ISENTRESS is non-inferior to efavirenz (p-value for non-inferiority < 0.001). At Week 240, the treatment difference (ISENTRESS – 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 ISENTRESS 400 mg twice daily from STARTMRK are shown in Table 5.

### Table 5

#### Efficacy Outcome at Weeks 48 and 240

<table>
<thead>
<tr>
<th>Parameter</th>
<th>48 Weeks</th>
<th></th>
<th>240 Weeks</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ISENTRESS 400 mg twice daily (N = 281)</td>
<td>Efavirenz 600 mg at bedtime (N = 282)</td>
<td>ISENTRESS 400 mg twice daily (N = 281)</td>
<td>Efavirenz 600 mg at bedtime (N = 282)</td>
</tr>
<tr>
<td><strong>Percent HIV-RNA &lt; 50 copies/ml (95 % CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>86 (81, 90)</td>
<td>82 (77, 86)</td>
<td>71 (65, 76)</td>
<td>61 (55, 67)</td>
</tr>
<tr>
<td>Baseline Characteristic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml</td>
<td>91 (85, 95)</td>
<td>89 (83, 94)</td>
<td>70 (62, 77)</td>
<td>65 (56, 72)</td>
</tr>
<tr>
<td>≤ 100,000 copies/ml</td>
<td>93 (86, 97)</td>
<td>89 (82, 94)</td>
<td>72 (64, 80)</td>
<td>58 (49, 66)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm³</td>
<td>84 (64, 95)</td>
<td>86 (67, 96)</td>
<td>58 (37, 77)</td>
<td>77 (58, 90)</td>
</tr>
<tr>
<td>&gt; 50 and ≤ 200 cells/mm³</td>
<td>89 (81, 95)</td>
<td>86 (77, 92)</td>
<td>67 (57, 76)</td>
<td>60 (50, 69)</td>
</tr>
<tr>
<td>&gt; 200 cells/mm³</td>
<td>94 (89, 98)</td>
<td>92 (87, 96)</td>
<td>76 (68, 82)</td>
<td>60 (51, 68)</td>
</tr>
<tr>
<td>Viral Subtype Clade B</td>
<td>90 (85, 94)</td>
<td>89 (83, 93)</td>
<td>71 (65, 77)</td>
<td>59 (52, 65)</td>
</tr>
<tr>
<td>Non-Clade B</td>
<td>96 (87, 100)</td>
<td>91 (78, 97)</td>
<td>68 (54, 79)</td>
<td>70 (54, 82)</td>
</tr>
<tr>
<td><strong>Mean CD4 Cell Change (95 % CI), cells/mm³</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>189 (174, 204)</td>
<td>163 (148, 178)</td>
<td>374 (345, 403)</td>
<td>312 (284, 339)</td>
</tr>
<tr>
<td>Baseline Characteristic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml</td>
<td>196 (174, 219)</td>
<td>192 (169, 214)</td>
<td>392 (350, 435)</td>
<td>329 (293, 364)</td>
</tr>
<tr>
<td>≤ 100,000 copies/ml</td>
<td>180 (160, 200)</td>
<td>134 (115, 153)</td>
<td>350 (312, 388)</td>
<td>294 (251, 337)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm³</td>
<td>170 (122, 218)</td>
<td>152 (123, 180)</td>
<td>304 (209, 399)</td>
<td>314 (242, 386)</td>
</tr>
<tr>
<td>&gt; 50 and ≤ 200 cells/mm³</td>
<td>193 (169, 217)</td>
<td>175 (151, 198)</td>
<td>413 (360, 465)</td>
<td>306 (264, 348)</td>
</tr>
<tr>
<td>&gt; 200 cells/mm³</td>
<td>190 (168, 212)</td>
<td>157 (134, 181)</td>
<td>358 (321, 395)</td>
<td>316 (272, 359)</td>
</tr>
<tr>
<td>Viral Subtype Clade B</td>
<td>187 (170, 204)</td>
<td>164 (147, 181)</td>
<td>380 (346, 414)</td>
<td>303 (272, 333)</td>
</tr>
<tr>
<td>Non-Clade B</td>
<td>189 (153, 225)</td>
<td>156 (121, 190)</td>
<td>332 (275, 388)</td>
<td>329 (260, 398)</td>
</tr>
</tbody>
</table>

‡ 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.

ISENTRESS and efavirenz were administered with emtricitabine (+) tenofovir.
**Paediatric population**

**Children and adolescents 2 to 18 years of age**

IMPAACT P1066 is a Phase I/II open label multicenter trial to evaluate the pharmacokinetic profile, safety, tolerability, and efficacy of raltegravir in HIV infected children. This study enrolled 126 treatment experienced children and adolescents 2 to 18 years of age. Patients were stratified by age, enrolling adolescents first and then successively younger children. Patients received either the 400 mg tablet formulation (6 to 18 years of age) or the chewable tablet formulation (2 to less than 12 years of age). Raltegravir was administered with an optimized background regimen.

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

**Table 6**

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

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

**Infants and toddlers 4 weeks to less than 2 years of age**

IMPAACT P1066 also enrolled HIV-infected, infants and toddlers 4 weeks to less than 2 years of age who had received prior antiretroviral therapy either as prophylaxis for prevention of mother to child transmission (PMTCT) and/or as combination antiretroviral therapy for treatment of HIV infection. Raltegravir was administered as granules for oral suspension formulation without regard to food in combination with an optimized background regimen that included lopinavir plus ritonavir in two-thirds of patients.
Table 7
Baseline Characteristics and Efficacy Outcomes at Weeks 24 and 48 from IMPAACT P1066
(4 weeks to less than 2 years of age)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N=26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age (weeks), median [range]</td>
<td>28 [4 -100]</td>
</tr>
<tr>
<td>Male Gender</td>
<td>65 %</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>8 %</td>
</tr>
<tr>
<td>Black</td>
<td>85 %</td>
</tr>
<tr>
<td>Baseline Characteristics</td>
<td></td>
</tr>
<tr>
<td>Plasma HIV-1 RNA (log_{10} copies/ml), mean [range]</td>
<td>5.7 [3.1 - 7]</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm$^3$), median [range]</td>
<td>1400 [131 -3648]</td>
</tr>
<tr>
<td>CD4 percent, median [range]</td>
<td>18.6 % [3.3 – 39.3]</td>
</tr>
<tr>
<td>HIV-1 RNA &gt;100,000 copies/ml</td>
<td>69 %</td>
</tr>
<tr>
<td>CDC HIV category B or C</td>
<td>23 %</td>
</tr>
<tr>
<td>Prior ART Use by Class</td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>73 %</td>
</tr>
<tr>
<td>NRTI</td>
<td>46%</td>
</tr>
<tr>
<td>PI</td>
<td>19 %</td>
</tr>
<tr>
<td>Response</td>
<td></td>
</tr>
<tr>
<td>Achieved ≥1 log_{10} HIV RNA drop from baseline or &lt;400 copies/ml</td>
<td>91 %</td>
</tr>
<tr>
<td>Achieved HIV RNA &lt;50 copies/ml</td>
<td>43 %</td>
</tr>
<tr>
<td>Mean CD4 cell count (%) increase from baseline</td>
<td>500 cells/mm$^3$ (7.5 %)</td>
</tr>
<tr>
<td>Virologic failure</td>
<td></td>
</tr>
<tr>
<td>Non-responder</td>
<td>0</td>
</tr>
<tr>
<td>Rebounder</td>
<td>0</td>
</tr>
<tr>
<td>Number with genotype available*</td>
<td>0</td>
</tr>
</tbody>
</table>

*One patient had a mutation at the 155 position.

The European Medicines Agency has deferred the obligation to submit the results of studies with ISENTRESS in one or more subsets of the paediatric population in Human Immunodeficiency virus infection (see section 4.2 for information on paediatric use).

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 $t_{\text{max}}$ of approximately 3 hours postdose. Raltegravir AUC and $C_{\text{max}}$ increase dose proportionally over the dose range 100 mg to 1,600 mg. Raltegravir $C_{12\ hr}$ increases dose proportionally over the dose range of 100 to 800 mg and increases slightly less than dose proportionally over the dose range 100 mg to 1,600 mg. Dose proportionality has not been established in patients.

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

ISENTRESS 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 $C_{\text{max}}$ was 5 % higher following a moderate-fat meal compared to fasting. Administration of raltegravir following a high-fat meal increased AUC and $C_{\text{max}}$ by approximately 2-fold and increased $C_{12\ hr}$ by 4.1-fold. Administration of raltegravir following a low-fat meal decreased AUC and $C_{\text{max}}$ by 46 % and
52 %, respectively; \( C_{12\text{hr}} \) was essentially unchanged. Food appears to increase pharmacokinetic variability relative to fasting.

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

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

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

Biotransformation and excretion
The apparent terminal half-life of raltegravir is approximately 9 hours, with a shorter \( \alpha \)-phase half-life (~1 hour) accounting for much of the AUC. Following administration of an oral dose of radiolabeled raltegravir, approximately 51 and 32 % of the dose was excreted in faeces and urine, respectively. In faeces, only raltegravir was present, most of which is likely to be derived from hydrolysis of raltegravir-glucuronide secreted in bile as observed in preclinical species. Two components, namely raltegravir and raltegravir-glucuronide, were detected in urine and accounted for approximately 9 and 23 % of the dose, respectively. The major circulating entity was raltegravir and represented approximately 70 % of the total radioactivity; the remaining radioactivity in plasma was accounted for by raltegravir-glucuronide. Studies using isoform-selective chemical inhibitors and cDNA-expressed UDP-glucuronosyltransferases (UGT) show that UGT1A1 is the main enzyme responsible for the formation of raltegravir-glucuronide. Thus the data indicate that the major mechanism of clearance of raltegravir in humans is UGT1A1-mediated glucuronidation.

UGT1A1 Polymorphism
In a comparison of 30 subjects with *28/*28 genotype to 27 subjects with wild-type genotype, the geometric mean ratio (90 % CI) of AUC was 1.41 (0.96, 2.09) and the geometric mean ratio of \( C_{12\text{hr}} \) 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 \( C_{\text{max}} \) and 188 % increase in \( C_{12\text{hr}} \) compared to administration in the fasted state. Administration of the chewable tablet with a high fat meal does not affect raltegravir pharmacokinetics to a clinically meaningful degree and the chewable tablet can be administered without regard to food. The effect of food on the granules for oral suspension formulation was not studied.

Table 8 displays pharmacokinetic parameters in the 400 mg tablet, the chewable tablet), and the granules for oral suspension, by body weight.
Table 8
Raltegravir Pharmacokinetic Parameters IMPAACT P1066 Following Administration of Doses in Section 4.2

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Formulation</th>
<th>Dose</th>
<th>N*</th>
<th>Geometric mean (%CV) AUC_{0-12hr} (μM h)</th>
<th>Geometric mean (%CV) C_{12hr} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥25 kg</td>
<td>Film-coated tablet</td>
<td>400 mg twice daily</td>
<td>18</td>
<td>14.1 (121 %)</td>
<td>233 (157 %)</td>
</tr>
<tr>
<td>≥25 kg</td>
<td>Chewable tablet</td>
<td>Weight based dosing, see</td>
<td>9</td>
<td>22.1 (36 %)</td>
<td>113 (80 %)</td>
</tr>
<tr>
<td>11 to less</td>
<td>Chewable tablet</td>
<td>Weight based dosing, see</td>
<td>13</td>
<td>18.6 (68 %)</td>
<td>82 (123 %)</td>
</tr>
<tr>
<td>than 25 kg</td>
<td>Chewing tablet</td>
<td>dosing Table 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 to less</td>
<td>Oral suspension</td>
<td>Weight based dosing, see</td>
<td>19</td>
<td>24.5 (43 %)</td>
<td>113 (69 %)</td>
</tr>
<tr>
<td>than 20 kg</td>
<td></td>
<td>dosing table for granules</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>for oral suspension</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

†Geometric coefficient of variation.

The pharmacokinetics of raltegravir in infants under 4 weeks of age has not been established.

Elderly
There was no clinically meaningful effect of age on raltegravir pharmacokinetics over the age range studied (19 to 71 years, with few (8) subjects over the age of 65).

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

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

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

5.3 Preclinical safety data

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

Mutagenicity
No evidence of mutagenicity or genotoxicity was observed in in vitro microbial mutagenesis (Ames) tests, in vitro alkaline elution assays for DNA breakage and in vitro and in vivo chromosomal aberration studies.

Carcinogenicity
A carcinogenicity study of raltegravir in mice did not show any carcinogenic potential. At the highest dose levels, 400 mg/kg/day in females and 250 mg/kg/day in males, systemic exposure was similar to that at the clinical dose of 400 mg twice daily. In rats, tumours (squamous cell carcinoma) of the
nose/nasopharynx were identified at 300 and 600 mg/kg/day in females and at 300 mg/kg/day in males. These 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 they are of limited relevance for the intended clinical use. At the NOAEL, systemic exposure was similar to that at the clinical dose of 400 mg twice daily. Standard genotoxicity studies to evaluate mutagenicity and clastogenicity were negative.

Developmental toxicity
Raltegravir was not teratogenic in developmental toxicity studies in rats and rabbits. A slight increase in incidence of supernumerary ribs was observed in rat pups of dams exposed to raltegravir at approximately 4.4-fold human exposure at 400 mg twice daily based on AUC$_{0-24	ext{ hr}}$. No development effects were seen at 3.4-fold human exposure at 400 mg twice daily based on AUC$_{0-24	ext{ hr}}$ (see section 4.6). Similar findings were not observed in rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Hydroxypropyl cellulose
- Sucralose
- Saccharin sodium
- Sodium citrate dihydrate
- Mannitol
- Monoammonium glycyrrhizinate
- Sorbitol (E420)
- Fructose
- Banana flavour
- Orange flavour
- Masking flavour
- Aspartame (E951)
- Crospovidone, Type A
- Sodium stearyl fumarate- Magnesium stearate
- Hypromellose 2910/6cP
- Macrogol/PEG 400
- Ethylecellulose 20 cP
- Ammonium hydroxide
- Medium chain triglycerides
- Oleic acid
- Red iron oxide
- Yellow iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Keep the bottle tightly closed, with the desiccant in order to protect from moisture.
6.5 Nature and contents of container

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

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.emea.europa.eu.
1. **NAME OF THE MEDICINAL PRODUCT**

ISENTRESS 25 mg chewable tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

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

*Excipients with known effect:*
Each chewable tablet contains approximately 0.46 mg fructose, approximately 0.05 mg phenylalanine (as a component of aspartame) and approximately 1.4 mg sorbitol.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Chewable tablet.
Pale yellow, round, chewable tablet with Merck logo on one side and 473 on the other side.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

ISENTRESS is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adults, adolescents, children, toddlers and infants from the age of 4 weeks (see sections 4.2, 4.4, 5.1 and 5.2).

4.2 **Posology and method of administration**

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

**Posology**
ISENTRESS should be used in combination with other active anti-retroviral therapies (ARTs) (see sections 4.4 and 5.1).
The maximum dose of the chewable tablet is 300 mg twice daily.
Because the formulations are not bioequivalent, neither the chewable tablets nor the granules for oral suspension should be substituted for the 400 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.

*Children*
Children at least 11 kg: weight based dose of the chewable tablet to a maximum dose of 300 mg, twice daily as specified in Tables 1 and 2. The chewable tablets are available in 25 mg and scored 100 mg strengths.
See section 5.2 regarding the limited data on which these dose recommendations are based.
Table 1
Recommended Dose* for ISENTRESS Chewable Tablets for Paediatric Patients Weighing at Least 25 kg

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Dose</th>
<th>Number of chewable tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 to less than 28</td>
<td>150 mg twice daily</td>
<td>1.5 x 100 mg† twice daily</td>
</tr>
<tr>
<td>28 to less than 40</td>
<td>200 mg twice daily</td>
<td>2 x 100 mg twice daily</td>
</tr>
<tr>
<td>At least 40</td>
<td>300 mg twice daily</td>
<td>3 x 100 mg twice daily</td>
</tr>
</tbody>
</table>

*The weight-based dosing recommendation for the chewable tablet is based on approximately 6 mg/kg/dose twice daily (see section 5.2).
†The 100 mg chewable tablet can be divided into equal 50 mg doses. However, breaking the tablets should be avoided whenever possible.

If at least 4 weeks of age and weighing at least 3 kg to less than 25 kg: Weight based dosing, as specified in Table 2.

For patients weighing between 11 and 20 kg, either the chewable tablet or oral suspension can be used, as specified in Table 2. Patients can remain on the oral suspension as long as their weight is below 20 kg. Refer to Table 2 for appropriate dosing (see section 5.1).

Table 2
Recommended Dose* for ISENTRESS Granules For Oral Suspension and Chewable Tablets in Paediatric Patients Weighing Less than 25 kg

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Volume (dose) of suspension to be administered</th>
<th>Number of chewable tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 to less than 4</td>
<td>1 ml (20 mg) twice daily</td>
<td></td>
</tr>
<tr>
<td>4 to less than 6</td>
<td>1.5 ml (30 mg) twice daily</td>
<td></td>
</tr>
<tr>
<td>6 to less than 8</td>
<td>2 ml (40 mg) twice daily</td>
<td></td>
</tr>
<tr>
<td>8 to less than 11</td>
<td>3 ml (60 mg) twice daily</td>
<td></td>
</tr>
<tr>
<td>11 to less than 14†</td>
<td>4 ml (80 mg) twice daily</td>
<td>3 x 25 mg twice daily</td>
</tr>
<tr>
<td>14 to less than 20†</td>
<td>5 ml (100 mg) twice daily</td>
<td>1 x 100 mg twice daily</td>
</tr>
<tr>
<td>20 to less than 25</td>
<td></td>
<td>1.5 x 100 mg‡ twice daily</td>
</tr>
</tbody>
</table>

*The weight-based dosing recommendation for the chewable tablet and oral suspension is based on approximately 6 mg/kg/dose twice daily (see section 5.2).
†For weight between 11 and 20 kg either formulation can be used.
‡The 100 mg chewable tablet can be divided into equal 50 mg doses. However, breaking the tablets should be avoided whenever possible.

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

ISENTRESS is also available in a 400 mg tablet for use in adults, adolescents and children weighing at least 25 kg and able to swallow a tablet; and as granules for oral suspension for use in infants and toddlers from 4 weeks of age and weighing at least 3 kg to less than 20 kg. Refer to the 400 mg tablet and granules for oral suspension EU-SmPCs for additional dosing information.

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

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

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

**Paediatric population**
Safety and efficacy of raltegravir in infants below 4 weeks of age have not yet been established. No data are available.

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

### 4.3 Contraindications

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

### 4.4 Special warnings and precautions for use

Patients should be advised that current anti-retroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV to others through blood contact. While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Overall, considerable inter- and intra-subject variability was observed in the pharmacokinetics of raltegravir (see sections 4.5 and 5.2).

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, ISENTRESS 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 etiology 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) have also been reported to occur in the setting of immune reactivation: however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Antacids
Co-administration of 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 section 4.5).

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

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

Severe skin and hypersensitivity reactions
Severe, potentially life-threatening, and fatal skin reactions have been reported in patients taking ISENTRESS, 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 characterized by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure. Discontinue ISENTRESS 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 ISENTRESS 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 ISENTRESS and darunavir compared to patients receiving ISENTRESS without darunavir or darunavir without ISENTRESS (see section 4.8).

Fructose
ISENTRRESS chewable tablets contain fructose and sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.
4.5 Interaction with other medicinal products and other forms of interaction

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

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

Although *in vitro* studies indicated that raltegravir is not an inhibitor of the UDP glucuronosyltransferases (UGTs) 1A1 and 2B7, one clinical study has suggested that some inhibition of UGT1A1 may occur *in vivo* based on effects observed on bilirubin glucuronidation. However, the magnitude of the effect seems unlikely to result in clinically important drug-drug interactions.

Considerable inter- and intra-individual variability was observed in the pharmacokinetics of raltegravir. The following drug interaction information is based on Geometric Mean values; the effect for an individual patient cannot be predicted precisely.

**Effect of raltegravir on the pharmacokinetics of other medicinal products**

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

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

**Effect of other agents on the pharmacokinetics of raltegravir**

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

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

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 required.

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

Table 3
Pharmacokinetic Interaction Data in Adults

<table>
<thead>
<tr>
<th>Medicinal products by therapeutic area</th>
<th>Interaction (mechanism, if known)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-RETROVIRAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease inhibitors (PI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 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 ISENTRESS. |
| 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 ISENTRESS. |
| **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 ISENTRESS. |
| 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 ISENTRESS or etravirine. |
| **Nucleoside/tide reverse transcriptase inhibitors** |                                   |                                             |
| tenofovir (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 ISENTRESS or tenofovir disoproxil fumarate. |
<table>
<thead>
<tr>
<th>Medicinal products by therapeutic area</th>
<th>Interaction (mechanism, if known)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCR5 inhibitors</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| maraviroc (raltegravir 400 mg Twice Daily) | raltegravir AUC ↓ 37 %  
raltegravir C<sub>12hr</sub> ↓ 28 %  
raltegravir C<sub>max</sub> ↓ 33 %  
(mechanism of interaction unknown)  
maraviroc AUC ↓ 14 %  
maraviroc C<sub>12hr</sub> ↓ 10 %  
maraviroc C<sub>max</sub> ↓ 21 % | No dose adjustment required for ISENTRESS or maraviroc. |
| **HCV ANTIVIRALS**                    |                                  |                                               |
| **NS3/4A protease inhibitors (PI)**   |                                  |                                               |
| boceprevir (raltegravir 400 mg Single Dose) | raltegravir AUC ↑ 4 %  
raltegravir C<sub>12hr</sub> ↓ 25 %  
raltegravir C<sub>max</sub> ↑ 11 %  
(mechanism of interaction unknown) | No dose adjustment required for ISENTRESS or boceprevir. |
| **ANTIMICROBIALS**                    |                                  |                                               |
| **Antimycobacterial**                 |                                  |                                               |
| rifampicin (raltegravir 400 mg Single Dose) | raltegravir AUC ↓ 40 %  
raltegravir C<sub>12hr</sub> ↓ 61 %  
raltegravir C<sub>max</sub> ↓ 38 %  
(UGT1A1 induction) | Rifampicin reduces plasma levels of ISENTRESS. If co-administration with rifampicin is unavoidable, a doubling of the dose of ISENTRESS can be considered (see section 4.4). |
| **SEDATIVE**                          |                                  |                                               |
| midazolam (raltegravir 400 mg Twice Daily) | midazolam AUC ↓ 8 %  
midazolam C<sub>max</sub> ↑ 3 % | No dosage adjustment required for ISENTRESS 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. |
<table>
<thead>
<tr>
<th>Medicinal products by therapeutic area</th>
<th>Interaction (mechanism, if known)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>METAL CATION ANTACIDS</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| aluminium and magnesium hydroxide antacid (raltegravir 400 mg Twice Daily) | raltegravir AUC ↓ 49 %  
raltegravir C_{12 hr} ↓ 63 %  
raltegravir C_{max} ↓ 44 %  
2 hours before raltegravir  
raltegravir AUC ↓ 51 %  
raltegravir C_{12 hr} ↓ 56 %  
raltegravir C_{max} ↓ 51 %  
2 hours after raltegravir  
raltegravir AUC ↓ 30 %  
raltegravir C_{12 hr} ↓ 57 %  
raltegravir C_{max} ↓ 24 %  
6 hours before raltegravir  
raltegravir AUC ↓ 13 %  
raltegravir C_{12 hr} ↓ 50 %  
raltegravir C_{max} ↓ 10 %  
6 hours after raltegravir  
raltegravir AUC ↓ 11 %  
raltegravir C_{12 hr} ↓ 49 %  
raltegravir C_{max} ↓ 10 %  | Aluminium and magnesium containing antacids reduce raltegravir plasma levels. Co-administration of ISENTRESS with aluminium and/or magnesium containing antacids is not recommended. |
| calcium carbonate antacid (raltegravir 400 mg Twice Daily) | raltegravir AUC ↓ 55 %  
raltegravir C_{12 hr} ↓ 32 %  
raltegravir C_{max} ↓ 52 %  | (chelation of metal cations) |
|                                       |                                  | No dose adjustment required for ISENTRESS. |
| **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) |
| famotidine (raltegravir 400 mg Twice Daily) | raltegravir AUC ↑ 44 %  
raltegravir C_{12 hr} ↑ 6 %  
raltegravir C_{max} ↑ 60 %  | (increased solubility) |
| **HORMONAL CONTRACEPTIVES** | Ethinyl Estradiol AUC ↓ 2 %  
Ethinyl Estradiol C_{max} ↑ 6 %  
Norelgestromin AUC ↑ 14 %  
Norelgestromin C_{max} ↑ 29 %  | No dosage adjustment required for ISENTRESS or hormonal contraceptives (estrogen- and/or progesterone-based). |
| **OPIOID ANALGESICS** | methadone AUC ↔  
methadone C_{max} ↔  | No dose adjustment required for ISENTRESS or methadone. |
4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of raltegravir in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. ISENTRESS should not be used during pregnancy.

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

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

Breast-feeding
It is not known whether raltegravir is secreted in human milk. However, raltegravir is secreted in the milk of lactating rats. In rats, at a maternal dose of 600 mg/kg/day, mean active substance concentrations in milk were approximately 3-fold greater than in maternal plasma. Breastfeeding is not recommended while taking ISENTRESS. As a general rule, it is recommended that mothers infected by HIV do not breast-feed their babies in order to avoid transmission of HIV.

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

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

4.8 Undesirable effects

Summary of the safety profile
The safety profile of ISENTRESS was based on the pooled safety data from two Phase III clinical studies in treatment-experienced adult patients and one Phase III clinical study in treatment-naïve adult patients. The most frequently reported adverse reactions during treatment were headache and nausea, occurring at 5% or greater. The most frequently reported serious adverse reaction was immune reconstitution syndrome.

In treatment-experienced patients, the two randomised clinical studies used the recommended dose of 400 mg twice daily in combination with optimised background therapy (OBT) in 462 patients, in comparison to 237 patients taking placebo in combination with OBT. During double-blind treatment, the total follow-up was 708 patient-years in the group receiving ISENTRESS 400 mg twice daily, and 244 patient-years in the group receiving placebo.

In treatment-naïve patients, the multi-centre, randomised, double-blind, active-controlled clinical study used the recommended dose of 400 mg twice daily in combination with a fixed dose of emtricitabine 200 mg (+) tenofovir 245 mg in 281 patients, in comparison to 282 patients taking efavirenz (EFV) 600 mg (at bedtime) in combination with emtricitabine (+) tenofovir. During double-blind treatment, the total follow-up was 1104 patient-years in the group receiving ISENTRESS 400 mg twice daily, and 1036 patient-years in the group receiving efavirenz 600 mg at bedtime.

In the pooled analysis of treatment-experienced patients, the rates of discontinuation of therapy due to adverse reactions were 3.9% in patients receiving ISENTRESS + OBT and 4.6% in patients receiving
placebo + OBT. The rates of discontinuation of therapy in naïve patients due to adverse reactions were 5.0% in patients receiving ISENTRESS + emtricitabine (+) tenofovir and 10.0% in patients receiving efavirenz + emtricitabine (+) tenofovir.

Tabulated summary of adverse reactions
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).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse reactions ISENTRESS (alone or in combination with other ART)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Uncommon</td>
<td>genital herpes, folliculitis, gastroenteritis, herpes simplex, herpes virus infection, herpes zoster, influenza, lymph node abscess, molluscum contagiosum, nasopharyngitis, upper respiratory tract infection</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (including cysts and polyps)</td>
<td>Uncommon</td>
<td>skin papilloma</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Uncommon</td>
<td>anaemia, iron deficiency anaemia, lymph node pain, lymphadenopathy, neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Uncommon</td>
<td>immune reconstitution syndrome, drug hypersensitivity, hypersensitivity</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>decreased appetite</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>cachexia, diabetes mellitus, dyslipidaemia, hypercholesterolaemia, hyperglycaemia, hyperlipidaemia, hyperphagia, increased appetite, polydipsia, body fat disorder</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>common</td>
<td>abnormal dreams, insomnia, nightmare, abnormal behaviour, depression</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>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)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>common</td>
<td>dizziness, headache, psychomotor hyperactivity</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>amnesia, carpal tunnel syndrome, cognitive disorder, disturbance in attention, dizziness postural, dysgeusia, hypersonnia, hypoaesthesia, lethargy, memory impairment, migraine, neuropathy peripheral, paraesthesia, somnolence, tension headache, tremor, poor quality sleep</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Uncommon</td>
<td>visual impairment</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>common</td>
<td>Vertigo</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>tinnitus</td>
</tr>
<tr>
<td><strong>System Organ Class</strong></td>
<td><strong>Frequency</strong></td>
<td><strong>Adverse reactions ISENTRESS (alone or in combination with other ART)</strong></td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>palpitations, sinus bradycardia, ventricular extrasystoles</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon</td>
<td>hot flush, hypertension</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Uncommon</td>
<td>dysphonia, epistaxis, nasal congestion</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>common</td>
<td>abdominal distention, abdominal pain, diarrhoea, flatulence, nausea, vomiting, dyspepsia</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>gastritis, abdominal discomfort, abdominal pain upper, abdominal tenderness, anorectal discomfort, constipation, dry mouth, epigastric discomfort, erosive duodenitis, eructation, gastrooesophageal reflux disease, gingivitis, glossitis, odynophagia, pancreatitis acute, peptic ulcer, rectal haemorrhage</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Uncommon</td>
<td>hepatitis, hepatic steatosis, hepatitis alcoholic, hepatic failure</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>common</td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>acne, alopecia, dermatitis acniforme, dry skin, erythema, facial wasting, hyperhidrosis, lipoatrophy, lipodystrophy acquired, lipohypertrophy, night sweats, prurigo, pruritus, pruritus generalised, rash macular, rash maculopapular, rash pruritic, skin lesion, urticaria, xeroderma, Stevens Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Uncommon</td>
<td>arthralgia, arthritis, back pain, flank pain, musculoskeletal pain, myalgia, neck pain, osteopenia, pain in extremity, tendonitis, rhabdomyolysis</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Uncommon</td>
<td>renal failure, nephritis, nephrolithiasis, nocturia, renal cyst, renal impairment, tubulointerstitial nephritis</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Uncommon</td>
<td>erectile dysfunction, gynaecomastia, menopausal symptoms</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>common</td>
<td>asthenia, fatigue, pyrexia</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>chest discomfort, chills, face oedema, fat tissue increased, feeling jittery, malaise, submandibular mass, oedema peripheral, pain</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency</td>
<td>Adverse reactions ISENTRESS (alone or in combination with other ART)</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Investigations</td>
<td>common</td>
<td>alanine aminotransferase increased, atypical lymphocytes, aspartate aminotransferase increased, blood triglycerides increased, lipase increased, blood pancreatic amylase increased</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>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</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Uncommon</td>
<td>accidental overdose</td>
</tr>
</tbody>
</table>

Description of selected adverse reactions

Cancers were reported in treatment-experienced and treatment-naïve patients who initiated ISENTRESS 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 ISENTRESS and in the groups receiving comparators.

Grade 2-4 creatine kinase laboratory abnormalities were observed in subjects treated with ISENTRESS. 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) 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 ISENTRESS and darunavir compared to those containing ISENTRESS without darunavir or darunavir without ISENTRESS. 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 Phase III studies, treatment-experienced patients (N = 114/699 or 16%; HBV=6 %, HCV=9 %, HBV+HCV=1 %) and treatment-naïve patients (N = 34/563 or 6 %; HBV=4%, HCV=2%, HBV+HCV=0.2 %) 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 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 with hepatitis B and/or hepatitis C virus co-infection for both treatment groups. 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 subjects treated with ISENTRESS as compared to 11 %, 10 % and 9 % of all other subjects treated with ISENTRESS. 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 subjects treated with ISENTRESS as compared to 13 %, 13 % and 5 % of all other subjects treated with ISENTRESS.

The following adverse reactions were identified through post-marketing surveillance but not reported as drug-related in randomised controlled Phase III clinical trials (Protocols 018, 019, and 021): thrombocytopenia, suicidal ideation, suicidal behaviour (particularly in patients with a pre-existing history of psychiatric illness), hepatic failure, Stevens Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rhabdomyolysis.

Paediatric population

Children and adolescents 2 to 18 years of age

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

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

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

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

Infants and toddlers 4 weeks to less than 2 years of age

Raltegravir has also been studied in 26 HIV-1 infected infants and toddlers 4 weeks to less than 2 years of age, in combination with other antiretroviral agents in IMPAACT P1066 (see sections 5.1 and 5.2).

In these 26 infants and toddlers, the frequency, type and severity of drug related adverse reactions through Week 48 were comparable to those observed in adults.

One patient experienced a Grade 3 serious drug related allergic rash that resulted in treatment discontinuation.

Reporting of suspected adverse reactions

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

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

In the event of an overdose, it is reasonable to employ the standard supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required. It should be taken into account that raltegravir is presented for clinical use as the potassium salt. The extent to which raltegravir may be dialysable is unknown.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, other antivirals, ATC code: J05AX08.

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

Antiviral activity in vitro
Raltegravir at concentrations of 31 ± 20 nM resulted in 95% inhibition (IC_{95})) of HIV-1 replication (relative to an untreated virus-infected culture) in human T-lymphoid cell cultures infected with the cell-line adapted HIV-1 variant H9IIIB. In addition, raltegravir inhibited viral replication in cultures of mitogen-activated human peripheral blood mononuclear cells infected with diverse, primary clinical isolates of HIV-1, including isolates from 5 non-B subtypes, and isolates resistant to reverse transcriptase inhibitors and protease inhibitors. In a single-cycle infection assay, raltegravir inhibited infection of 23 HIV isolates representing 5 non-B subtypes and 5 circulating recombinant forms with IC50 values ranging from 5 to 12 nM.

Resistance
Most viruses isolated from patients failing raltegravir had high-level raltegravir resistance resulting from the appearance of two or more mutations. 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 ISENTRESS was based on the analyses of 96-week data from two randomised, double-blind, placebo-controlled trials, (BENCHMRK 1 and BENCHMRK 2, Protocols 018 and 019) in antiretroviral treatment-experienced HIV-1 infected adult patients and the analysis of 240-week data from a randomised, double-blind, active-control trial, (STARTMRK, Protocol 021) in antiretroviral treatment-naïve HIV-1 infected adult patients.

Efficacy
Treatment-experienced adult patients
BENCHMRK 1 and BENCHMRK 2 (multi-centre, randomised, double-blind, placebo-controlled trials) evaluated the safety and anti-retroviral activity of ISENTRESS 400 mg twice daily vs. placebo in a combination with optimized 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 randomization, 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 ISENTRESS 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 ISENTRESS 400 mg twice daily from the pooled studies BENCHMRK 1 and BENCHMRK 2 are shown in Table 4.

Table 4
Efficacy Outcome at Weeks 48 and 96

<table>
<thead>
<tr>
<th>Parameter</th>
<th>48 Weeks</th>
<th>96 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ISENTRESS 400 mg twice daily + OBT (N = 462)</td>
<td>Placebo + OBT (N = 237)</td>
</tr>
<tr>
<td><strong>Percent HIV-RNA &lt; 400 copies/ml (95 % CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients †</td>
<td>72 (68, 76)</td>
<td>37 (31, 44)</td>
</tr>
<tr>
<td>Baseline Characteristic ‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml ≤ 100,000 copies/ml</td>
<td>62 (53, 69)</td>
<td>17 (9, 27)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm³ &gt; 50 and ≤ 200 cells/mm³ &gt; 200 cells/mm³</td>
<td>61 (53, 69)</td>
<td>21 (13, 32)</td>
</tr>
<tr>
<td>Sensitivity score (GSS) §</td>
<td>80 (73, 85)</td>
<td>44 (33, 55)</td>
</tr>
<tr>
<td>0</td>
<td>83 (76, 89)</td>
<td>51 (39, 63)</td>
</tr>
<tr>
<td>1</td>
<td>81 (75, 87)</td>
<td>40 (30, 51)</td>
</tr>
<tr>
<td>2 and above</td>
<td>84 (77, 89)</td>
<td>65 (52, 76)</td>
</tr>
<tr>
<td><strong>Percent HIV-RNA &lt; 50 copies/ml (95 % CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients †</td>
<td>62 (57, 67)</td>
<td>33 (27, 39)</td>
</tr>
<tr>
<td>Baseline Characteristic ‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml ≤ 100,000 copies/ml</td>
<td>48 (40, 56)</td>
<td>16 (8, 26)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm³ &gt; 50 and ≤ 200 cells/mm³ &gt; 200 cells/mm³</td>
<td>73 (68, 78)</td>
<td>43 (35, 52)</td>
</tr>
<tr>
<td>Sensitivity score (GSS) §</td>
<td>50 (41, 58)</td>
<td>20 (12, 31)</td>
</tr>
<tr>
<td>0</td>
<td>67 (59, 74)</td>
<td>39 (28, 50)</td>
</tr>
<tr>
<td>1</td>
<td>76 (68, 83)</td>
<td>44 (32, 56)</td>
</tr>
<tr>
<td>2 and above</td>
<td>45 (35, 54)</td>
<td>3 (0, 11)</td>
</tr>
<tr>
<td>1</td>
<td>67 (59, 74)</td>
<td>37 (27, 48)</td>
</tr>
</tbody>
</table>
### Raltegravir Achieved Virologic Responses

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

### Switch to Raltegravir

The SWITCHMRK 1 & 2 (Protocols 032 & 033) studies evaluated HIV-infected patients receiving suppressive (screening HIV RNA < 50 copies/ml; stable regimen > 3 months) therapy with lopinavir 200 mg (+) ritonavir 50 mg 2 tablets twice daily plus at least 2 nucleoside reverse transcriptase inhibitors and randomized 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-naive Adult Patients

STARTMRK (multi-centre, randomised, double-blind, active-control trial) evaluated the safety and anti-retroviral activity of ISENTRESS 400 mg twice daily vs. efavirenz 600 mg at bedtime, in a combination with emtricitabine (+) tenofovir, in treatment-naïve HIV-infected patients with HIV RNA > 5,000 copies/ml. Randomization 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).

---

### Table: Mean CD4 Cell Change (95% CI), cells/mm³

<table>
<thead>
<tr>
<th>Parameter</th>
<th>48 Weeks</th>
<th>96 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ISENTRESS 400 mg twice daily + OBT (N = 462)</td>
<td>Placebo + OBT (N = 237)</td>
</tr>
<tr>
<td>2 and above</td>
<td>75 (68, 82)</td>
<td>59 (46, 71)</td>
</tr>
<tr>
<td>Mean CD4 Cell Change (95% CI),</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cells/mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>109 (98, 121)</td>
<td>45 (32, 57)</td>
</tr>
<tr>
<td>Baseline Characteristic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml</td>
<td>126 (107, 144)</td>
<td>36 (17, 55)</td>
</tr>
<tr>
<td>≤ 100,000 copies/ml</td>
<td>100 (86, 115)</td>
<td>49 (33, 65)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm³</td>
<td>121 (100, 142)</td>
<td>33 (18, 48)</td>
</tr>
<tr>
<td>&gt; 50 and ≤ 200 cells/mm³</td>
<td>104 (88, 119)</td>
<td>47 (28, 66)</td>
</tr>
<tr>
<td>&gt; 200 cells/mm³</td>
<td>104 (80, 129)</td>
<td>54 (24, 84)</td>
</tr>
<tr>
<td>Sensitivity score (GSS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>81 (55, 106)</td>
<td>11 (4, 26)</td>
</tr>
<tr>
<td>1</td>
<td>113 (96, 130)</td>
<td>44 (24, 63)</td>
</tr>
<tr>
<td>2 and above</td>
<td>125 (105, 144)</td>
<td>76 (48, 103)</td>
</tr>
</tbody>
</table>

1 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.

2 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.

3 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.
Patient demographics (gender, age and race) and baseline characteristics were comparable between the group receiving ISENTRESS 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 ISENTRESS and 230/281 (81.9 %) in the group receiving efavirenz. The treatment difference (ISENTRESS – efavirenz) was 4.2 % with an associated 95 % CI of (-1.9, 10.3) establishing that ISENTRESS is non-inferior to efavirenz (p-value for non-inferiority < 0.001). At Week 240, the treatment difference (ISENTRESS – 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 ISENTRESS 400 mg twice daily from STARTMRK are shown in Table 5.

Table 5
Efficacy Outcome at Weeks 48 and 240

<table>
<thead>
<tr>
<th>STARTMRK Study</th>
<th>48 Weeks</th>
<th>240 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>ISENTRESS 400 mg twice daily (N = 281)</td>
<td>Efavirenz 600 mg at bedtime (N = 282)</td>
</tr>
<tr>
<td>Percent HIV-RNA &lt; 50 copies/ml (95 % CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients‡</td>
<td>86 (81, 90)</td>
<td>82 (77, 86)</td>
</tr>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml</td>
<td>91 (85, 95)</td>
<td>89 (83, 94)</td>
</tr>
<tr>
<td>≤ 100,000 copies/ml</td>
<td>93 (86, 97)</td>
<td>89 (82, 94)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm³</td>
<td>84 (64, 95)</td>
<td>86 (67, 96)</td>
</tr>
<tr>
<td>&gt; 50 and ≤ 200 cells/mm³</td>
<td>89 (81, 95)</td>
<td>86 (77, 92)</td>
</tr>
<tr>
<td>&gt; 200 cells/mm³</td>
<td>94 (89, 98)</td>
<td>92 (87, 96)</td>
</tr>
<tr>
<td>Viral Subtype Clade B</td>
<td>90 (85, 94)</td>
<td>89 (83, 93)</td>
</tr>
<tr>
<td>Non-Clade B</td>
<td>96 (87, 100)</td>
<td>91 (78, 97)</td>
</tr>
</tbody>
</table>

Mean CD4 Cell Change (95 % CI), cells/mm³
| All patients‡ | 189 (174, 204) | 163 (148, 178) | 374 (345, 403) | 312 (284, 339) |
| 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/mm³ | 170 (122, 218) | 152 (123, 180) | 304 (209, 399) | 314 (242, 386) |
| > 50 and ≤ 200 cells/mm³ | 193 (169, 217) | 175 (151, 198) | 413 (360, 465) | 306 (264, 348) |
| > 200 cells/mm³ | 190 (168, 212) | 157 (134, 181) | 358 (321, 395) | 316 (272, 359) |
**STARTMRK Study**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>48 Weeks</th>
<th>240 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ISENTRESS 400 mg twice daily (N = 281)</td>
<td>ISENTRESS 400 mg twice daily (N = 281)</td>
</tr>
<tr>
<td></td>
<td>Efavirenz 600 mg at bedtime (N = 282)</td>
<td>Efavirenz 600 mg at bedtime (N = 282)</td>
</tr>
<tr>
<td>Viral Subtype Clade B</td>
<td>187 (170, 204)</td>
<td>380 (346, 414)</td>
</tr>
<tr>
<td></td>
<td>164 (147, 181)</td>
<td>303 (272, 333)</td>
</tr>
<tr>
<td>Non-Clade B</td>
<td>189 (153, 225)</td>
<td>332 (275, 388)</td>
</tr>
<tr>
<td></td>
<td>156 (121, 190)</td>
<td>329 (260, 398)</td>
</tr>
</tbody>
</table>

† 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.
ISENTRESS and efavirenz were administered with emtricitabine (+) tenofovir.

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**Paediatric population**

*Children and adolescents 2 to 18 years of age*

IMPAACT P1066 is a Phase I/II open label multicenter trial to evaluate the pharmacokinetic profile, safety, tolerability, and efficacy of raltegravir in HIV infected children. This study enrolled 126 treatment experienced children and adolescents 2 to 18 years of age. Patients were stratified by age, enrolling adolescents first and then successively younger children. Patients received either the 400 mg tablet formulation (6 to 18 years of age) or the chewable tablet formulation (2 to less than 12 years of age). Raltegravir was administered with an optimized background regimen.

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

**Table 6**

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Final dose population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=96</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age (years), median [range]</td>
<td>13 [2 – 18]</td>
</tr>
<tr>
<td>Male Gender</td>
<td>49 %</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>34 %</td>
</tr>
<tr>
<td>Black</td>
<td>59 %</td>
</tr>
<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Plasma HIV-1 RNA (log_{10} copies/ml), mean [range]</td>
<td>4.3 [2.7 - 6]</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm^3), median [range]</td>
<td>481 [0 – 2361]</td>
</tr>
<tr>
<td>CD4 percent, median [range]</td>
<td>23.3 % [0 – 44]</td>
</tr>
<tr>
<td>HIV-1 RNA &gt;100,000 copies/ml</td>
<td>8 %</td>
</tr>
<tr>
<td>CDC HIV category B or C</td>
<td>59 %</td>
</tr>
<tr>
<td><strong>Prior ART Use by Class</strong></td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>78 %</td>
</tr>
<tr>
<td>PI</td>
<td>83 %</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td></td>
</tr>
<tr>
<td>Achieved ≥1 log_{10} HIV RNA drop from baseline or &lt;400 copies/ml</td>
<td>72 %</td>
</tr>
<tr>
<td>Achieved HIV RNA &lt;50 copies/ml</td>
<td>54 %</td>
</tr>
<tr>
<td>Mean CD4 cell count (%) increase from baseline</td>
<td>119 cells/mm^3 (3.8 %)</td>
</tr>
</tbody>
</table>
Infants and toddlers 4 weeks to less than 2 years of age

IMPAACT P1066 also enrolled HIV-infected, infants and toddlers 4 weeks to less than 2 years of age who had received prior antiretroviral therapy either as prophylaxis for prevention of mother to child transmission (PMTCT) and/or as combination antiretroviral therapy for treatment of HIV infection. Raltegravir was administered as granules for oral suspension formulation without regard to food in combination with an optimized background regimen that included lopinavir plus ritonavir in two-thirds of patients.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N=26</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age (weeks), median [range]</td>
<td>28 [4 -100]</td>
</tr>
<tr>
<td>Male Gender</td>
<td>65 %</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>8 %</td>
</tr>
<tr>
<td>Black</td>
<td>85 %</td>
</tr>
<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Plasma HIV-1 RNA (log_{10} copies/ml), mean [range]</td>
<td>5.7 [3.1 - 7]</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm$^3$), median [range]</td>
<td>1400 [131 -3648]</td>
</tr>
<tr>
<td>CD4 percent, median [range]</td>
<td>18.6 % [3.3 – 39.3]</td>
</tr>
<tr>
<td>HIV-1 RNA &gt;100,000 copies/ml</td>
<td>69 %</td>
</tr>
<tr>
<td>CDC HIV category B or C</td>
<td>23 %</td>
</tr>
<tr>
<td><strong>Prior ART Use by Class</strong></td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>73 %</td>
</tr>
<tr>
<td>NRTI</td>
<td>46%</td>
</tr>
<tr>
<td>PI</td>
<td>19 %</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td>Week 24</td>
</tr>
<tr>
<td>Achieved ≥1 log_{10} HIV RNA drop from baseline or &lt;400 copies/ml</td>
<td>91 %</td>
</tr>
<tr>
<td>Achieved HIV RNA &lt;50 copies/ml</td>
<td>43 %</td>
</tr>
<tr>
<td>Mean CD4 cell count (%) increase from baseline</td>
<td>500 cells/mm$^3$ (7.5 %)</td>
</tr>
<tr>
<td><strong>Virologic failure</strong></td>
<td>Week 24</td>
</tr>
<tr>
<td>Non-responder</td>
<td>0</td>
</tr>
<tr>
<td>Rebounder</td>
<td>0</td>
</tr>
<tr>
<td>Number with genotype available$^*$</td>
<td>0</td>
</tr>
</tbody>
</table>

$^*$One patient had a mutation at the 155 position.

The European Medicines Agency has deferred the obligation to submit the results of studies with ISENTRESS in one or more subsets of the paediatric population in Human Immunodeficiency virus infection (see section 4.2 for information on paediatric use).

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 $C_{12hr}$ increases dose proportionally over the dose range of 100 to 800 mg and increases slightly less than dose proportionally over the dose range 100 mg to 1,600 mg. Dose proportionality has not been established in patients.
With twice-daily dosing, pharmacokinetic steady state is achieved rapidly, within approximately the first 2 days of dosing. There is little to no accumulation in AUC and C\text{max}, and evidence of slight accumulation in C\text{12 hr}. The absolute bioavailability of raltegravir has not been established.

ISENTRESS 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\text{12 hr} was 66 % higher and C\text{max} was 5 % higher following a moderate-fat meal compared to fasting. Administration of raltegravir following a high-fat meal increased AUC and C\text{max} by approximately 2-fold and increased C\text{12 hr} by 4.1-fold. Administration of raltegravir following a low-fat meal decreased AUC and C\text{max} by 46 % and 52 %, respectively; C\text{12 hr} was essentially unchanged. Food appears to increase pharmacokinetic variability relative to fasting.

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

**Distribution**

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

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

**Biotransformation and excretion**

The apparent terminal half-life of raltegravir is approximately 9 hours, with a shorter α-phase half-life (~1 hour) accounting for much of the AUC. Following administration of an oral dose of radiolabeled raltegravir, approximately 51 and 32 % of the dose was excreted in faeces and urine, respectively. In faeces, only raltegravir was present, most of which is likely to be derived from hydrolysis of raltegravir-glucuronide secreted in bile as observed in preclinical species. Two components, namely raltegravir and raltegravir-glucuronide, were detected in urine and accounted for approximately 9 and 23 % of the dose, respectively. The major circulating entity was raltegravir and represented approximately 70 % of the total radioactivity; the remaining radioactivity in plasma was accounted for by raltegravir-glucuronide. Studies using isoform-selective chemical inhibitors and cDNA-expressed UDP-glucuronosyltransferases (UGT) show that UGT1A1 is the main enzyme responsible for the formation of raltegravir-glucuronide. Thus the data indicate that the major mechanism of clearance of raltegravir in humans is UGT1A1-mediated glucuronidation.

**UGT1A1 Polymorphism**

In a comparison of 30 subjects with *28/*28 genotype to 27 subjects with wild-type genotype, the geometric mean ratio (90 % CI) of AUC was 1.41 (0.96, 2.09) and the geometric mean ratio of C\text{}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,
The administration of the chewable tablet with a high fat meal led to an average 6% decrease in AUC, 62% decrease in \(C_{\text{max}}\), and 188% increase in \(C_{12\text{hr}}\) compared to administration in the fasted state. Administration of the chewable tablet with a high fat meal does not affect raltegravir pharmacokinetics to a clinically meaningful degree and the chewable tablet can be administered without regard to food. The effect of food on the granules for oral suspension formulation was not studied.

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

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

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Formulation</th>
<th>Dose</th>
<th>N*</th>
<th>(\text{Geometric mean (%CV)}) AUC(_{0-12\text{hr}}) (μM●hr)</th>
<th>(\text{Geometric mean (%CV)}) (C_{12\text{hr}}) (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥25 kg</td>
<td>Film-coated tablet</td>
<td>400 mg twice daily</td>
<td>18</td>
<td>14.1 (121 %)</td>
<td>233 (157 %)</td>
</tr>
<tr>
<td>≥25 kg</td>
<td>Chewable tablet</td>
<td>Weight based dosing, see dosing Table 1</td>
<td>9</td>
<td>22.1 (36 %)</td>
<td>113 (80 %)</td>
</tr>
<tr>
<td>11 to less than 25 kg</td>
<td>Chewable tablet</td>
<td>Weight based dosing, see dosing Table 2</td>
<td>13</td>
<td>18.6 (68 %)</td>
<td>82 (123 %)</td>
</tr>
<tr>
<td>3 to less than 20 kg</td>
<td>Oral suspension</td>
<td>Weight based dosing, see dosing table for granules for oral suspension</td>
<td>19</td>
<td>24.5 (43 %)</td>
<td>113 (69 %)</td>
</tr>
</tbody>
</table>

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

The pharmacokinetics of raltegravir in infants under 4 weeks of age has not been established.

**Elderly**

There was no clinically meaningful effect of age on raltegravir pharmacokinetics over the age range studied (19 to 71 years, with few (8) subjects over the age of 65).

**Gender, race and BMI**

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

**Renal impairment**

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

**Hepatic impairment**

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

### 5.3 Preclinical safety data

Non-clinical toxicology studies, including conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, developmental toxicity and juvenile toxicity, have been conducted with raltegravir, in mice, rats, dogs and rabbits. Effects at exposure levels sufficiently in excess of clinical exposure levels indicate no special hazard for humans.
Mutagenicity
No evidence of mutagenicity or genotoxicity was observed in in vitro microbial mutagenesis (Ames) tests, in vitro alkaline elution assays for DNA breakage and in vitro and in vivo chromosomal aberration studies.

Carcinogenicity
A carcinogenicity study of raltegravir in mice did not show any carcinogenic potential. At the highest dose levels, 400 mg/kg/day in females and 250 mg/kg/day in males, systemic exposure was similar to that at the clinical dose of 400 mg twice daily. In rats, tumours (squamous cell carcinoma) of the nose/nasopharynx were identified at 300 and 600 mg/kg/day in females and at 300 mg/kg/day in males. These 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 they are of limited relevance for the intended clinical use. At the NOAEL, systemic exposure was similar to that at the clinical dose of 400 mg twice daily. Standard genotoxicity studies to evaluate mutagenicity and clastogenicity were negative.

Developmental toxicity
Raltegravir was not teratogenic in developmental toxicity studies in rats and rabbits. A slight increase in incidence of supernumerary ribs was observed in rat pups of dams exposed to raltegravir at approximately 4.4-fold human exposure at 400 mg twice daily based on AUC₀⁻²₄ hr. No development effects were seen at 3.4-fold human exposure at 400 mg twice daily based on AUC₀⁻²₄ hr (see section 4.6). Similar findings were not observed in rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
- Hydroxypropyl cellulose
- Sucralose
- Saccharin sodium
- Sodium citrate dihydrate
- Mannitol
- Monoammonium glycyrrhizinate
- Sorbitol (E420)
- Fructose
- Banana flavour
- Orange flavour
- Masking flavour
- Aspartame (E951)
- Crospovidone, Type A
- Sodium stearyl fumarate
- Magnesium stearate
- Hypromellose 2910/6cP
- Macrogol/PEG 400
- Ethylcellulose 20 cP
- Ammonium hydroxide
- Medium chain triglycerides
- Oleic acid
- Yellow iron oxide

6.2 Incompatibilities
Not applicable.
6.3  Shelf life

2 years

6.4  Special precautions for storage

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

6.5  Nature and contents of container

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

6.6  Special precautions for disposal

No special requirements for disposal.

7.  MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8.  MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/003

9.  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10.  DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.emea.europa.eu.
1. NAME OF THE MEDICINAL PRODUCT
ISENTRESS 100 mg granules for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each sachet contains 100 mg of raltegravir (as potassium). Following reconstitution the oral suspension has a concentration of 20 mg per ml.

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

For the full list of excipients, see section 6.1.

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

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
ISENTRESS is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adults, adolescents, children, toddlers and infants from the age of 4 weeks (see sections 4.2, 4.4, 5.1 and 5.2).

4.2 Posology and method of administration
Therapy should be initiated by a physician experienced in the management of HIV infection.

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

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

Infants and Toddlers from the age of 4 weeks
Dosing is weight based from the age of 4 weeks and a weight of 3 kg as specified in Table 1. Patients can remain on the granules for oral suspension as long as their weight is below 20 kg.
For patients weighing between 11 and 20 kg, either the granules for oral suspension or the chewable tablet can be used as specified in Table 1 (see section 5.2). Refer to the chewable tablet EU-SmPC for additional dosing information.
Table 1
Recommended Dose* for ISENTRESS Granules For Oral Suspension and Chewable Tablets in Paediatric Patients Weighing Less than 25 kg

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Volume (dose) of suspension to be administered</th>
<th>Number of chewable tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 to less than 4</td>
<td>1 ml (20 mg) twice daily</td>
<td></td>
</tr>
<tr>
<td>4 to less than 6</td>
<td>1.5 ml (30 mg) twice daily</td>
<td></td>
</tr>
<tr>
<td>6 to less than 8</td>
<td>2 ml (40 mg) twice daily</td>
<td></td>
</tr>
<tr>
<td>8 to less than 11</td>
<td>3 ml (60 mg) twice daily</td>
<td></td>
</tr>
<tr>
<td>11 to less than 14†</td>
<td>4 ml (80 mg) twice daily</td>
<td>3 x 25 mg twice daily</td>
</tr>
<tr>
<td>14 to less than 20†</td>
<td>5 ml (100 mg) twice daily</td>
<td>1 x 100 mg twice daily</td>
</tr>
<tr>
<td>20 to less than 25</td>
<td>1.5 x 100 mg‡ twice daily</td>
<td></td>
</tr>
</tbody>
</table>

*The weight-based dosing recommendation for the chewable tablet and oral suspension is based on approximately 6 mg/kg/dose twice daily (see section 5.2).
†For weight between 11 and 20 kg either formulation can be used.
‡The 100 mg chewable tablet can be divided into equal 50 mg doses. However, breaking the tablets should be avoided whenever possible.

After administration of the required volume from the 5 ml syringe with the dissolved suspension of raltegravir, the remaining suspended medicine cannot be re-used and should be discarded (see section 6.6).

Maximum dose of oral suspension is 100 mg twice daily.

Each single-use sachet contains 100 mg of raltegravir which is to be suspended in 5 ml of water giving a final concentration of 20 mg per ml.

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

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

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

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

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

**Paediatric population**
Safety and efficacy of raltegravir in infants below 4 weeks of age have not yet been established. No data are available.

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

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

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

4.4 Special warnings and precautions for use

Patients should be advised that current anti-retroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV to others through blood contact. While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Overall, considerable inter- and intra-subject variability was observed in the pharmacokinetics of raltegravir (see sections 4.5 and 5.2).

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, ISENTRESS 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 etiology 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) have also been reported to occur in the setting of immune reactivation: however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

**Antacids**
Co-administration of 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 section 4.5).

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

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

**Severe skin and hypersensitivity reactions**
Severe, potentially life-threatening, and fatal skin reactions have been reported in patients taking ISENTRESS, 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 characterized by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure. Discontinue ISENTRESS 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 ISENTRESS 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 ISENTRESS and darunavir compared to patients receiving ISENTRESS without darunavir or darunavir without ISENTRESS (see section 4.8).

**Fructose/Sucrose**
ISENTRESS granules for oral suspension contain fructose, sorbitol and sucrose. Patients with rare hereditary problems of fructose intolerance glucosegalactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

### 4.5 Interaction with other medicinal products and other forms of interaction

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

Based on *in vitro* and *in vivo* studies, raltegravir is eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway.
Although *in vitro* studies indicated that raltegravir is not an inhibitor of the UDP glucuronosyltransferases (UGTs) 1A1 and 2B7, one clinical study has suggested that some inhibition of UGT1A1 may occur *in vivo* based on effects observed on bilirubin glucuronidation. However, the magnitude of the effect seems unlikely to result in clinically important drug-drug interactions.

Considerable inter- and intra-individual variability was observed in the pharmacokinetics of raltegravir. The following drug interaction information is based on Geometric Mean values; the effect for an individual patient cannot be predicted precisely.

**Effect of raltegravir on the pharmacokinetics of other medicinal products**

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

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

**Effect of other agents on the pharmacokinetics of raltegravir**

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

Co-administration of ISENTRESS with medicinal products that are known to be potent UGT1A1 inhibitors (e.g., atazanavir) may increase plasma levels of raltegravir. Less potent UGT1A1 inhibitors (e.g., indinavir, saquinavir) may also increase plasma levels of raltegravir, but to a lesser extent compared with atazanavir. In addition, tenofovir may increase plasma levels of raltegravir, however, the mechanism for this effect is unknown (see Table 2). From the clinical trials, a large proportion of patients used atazanavir and / or tenofovir, both agents that result in increases in raltegravir plasma levels, in the optimised background regimens. The safety profile observed in patients who used atazanavir and / or tenofovir was generally similar to the safety profile of patients who did not use these agents. Therefore no dose adjustment is required.

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 required.

Co-administration of ISENTRESS with other agents that increase gastric pH (e.g., omeprazole and famotidine) may increase the rate of raltegravir absorption and result in increased plasma levels of raltegravir (see Table 2). Safety profiles in the subgroup of patients in Phase III trials taking proton pump inhibitors or H2 antagonists were comparable with those who were not taking these antacids. Therefore no dose adjustment is required with use of proton pump inhibitors or H2 antagonists.

All interaction studies were performed in adults.
### Table 2
Pharmacokinetic Interaction Data

<table>
<thead>
<tr>
<th>Medicinal products by therapeutic area</th>
<th>Interaction (mechanism, if known)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-RETROVIRAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Protease inhibitors (PI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>atazanavir /ritonavir</td>
<td>raltegravir AUC ↑ 41 %</td>
<td>No dose adjustment required for ISENTRESS.</td>
</tr>
<tr>
<td>(raltegravir 400 mg Twice Daily)</td>
<td>raltegravir C\textsubscript{12hr} ↑ 77 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>raltegravir C\textsubscript{max} ↑ 24 %</td>
<td></td>
</tr>
<tr>
<td>(UGT1A1 inhibition)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tipranavir /ritonavir</td>
<td>raltegravir AUC ↓ 24 %</td>
<td>No dose adjustment required for ISENTRESS.</td>
</tr>
<tr>
<td>(raltegravir 400 mg Twice Daily)</td>
<td>raltegravir C\textsubscript{12hr} ↓ 55 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>raltegravir C\textsubscript{max} ↓ 18 %</td>
<td></td>
</tr>
<tr>
<td>(UGT1A1 induction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>efavirenz</td>
<td>raltegravir AUC ↓ 36 %</td>
<td>No dose adjustment required for ISENTRESS.</td>
</tr>
<tr>
<td>(raltegravir 400 mg Single Dose)</td>
<td>raltegravir C\textsubscript{12hr} ↓ 21 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>raltegravir C\textsubscript{max} ↓ 36 %</td>
<td></td>
</tr>
<tr>
<td>(UGT1A1 induction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>etravirine</td>
<td>raltegravir AUC ↓ 10 %</td>
<td>No dose adjustment required for ISENTRESS or etravirine.</td>
</tr>
<tr>
<td>(raltegravir 400 mg Twice Daily)</td>
<td>raltegravir C\textsubscript{12hr} ↓ 34 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>raltegravir C\textsubscript{max} ↓ 11 %</td>
<td></td>
</tr>
<tr>
<td>(UGT1A1 induction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>etravirine AUC ↑ 10 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>etravirine C\textsubscript{12hr} ↑ 17 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>etravirine C\textsubscript{max} ↑ 4 %</td>
<td></td>
</tr>
<tr>
<td><strong>Nucleoside/tide reverse transcriptase inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tenofovir</td>
<td>raltegravir AUC ↑ 49 %</td>
<td>No dose adjustment required for ISENTRESS or tenofovir disoproxil fumarate.</td>
</tr>
<tr>
<td>(raltegravir 400 mg Twice Daily)</td>
<td>raltegravir C\textsubscript{12hr} ↑ 3 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>raltegravir C\textsubscript{max} ↑ 64 %</td>
<td></td>
</tr>
<tr>
<td>(mechanism of interaction unknown)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>tenofovir AUC ↓ 10 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>tenofovir C\textsubscript{24hr} ↓ 13 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>tenofovir C\textsubscript{max} ↓ 23 %</td>
<td></td>
</tr>
<tr>
<td><strong>CCR5 inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>maraviroc</td>
<td>raltegravir AUC ↓ 37 %</td>
<td>No dose adjustment required for ISENTRESS or maraviroc.</td>
</tr>
<tr>
<td>(raltegravir 400 mg Twice Daily)</td>
<td>raltegravir C\textsubscript{12hr} ↓ 28 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>raltegravir C\textsubscript{max} ↓ 33 %</td>
<td></td>
</tr>
<tr>
<td>(mechanism of interaction unknown)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>maraviroc AUC ↓ 14 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>maraviroc C\textsubscript{12hr} ↓ 10 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td>maraviroc C\textsubscript{max} ↓ 21 %</td>
<td></td>
</tr>
<tr>
<td>Medicinal products by therapeutic area</td>
<td>Interaction (mechanism, if known)</td>
<td>Recommendations concerning co-administration</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td><strong>HCV ANTIVIRALS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NS3/4A protease inhibitors (PI)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **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 ISENTRESS 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 ISENTRESS. If co-administration with rifampicin is unavoidable, a doubling of the dose of ISENTRESS can be considered (see section 4.4). |
| **SEDATIVE**                           |                                  |                                             |
| **midazolam** (raltegravir 400 mg Twice Daily) | midazolam AUC ↓ 8 %  
midazolam C\(_{max}\) ↑ 3 % | No dosage adjustment required for ISENTRESS 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\(_{12hr}\) ↓ 63 %  
raltegravir C\(_{max}\) ↓ 44 %  
2 hours before raltegravir  
raltegravir AUC ↓ 51 %  
raltegravir C\(_{12hr}\) ↓ 56 %  
raltegravir C\(_{max}\) ↓ 51 %  
2 hours after raltegravir  
raltegravir AUC ↓ 30 %  
raltegravir C\(_{12hr}\) ↓ 57 %  
raltegravir C\(_{max}\) ↓ 24 %  
6 hours before raltegravir  
raltegravir AUC ↓ 13 %  
raltegravir C\(_{12hr}\) ↓ 50 %  
raltegravir C\(_{max}\) ↓ 10 %  
6 hours after raltegravir  
raltegravir AUC ↓ 11 %  
raltegravir C\(_{12hr}\) ↓ 49 %  
raltegravir C\(_{max}\) ↓ 10 %  
(chelation of metal cations) | Aluminium and magnesium containing antacids reduce raltegravir plasma levels. Co-administration of ISENTRESS with aluminium and/or magnesium containing antacids is not recommended. |
### Medicinal products by therapeutic area

<table>
<thead>
<tr>
<th>Interaction (mechanism, if known)</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
</table>
| **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 ISENTRESS. |

### 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 ISENTRESS. |
| famotidine (raltegravir 400 mg Twice Daily) | raltegravir AUC ↑ 44 %  
raltegravir C$_{12}$hr ↑ 6 %  
raltegravir C$_{max}$ ↑ 60 %  
(increased solubility) | No dose adjustment required for ISENTRESS. |

### 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 ISENTRESS 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 ISENTRESS or methadone. |

### 4.6 Fertility, pregnancy and lactation

#### Pregnancy

There are no adequate data from the use of raltegravir in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. ISENTRESS should not be used during pregnancy.

**Anti-retroviral Pregnancy Registry**

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

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

**Breast-feeding**

It is not known whether raltegravir is secreted in human milk. However, raltegravir is secreted in the milk of lactating rats. In rats, at a maternal dose of 600 mg/kg/day, mean active substance concentrations in milk were approximately 3-fold greater than in maternal plasma. Breastfeeding is not recommended while taking ISENTRESS. As a general rule, it is recommended that mothers infected by HIV do not breast-feed their babies in order to avoid transmission of HIV.

**Fertility**

No effect on fertility was seen in male and female rats at doses up to 600 mg/kg/day which resulted in 3-fold exposure above the 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 ISENTRESS. Dizziness may influence some patients' ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety profile of ISENTRESS was based on the pooled safety data from two Phase III clinical studies in treatment-experienced adult patients and one Phase III clinical study in treatment-naïve adult patients. The most frequently reported adverse reactions during treatment were headache and nausea, occurring at 5% or greater. The most frequently reported serious adverse reaction was immune reconstitution syndrome.

In treatment-experienced patients, the two randomised clinical studies used the recommended dose of 400 mg twice daily in combination with optimised background therapy (OBT) in 462 patients, in comparison to 237 patients taking placebo in combination with OBT. During double-blind treatment, the total follow-up was 708 patient-years in the group receiving ISENTRESS 400 mg twice daily, and 244 patient-years in the group receiving placebo.

In treatment-naïve patients, the multi-centre, randomised, double-blind, active-controlled clinical study used the recommended dose of 400 mg twice daily in combination with a fixed dose of emtricitabine 200 mg (+) tenofovir 245 mg in 281 patients, in comparison to 282 patients taking efavirenz (EFV) 600 mg (at bedtime) in combination with emtricitabine (+) tenofovir. During double-blind treatment, the total follow-up was 1104 patient-years in the group receiving ISENTRESS 400 mg twice daily, and 1036 patient-years in the group receiving efavirenz 600 mg at bedtime.

In the pooled analysis of treatment-experienced patients, the rates of discontinuation of therapy due to adverse reactions were 3.9% in patients receiving ISENTRESS + OBT and 4.6% in patients receiving placebo + OBT. The rates of discontinuation of therapy in naïve patients due to adverse reactions were 5.0% in patients receiving ISENTRESS + emtricitabine (+) tenofovir and 10.0% in patients receiving efavirenz + emtricitabine (+) tenofovir.

Tabulated summary of adverse reactions

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).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse reactions ISENTRESS (alone or in combination with other ART)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Uncommon</td>
<td>genital herpes, folliculitis, gastroenteritis, herpes simplex, herpes virus infection, herpes zoster, influenza, lymph node abscess, molluscum contagiosum, nasopharyngitis, upper respiratory tract infection</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (including cysts and polyps)</td>
<td>Uncommon</td>
<td>skin papilloma</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Uncommon</td>
<td>anaemia, iron deficiency anaemia, lymph node pain, lymphadenopathy, neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Uncommon</td>
<td>immune reconstitution syndrome, drug hypersensitivity, hypersensitivity</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency</td>
<td>Adverse reactions</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-----------</td>
<td>-------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>ISENTRESS (alone or in combination with other ART)</strong></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>decreased appetite</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>cachexia, diabetes mellitus, dyslipidaemia, hypercholesterolaemia, hyperglycaemia, hyperlipidaemia,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hyperphagia, increased appetite, polydipsia, body fat disorder</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>common</td>
<td>abnormal dreams, insomnia, nightmare, abnormal behaviour, depression</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>mental disorder, suicide attempt, anxiety, confusional state, depressed mood, major depression, middle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>insomnia, mood altered, panic attack, sleep disorder, suicidal ideation, suicidal behaviour (particularly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in patients with a pre-existing history of psychiatric illness)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>common</td>
<td>dizziness, headache, psychomotor hyperactivity</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>amnesia, carpal tunnel syndrome, cognitive disorder, disturbance in attention, dizziness postural,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dysgeusia, hypersomnia, hypoaesthesia, lethargy, memory impairment, migraine, neuropathy peripheral,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>paraesthesia, somnolence, tension headache, tremor, poor quality sleep</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Uncommon</td>
<td>visual impairment</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>common</td>
<td>vertigo</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>tinnitus</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>palpitations, sinus bradycardia, ventricular extrasystoles</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon</td>
<td>hot flush, hypertension</td>
</tr>
<tr>
<td>Respiratory, thoracic and</td>
<td>Uncommon</td>
<td>dysphonia, epistaxis, nasal congestion</td>
</tr>
<tr>
<td>mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>common</td>
<td>abdominal distention, abdominal pain, diarrhoea, flatulence, nausea, vomiting, dyspepsia</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>gastritis, abdominal discomfort, abdominal pain upper, abdominal tenderness, anorectal discomfort,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>constipation, dry mouth, epigastric discomfort, erosive duodenitis, eructation, gastrooesophageal reflux</td>
</tr>
<tr>
<td></td>
<td></td>
<td>disease, gingivitis, glossitis, odynophagia, pancreatitis acute, peptic ulcer, rectal haemorrhage</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Uncommon</td>
<td>hepatitis, hepatic steatosis, hepatitis alcoholic, hepatic failure</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>common</td>
<td>rash</td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency</td>
<td>Adverse reactions</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------</td>
<td>-------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ISENTRESS (alone or in combination with other ART)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>acne, alopecia, dermatitis acneiforme, dry skin, erythema, facial wasting, hyperhidrosis, lipoatrophy, lipodystrophy acquired, lipohypertrophy, night sweats, prurigo, pruritus, pruritus generalised, rash macular, rash maculopapular, rash pruritic, skin lesion, urticaria, xeroderma, Stevens Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS)</td>
</tr>
<tr>
<td>Muscle and connective tissue disorders</td>
<td>Uncommon</td>
<td>arthralgia, arthritis, back pain, flank pain, musculoskeletal pain, myalgia, neck pain, osteopenia, pain in extremity, tendonitis, rhabdomyolysis</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Uncommon</td>
<td>renal failure, nephritis, nephrolithiasis, nocturia, renal cyst, renal impairment, tubulointerstitial nephritis</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Uncommon</td>
<td>erectile dysfunction, gynaecomastia, menopausal symptoms</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>common</td>
<td>asthenia, fatigue, pyrexia</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>chest discomfort, chills, face oedema, fat tissue increased, feeling jittery, malaise, submandibular mass, oedema peripheral, pain</td>
</tr>
<tr>
<td>Investigations</td>
<td>common</td>
<td>alanine aminotransferase increased, atypical lymphocytes, aspartate aminotransferase increased, blood triglycerides increased, lipase increased, blood pancreatic amylase increased</td>
</tr>
<tr>
<td></td>
<td>uncommon</td>
<td>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</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Uncommon</td>
<td>accidental overdose</td>
</tr>
</tbody>
</table>

**Description of selected adverse reactions**
Cancers were reported in treatment-experienced and treatment-naïve patients who initiated ISENTRESS 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 ISENTRESS and in the groups receiving comparators.

Grade 2-4 creatine kinase laboratory abnormalities were observed in subjects treated with ISENTRESS. 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) 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 ISENTRESS and darunavir compared to those containing ISENTRESS without darunavir or darunavir without ISENTRESS. 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 Phase III studies, treatment-experienced patients (N = 114/699 or 16%; HBV=6 %, HCV=9 %, HBV+HCV=1 %) and treatment-naïve patients (N = 34/563 or 6 %; HBV=4%, HCV=2%, HBV+HCV=0.2 %) 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 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 with hepatitis B and/or hepatitis C virus co-infection for both treatment groups. 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 subjects treated with ISENTRESS as compared to 11 %, 10 % and 9 % of all other subjects treated with ISENTRESS. 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 subjects treated with ISENTRESS as compared to 13 %, 13 % and 5 % of all other subjects treated with ISENTRESS.

The following adverse reactions were identified through post-marketing surveillance but not reported as drug-related in randomised controlled Phase III clinical trials (Protocols 018, 019, and 021): thrombocytopenia, suicidal ideation, suicidal behaviour (particularly in patients with a pre-existing history of psychiatric illness), hepatic failure, Stevens Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rhabdomyolysis.

Paediatric population

Children and adolescents 2 to 18 years of age

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

In these 96 children and adolescents, frequency, type and severity of drug related adverse reactions through Week 48 were comparable to those observed in adults.
One patient experienced drug related clinical adverse reactions of Grade 3 psychomotor hyperactivity, abnormal behaviour and insomnia; one patient experienced a Grade 2 serious drug related allergic rash.

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

Infants and toddlers 4 weeks to less than 2 years of age
Raltegravir has also been studied in 26 HIV-1 infected infants and toddlers 4 weeks to less than 2 years of age, in combination with other antiretroviral agents in IMPAACT P1066 (see sections 5.1 and 5.2).

In these 26 infants and toddlers, the frequency, type and severity of drug related adverse reactions through Week 48 were comparable to those observed in adults.

One patient experienced a Grade 3 serious drug related allergic rash that resulted in treatment discontinuation.

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

4.9 Overdose

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

In the event of an overdose, it is reasonable to employ the standard supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required. It should be taken into account that raltegravir is presented for clinical use as the potassium salt. The extent to which raltegravir may be dialysable is unknown.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, other antivirals, ATC code: J05AX08.

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

Antiviral activity in vitro
Raltegravir at concentrations of 31 ± 20 nM resulted in 95 % inhibition (IC\text{95}) of HIV-1 replication (relative to an untreated virus-infected culture) in human T-lymphoid cell cultures infected with the cell-line adapted HIV-1 variant H9IIIB. In addition, raltegravir inhibited viral replication in cultures of mitogen-activated human peripheral blood mononuclear cells infected with diverse, primary clinical isolates of HIV-1, including isolates from 5 non-B subtypes, and isolates resistant to reverse transcriptase inhibitors and protease inhibitors. In a single-cycle infection assay, raltegravir inhibited
infection of 23 HIV isolates representing 5 non-B subtypes and 5 circulating recombinant forms with IC50 values ranging from 5 to 12 nM.

Resistance
Most viruses isolated from patients failing raltegravir had high-level raltegravir resistance resulting from the appearance of two or more mutations. 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 ISSENTRESS was based on the analyses of 96-week data from two randomised, double-blind, placebo-controlled trials, (BENCHMRK 1 and BENCHMRK 2, Protocols 018 and 019) in antiretroviral treatment-experienced HIV-1 infected adult patients and the analysis of 240-week data from a randomised, double-blind, active-control trial, (STARTMRK, Protocol 021) in antiretroviral treatment-naïve HIV-1 infected adult patients.

Efficacy
Treatment-experienced adult patients
BENCHMRK 1 and BENCHMRK 2 (multi-centre, randomised, double-blind, placebo-controlled trials) evaluated the safety and anti-retroviral activity of ISSENTRESS 400 mg twice daily vs. placebo in a combination with optimized 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 randomization, 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 ISSENTRESS 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 ISSENTRESS 400 mg twice daily from the pooled studies BENCHMRK 1 and BENCHMRK 2 are shown in Table 3.
### Table 3
Efficacy Outcome at Weeks 48 and 96

<table>
<thead>
<tr>
<th>Parameter</th>
<th>48 Weeks</th>
<th>96 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ISENTRESS 400 mg twice daily + OBT (N = 462)</strong></td>
<td>ISENTRESS 400 mg twice daily + OBT (N = 462)</td>
<td>Placebo + OBT (N = 237)</td>
</tr>
<tr>
<td><strong>Percent HIV-RNA &lt; 400 copies/ml (95 % CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients†</td>
<td>72 (68, 76)</td>
<td>37 (31, 44)</td>
</tr>
<tr>
<td>Baseline Characteristic‡</td>
<td>72 (68, 76)</td>
<td>37 (31, 44)</td>
</tr>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml</td>
<td>62 (53, 69)</td>
<td>17 (9, 27)</td>
</tr>
<tr>
<td>≤ 100,000 copies/ml</td>
<td>82 (77, 86)</td>
<td>49 (41, 58)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm³</td>
<td>61 (53, 69)</td>
<td>21 (13, 32)</td>
</tr>
<tr>
<td>&gt; 50 and ≤ 200 cells/mm³</td>
<td>80 (73, 85)</td>
<td>44 (33, 55)</td>
</tr>
<tr>
<td>&gt; 200 cells/mm³</td>
<td>83 (76, 89)</td>
<td>51 (39, 63)</td>
</tr>
<tr>
<td>Sensitivity score (GSS) §</td>
<td>52 (42, 61)</td>
<td>8 (3, 17)</td>
</tr>
<tr>
<td>0</td>
<td>81 (75, 87)</td>
<td>40 (30, 51)</td>
</tr>
<tr>
<td>1</td>
<td>84 (77, 89)</td>
<td>65 (52, 76)</td>
</tr>
<tr>
<td>2 and above</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Percent HIV-RNA &lt; 50 copies/ml (95 % CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients†</td>
<td>62 (57, 67)</td>
<td>33 (27, 39)</td>
</tr>
<tr>
<td>Baseline Characteristic‡</td>
<td>62 (57, 67)</td>
<td>33 (27, 39)</td>
</tr>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml</td>
<td>48 (40, 56)</td>
<td>16 (8, 26)</td>
</tr>
<tr>
<td>≤ 100,000 copies/ml</td>
<td>73 (68, 78)</td>
<td>43 (35, 52)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm³</td>
<td>50 (41, 58)</td>
<td>20 (12, 31)</td>
</tr>
<tr>
<td>&gt; 50 and ≤ 200 cells/mm³</td>
<td>67 (59, 74)</td>
<td>39 (28, 50)</td>
</tr>
<tr>
<td>&gt; 200 cells/mm³</td>
<td>76 (68, 83)</td>
<td>44 (32, 56)</td>
</tr>
<tr>
<td>Sensitivity score (GSS) §</td>
<td>45 (35, 54)</td>
<td>3 (0, 11)</td>
</tr>
<tr>
<td>0</td>
<td>67 (59, 74)</td>
<td>37 (27, 48)</td>
</tr>
<tr>
<td>1</td>
<td>75 (68, 82)</td>
<td>59 (46, 71)</td>
</tr>
<tr>
<td>2 and above</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean CD4 Cell Change (95 % CI), cells/mm³</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients‡</td>
<td>109 (98, 121)</td>
<td>45 (32, 57)</td>
</tr>
<tr>
<td>Baseline Characteristic‡</td>
<td>109 (98, 121)</td>
<td>45 (32, 57)</td>
</tr>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml</td>
<td>126 (107, 144)</td>
<td>36 (17, 55)</td>
</tr>
<tr>
<td>≤ 100,000 copies/ml</td>
<td>100 (86, 115)</td>
<td>49 (33, 65)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm³</td>
<td>121 (100, 142)</td>
<td>33 (18, 48)</td>
</tr>
<tr>
<td>&gt; 50 and ≤ 200 cells/mm³</td>
<td>104 (88, 119)</td>
<td>47 (28, 66)</td>
</tr>
<tr>
<td>&gt; 200 cells/mm³</td>
<td>104 (80, 129)</td>
<td>54 (24, 84)</td>
</tr>
<tr>
<td>Sensitivity score (GSS) §</td>
<td>81 (55, 106)</td>
<td>11 (4, 26)</td>
</tr>
<tr>
<td>1</td>
<td>113 (96, 130)</td>
<td>44 (24, 63)</td>
</tr>
<tr>
<td>2 and above</td>
<td>125 (105, 144)</td>
<td>76 (48, 103)</td>
</tr>
</tbody>
</table>

† Non-completer is failure imputation: patients who discontinued prematurely are imputed as failure thereafter. Percent of patients with response and associated 95 % confidence interval (CI) are reported.
‡ For analysis by prognostic factors, virologic failures were carried forward for percent < 400 and 50 copies/ml. For mean CD4 changes, baseline-carry-forward was used for virologic failures.
§ The Genotypic Sensitivity Score (GSS) was defined as the total oral ARTs in the optimised background therapy (OBT) to which a patient's viral isolate showed genotypic sensitivity based upon genotypic resistance test. Enfuvirtide use in OBT in enfuvirtide-naïve patients was counted as one active drug in OBT. Similarly, darunavir use in OBT in darunavir-naïve patients was counted as one active drug in OBT.

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

The SWITCHMRK 1 & 2 (Protocols 032 & 033) studies evaluated HIV-infected patients receiving suppressive (screening HIV RNA < 50 copies/ml; stable regimen > 3 months) therapy with lopinavir 200 mg (+) ritonavir 50 mg 2 tablets twice daily plus at least 2 nucleoside reverse transcriptase inhibitors and randomized 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-naive adult patients

STARTMRK (multi-centre, randomised, double-blind, active-control trial) evaluated the safety and anti-retroviral activity of ISENTRESS 400 mg twice daily vs. efavirenz 600 mg at bedtime, in a combination with emtricitabine (+) tenofovir, in treatment-naive HIV-infected patients with HIV RNA > 5,000 copies/ml. Randomization 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 ISENTRESS 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 ISENTRESS and 230/281 (81.9 %) in the group receiving efavirenz. The treatment difference (ISENTRESS – efavirenz) was 4.2 % with an associated 95 % CI of (-1.9, 10.3) establishing that ISENTRESS is non-inferior to efavirenz (p-value for non-inferiority < 0.001). At Week 240, the treatment difference (ISENTRESS – 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 ISENTRESS 400 mg twice daily from STARTMRK are shown in Table 4.

<table>
<thead>
<tr>
<th>STARTMRK Study Parameter</th>
<th>48 Weeks</th>
<th>240 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ISENTRESS 400 mg twice daily (N = 281)</td>
<td>Efavirenz 600 mg at bedtime (N = 282)</td>
</tr>
<tr>
<td>Percent HIV-RNA &lt; 50 copies/ml (95 % CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>86 (81, 90)</td>
<td>82 (77, 86)</td>
</tr>
<tr>
<td>Baseline Characteristic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml</td>
<td>91 (85, 95)</td>
<td>89 (83, 94)</td>
</tr>
<tr>
<td>≤ 100,000 copies/ml</td>
<td>93 (86, 97)</td>
<td>89 (82, 94)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm³</td>
<td>84 (64, 95)</td>
<td>86 (67, 96)</td>
</tr>
<tr>
<td>&gt; 50 and ≤ 200 cells/mm³</td>
<td>89 (81, 95)</td>
<td>86 (77, 92)</td>
</tr>
<tr>
<td>&gt; 200 cells/mm³</td>
<td>94 (89, 98)</td>
<td>92 (87, 96)</td>
</tr>
<tr>
<td>Parameter</td>
<td>48 Weeks</td>
<td>240 Weeks</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td>ISENTRESS</td>
<td>Efavirenz</td>
</tr>
<tr>
<td></td>
<td>400 mg twice daily</td>
<td>600 mg at bedtime</td>
</tr>
<tr>
<td></td>
<td>(N = 281)</td>
<td>(N = 282)</td>
</tr>
<tr>
<td>Viral Subtype Clade B</td>
<td>90 (85, 94)</td>
<td>89 (83, 93)</td>
</tr>
<tr>
<td>Non-Clade B</td>
<td>96 (87, 100)</td>
<td>91 (78, 97)</td>
</tr>
</tbody>
</table>

**Mean CD4 Cell Change (95 % CI), cells/mm$^3$**

<table>
<thead>
<tr>
<th>Baseline Characteristic$^2$</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-RNA &gt; 100,000 copies/ml</td>
<td>196 (174, 219)</td>
<td>192 (169, 214)</td>
<td>392 (350, 435)</td>
<td>329 (293, 364)</td>
</tr>
<tr>
<td>≤ 100,000 copies/ml</td>
<td>180 (160, 200)</td>
<td>134 (115, 153)</td>
<td>350 (312, 388)</td>
<td>294 (251, 337)</td>
</tr>
<tr>
<td>CD4-count ≤ 50 cells/mm$^3$</td>
<td>170 (122, 218)</td>
<td>152 (123, 180)</td>
<td>304 (209, 399)</td>
<td>314 (242, 386)</td>
</tr>
<tr>
<td>&gt; 50 and ≤ 200 cells/mm$^3$</td>
<td>193 (169, 217)</td>
<td>175 (151, 198)</td>
<td>413 (360, 465)</td>
<td>306 (264, 348)</td>
</tr>
<tr>
<td>&gt; 200 cells/mm$^3$</td>
<td>190 (168, 212)</td>
<td>157 (134, 181)</td>
<td>358 (321, 395)</td>
<td>316 (272, 359)</td>
</tr>
<tr>
<td>Viral Subtype Clade B</td>
<td>187 (170, 204)</td>
<td>164 (147, 181)</td>
<td>380 (346, 414)</td>
<td>303 (272, 333)</td>
</tr>
<tr>
<td>Non-Clade B</td>
<td>189 (153, 225)</td>
<td>156 (121, 190)</td>
<td>332 (275, 388)</td>
<td>329 (260, 398)</td>
</tr>
</tbody>
</table>

$^1$ 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.

$^2$ 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.
ISENTRESS and efavirenz were administered with emtricitabine (+) tenofovir.

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**Paediatric population**

*Children and adolescents 2 to 18 years of age*

IMPAACT P1066 is a Phase I/II open label multicenter trial to evaluate the pharmacokinetic profile, safety, tolerability, and efficacy of raltegravir in HIV infected children. This study enrolled 126 treatment experienced children and adolescents 2 to 18 years of age. Patients were stratified by age, enrolling adolescents first and then successively younger children. Patients received either the 400 mg tablet formulation (6 to 18 years of age) or the chewable tablet formulation (2 to less than 12 years of age). Raltegravir was administered with an optimized background regimen.

The initial dose finding stage included intensive pharmacokinetic evaluation. Dose selection was based upon achieving similar raltegravir plasma exposure and trough concentration as seen in adults, and acceptable short term safety. After dose selection, additional patients were enrolled for evaluation of long term safety, tolerability and efficacy. Of the 126 patients, 96 received the recommended dose of ISENTRESS (see section 4.2).
Table 5
Baseline Characteristics and Efficacy Outcomes at Weeks 24 and 48 from IMPAACT P1066
(2 to 18 years of age)

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

Infants and toddlers 4 weeks to less than 2 years of age
IMPAACT P1066 also enrolled HIV-infected, infants and toddlers 4 weeks to less than 2 years of age who had received prior antiretroviral therapy either as prophylaxis for prevention of mother to child transmission (PMTCT) and/or as combination antiretroviral therapy for treatment of HIV infection. Raltegravir was administered as granules for oral suspension formulation without regard to food in combination with an optimized background regimen that included lopinavir plus ritonavir in two-thirds of patients.
Table 6
Baseline Characteristics and Efficacy Outcomes at Weeks 24 and 48 from IMPAACT P1066
(4 weeks to less than 2 years of age)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N=26</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age (weeks), median [range]</td>
<td>28 [4 - 100]</td>
</tr>
<tr>
<td>Male Gender</td>
<td>65 %</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>8 %</td>
</tr>
<tr>
<td>Black</td>
<td>85 %</td>
</tr>
<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Plasma HIV-1 RNA (log_{10} copies/ml), mean [range]</td>
<td>5.7 [3.1 - 7]</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm$^3$), median [range]</td>
<td>1400 [131 - 3648]</td>
</tr>
<tr>
<td>CD4 percent, median [range]</td>
<td>18.6 % [3.3 – 39.3]</td>
</tr>
<tr>
<td>HIV-1 RNA &gt;100,000 copies/ml</td>
<td>69 %</td>
</tr>
<tr>
<td>CDC HIV category B or C</td>
<td>23 %</td>
</tr>
<tr>
<td><strong>Prior ART Use by Class</strong></td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>73 %</td>
</tr>
<tr>
<td>NRTI</td>
<td>46 %</td>
</tr>
<tr>
<td>PI</td>
<td>19 %</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td>Week 24</td>
</tr>
<tr>
<td>Achieved ≥1 log_{10} HIV RNA drop from baseline or &lt;400 copies/ml</td>
<td>91 %</td>
</tr>
<tr>
<td>Achieved HIV RNA &lt;50 copies/ml</td>
<td>43 %</td>
</tr>
<tr>
<td>Mean CD4 cell count (%) increase from baseline</td>
<td>500 cells/mm$^3$ (7.5 %)</td>
</tr>
<tr>
<td><strong>Virologic failure</strong></td>
<td>Week 24</td>
</tr>
<tr>
<td>Non-responder</td>
<td>0</td>
</tr>
<tr>
<td>Rebounder</td>
<td>0</td>
</tr>
<tr>
<td>Number with genotype available*</td>
<td>0</td>
</tr>
</tbody>
</table>

One patient had a mutation at the 155 position.

The European Medicines Agency has deferred the obligation to submit the results of studies with ISENTRESS in one or more subsets of the paediatric population in Human Immunodeficiency virus infection (see section 4.2 for information on paediatric use).

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 $t_{\text{max}}$ of approximately 3 hours postdose. Raltegravir AUC and $C_{\text{max}}$ increase dose proportionally over the dose range 100 mg to 1,600 mg. Raltegravir $C_{12\text{ hr}}$ increases dose proportionally over the dose range of 100 to 800 mg and increases slightly less than dose proportionally over the dose range 100 mg to 1,600 mg. Dose proportionality has not been established in patients.

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

ISENTRESS 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 $C_{12\text{ hr}}$ was 66 % higher and $C_{\text{max}}$ was 5 % higher following a moderate-fat meal compared to fasting. Administration of raltegravir following a high-fat meal increased AUC and $C_{\text{max}}$ by approximately 2-fold and increased $C_{12\text{ hr}}$ by
Administration of raltegravir following a low-fat meal decreased AUC and $C_{\text{max}}$ by 46 % and 52 %, respectively; $C_{12\text{hr}}$ was essentially unchanged. Food appears to increase pharmacokinetic variability relative to fasting.

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

**Distribution**
Raltegravir is approximately 83 % bound to human plasma protein over the concentration range of 2 to 10 µM.

Raltegravir readily crossed the placenta in rats, but did not penetrate the brain to any appreciable extent.

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

**Biotransformation and excretion**
The apparent terminal half-life of raltegravir is approximately 9 hours, with a shorter α-phase half-life (~1 hour) accounting for much of the AUC. Following administration of an oral dose of radiolabeled raltegravir, approximately 51 and 32 % of the dose was excreted in faeces and urine, respectively. In faeces, only raltegravir was present, most of which is likely to be derived from hydrolysis of raltegravir-glucuronide secreted in bile as observed in preclinical species. Two components, namely raltegravir and raltegravir-glucuronide, were detected in urine and accounted for approximately 9 and 23 % of the dose, respectively. The major circulating entity was raltegravir and represented approximately 70 % of the total radioactivity; the remaining radioactivity in plasma was accounted for by raltegravir-glucuronide. Studies using isoform-selective chemical inhibitors and cDNA-expressed UDP-glucuronosyltransferases (UGT) show that UGT1A1 is the main enzyme responsible for the formation of raltegravir-glucuronide. Thus the data indicate that the major mechanism of clearance of raltegravir in humans is UGT1A1-mediated glucuronidation.

**UGT1A1 Polymorphism**
In a comparison of 30 subjects with *28/*28 genotype to 27 subjects with wild-type genotype, the geometric mean ratio (90 % CI) of AUC was 1.41 (0.96, 2.09) and the geometric mean ratio of $C_{12\text{hr}}$ 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 $C_{\text{max}}$, and 188 % increase in $C_{12\text{hr}}$ 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 7 displays pharmacokinetic parameters in the 400 mg tablet, the chewable tablet, and the granules for oral suspension, by body weight.

**Table 7**

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

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Formulation</th>
<th>Dose</th>
<th>N*</th>
<th>Geometric mean (CV)</th>
<th>Geometric mean (CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AUC(_{0-12hr}) (μM●hr)</td>
<td>C(_{12hr}) (nM)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥25 kg</td>
<td>Film-coated tablet</td>
<td>400 mg twice daily</td>
<td>18</td>
<td>14.1 (121 %)</td>
<td>233 (157 %)</td>
</tr>
<tr>
<td></td>
<td>Chewable tablet</td>
<td>Weight based dosing, see dosing tables for the chewable tablet</td>
<td>9</td>
<td>22.1 (36 %)</td>
<td>113 (80 %)</td>
</tr>
<tr>
<td>11 to less than 25 kg</td>
<td>Chewable tablet</td>
<td>Weight based dosing, see dosing tables for the chewable tablet</td>
<td>13</td>
<td>18.6 (68 %)</td>
<td>82 (123 %)</td>
</tr>
<tr>
<td>3 to less than 20 kg</td>
<td>Oral suspension</td>
<td>Weight based dosing, see dosing Table 1</td>
<td>19</td>
<td>24.5 (43 %)</td>
<td>113 (69 %)</td>
</tr>
</tbody>
</table>

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

The pharmacokinetics of raltegravir in infants under 4 weeks of age has not been established.

**Elderly**

There was no clinically meaningful effect of age on raltegravir pharmacokinetics over the age range studied (19 to 71 years, with few (8) subjects over the age of 65).

**Gender, race and BMI**

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

**Renal impairment**

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

**Hepatic impairment**

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

5.3 **Preclinical safety data**

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

**Mutagenicity**

No evidence of mutagenicity or genotoxicity was observed in *in vitro* microbial mutagenesis (Ames) tests, *in vitro* alkaline elution assays for DNA breakage and *in vitro* and *in vivo* chromosomal aberration studies.
Carcinogenicity
A carcinogenicity study of raltegravir in mice did not show any carcinogenic potential. At the highest dose levels, 400 mg/kg/day in females and 250 mg/kg/day in males, systemic exposure was similar to that at the clinical dose of 400 mg twice daily. In rats, tumours (squamous cell carcinoma) of the nose/nasopharynx were identified at 300 and 600 mg/kg/day in females and at 300 mg/kg/day in males. These 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 they are of limited relevance for the intended clinical use. At the NOAEL, systemic exposure was similar to that at the clinical dose of 400 mg twice daily. Standard genotoxicity studies to evaluate mutagenicity and clastogenicity were negative.

Developmental toxicity
Raltegravir was not teratogenic in developmental toxicity studies in rats and rabbits. A slight increase in incidence of supernumerary ribs was observed in rat pups of dams exposed to raltegravir at approximately 4.4-fold human exposure at 400 mg twice daily based on AUC$_{0-24\ hr}$. No development effects were seen at 3.4-fold human exposure at 400 mg twice daily based on AUC$_{0-24\ hr}$ (see section 4.6). Similar findings were not observed in rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
- Hydroxypropyl cellulose
- Sucralose
- Mannitol
- Monoammonium glycyrrhizinate
- Sorbitol (E420)
- Fructose
- Banana flavour
- Sucrose
- Crospovidone, Type A
- Magnesium stearate
- Hypromellose 2910/6cP
- Macrogol/PEG 400
- Ethylcellulose 20 cP
- Ammonium hydroxide
- Medium chain triglycerides
- Oleic acid
- Microcrystalline cellulose
- Carmellose sodium

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years for unopened sachet.
After reconstitution: 30 minutes when stored at or below 30° C.

6.4 Special precautions for storage
This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.
For storage conditions after reconstitution of the medicinal product, see section 6.3.
6.5 Nature and contents of container

PET/aluminium/LLDPE sachets.
One carton contains 60 sachets, two 5 ml oral dosing syringes and 2 mixing cups.

6.6 Special precautions for disposal and other handling

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

Each single-use sachet contains 100 mg of raltegravir which is to be suspended in 5 ml of water giving a final concentration of 20 mg per ml.

- Pour entire contents of the sachet into 5 ml of water and mix
- Once mixed, measure the recommended volume (dose) of suspension with a syringe and administer the dose orally
- The volume (dose) of suspension should be administered orally within 30 minutes of mixing
- Discard any remaining suspension
- For more details on preparation and administration of the suspension, see the Patient Information Leaflet, Instructions for Use section.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic Safety Update Reports

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

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

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
A. LABELLING
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

Carton for 400 mg film-coated tablets

1. **NAME OF THE MEDICINAL PRODUCT**

ISENTRESS 400 mg film-coated tablets
raltegravir

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

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

3. **LIST OF EXCIPIENTS**

Contains lactose. See leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

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

5. **METHOD AND ROUTES OF ADMINISTRATION**

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

Do not switch between the 400 mg tablet, chewable tablet or granules for oral suspension without first talking with your doctor, pharmacist or nurse.

8. **EXPIRY DATE**

EXP

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ISENTRESS 400 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle for ISENTRESS 400 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 400 mg film-coated tablets
raltegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not switch between the 400 mg tablet, chewable tablet or granules for oral suspension without first talking with your doctor, pharmacist or nurse.

8. EXPIRY DATE

EXP

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER

MSD

12. MARKETING AUTHORIZATION NUMBER(S)

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

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Carton for 100 mg chewable tablets

1. NAME OF THE MEDICINAL PRODUCT
ISENTRESS 100 mg chewable tablets
raltegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each tablet contains 100 mg of raltegravir (as potassium).

3. LIST OF EXCIPIENTS
Contains fructose, sorbitol and aspartame. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS
60 chewable tablets

5. METHOD AND ROUTES OF ADMINISTRATION
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN
Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
Do not switch between the 400 mg tablet, chewable tablet or granules for oral suspension without first talking with your doctor, pharmacist or nurse.

8. EXPIRY DATE
EXP

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/004

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ISENTRESS 100 mg chewable tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING
ISENTRESS 100 mg – bottle labeling

1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 100 mg chewable tablets
raltegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

60 chewable tablets

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not switch between the 400 mg tablet, chewable tablet or granules for oral suspension without first talking with your doctor, pharmacist or nurse.

8. EXPIRY DATE

EXP

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MSD

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/004

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**Carton for the 25 mg chewable tablets**

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<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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</thead>
<tbody>
<tr>
<td>ISENTRESS 25 mg chewable tablets</td>
</tr>
<tr>
<td>raltegravir</td>
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<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each tablet contains 25 mg of raltegravir (as potassium).</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
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</thead>
<tbody>
<tr>
<td>Contains fructose, sorbitol and aspartame. See leaflet for further information.</td>
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<table>
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<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
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<tr>
<td>60 chewable tablets</td>
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<table>
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<tr>
<th>5. METHOD AND ROUTES OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Oral use.</td>
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<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
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<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
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<table>
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<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
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<tbody>
<tr>
<td>Do not switch between the 400 mg tablet, chewable tablet or granules for oral suspension without first talking with your doctor, pharmacist or nurse.</td>
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<th>8. EXPIRY DATE</th>
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<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
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</thead>
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10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/436/003

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ISENTRESS 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 25 mg chewable tablets
raltegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

60 chewable tablets

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not switch between the 400 mg tablet, chewable tablet or granules for oral suspension without first talking with your doctor, pharmacist or nurse.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS
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<td>10.</td>
<td>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</td>
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<td>11.</td>
<td>NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</td>
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<td>EU/1/07/436/003</td>
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<td>13.</td>
<td>BATCH NUMBER</td>
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<td>Batch</td>
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<td>GENERAL CLASSIFICATION FOR SUPPLY</td>
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<tr>
<td>15.</td>
<td>INSTRUCTIONS ON USE</td>
</tr>
<tr>
<td>16.</td>
<td>INFORMATION IN BRAILLE</td>
</tr>
</tbody>
</table>
1. NAME OF THE MEDICINAL PRODUCT

ISENTRESS 100 mg granules for oral suspension
raltegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 100 mg of raltegravir (as potassium). Following reconstitution the oral suspension has a concentration of 20 mg per ml.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

60 sachets, two 5 ml oral dosing syringes and 2 mixing cups.

5. METHOD AND ROUTES OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not switch between the 400 mg tablet, chewable tablet or granules for oral suspension without first talking with your doctor, pharmacist or nurse.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORITY
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORIZATION NUMBER(S)
EU/1/07/436/005

13. BATCH NUMBER
Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
ISENTRESS 100 mg granules for oral suspension

17. UNIQUE IDENTIFIER – 2D BARCODE
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
PC:
SN:
NN:
### PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

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

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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</thead>
<tbody>
<tr>
<td>ISENTRESS 100 mg granules</td>
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<tr>
<td>Raltegravir</td>
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<tr>
<td>Oral use.</td>
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<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
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<td>MSD</td>
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<th>3. EXPIRY DATE</th>
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<tr>
<th>4. BATCH NUMBER</th>
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<td>Lot</td>
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| 5. OTHER        |
B. PACKAGE LEAFLET
Package leaflet: Information for the user

Isentress 400 mg film-coated tablets
raltegravir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

If you are the parent of a child taking Isentress, please read this information carefully with your child.

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

What is in this leaflet
1. What Isentress is and what it is used for
2. What you need to know before you take Isentress
3. How to take Isentress
4. Possible side effects
5. How to store Isentress
6. Contents of the pack and other information

1. What Isentress is and what it is used for

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

How Isentress works
The virus produces an enzyme called HIV integrase. This helps the virus to multiply in the cells in your body. Isentress stops this enzyme from working. When used with other medicines, Isentress may reduce the amount of HIV in your blood (this is called your "viral load") and increase your CD4-cell count (a type of white blood cells that plays an important role in maintaining a healthy immune system to help fight infection). Reducing the amount of HIV in the blood may improve the functioning of your immune system. This means your body may fight infection better. Isentress may not have these effects in all patients. Isentress is not a cure for HIV infection.

When Isentress should be used
Isentress is used to treat adults, adolescents, children, toddlers and infants 4 weeks of age and older who are infected by HIV. Your doctor has prescribed Isentress to help control your HIV infection.

2. What you need to know before you take Isentress

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

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

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

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

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

Passing HIV to others
HIV infection is spread by contact with blood or sexual contact with a person with HIV. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.

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

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

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

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

Children and adolescents
Isentress is not for use in infants below 4 weeks of age.
Other medicines and Isentress
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines with or without a prescription.

Isentress might interact with other medicines.
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take:
- antacids. It is not recommended to take Isentress with certain antacids (those containing aluminum and/or magnesium). Talk to your doctor about other antacids you can take.
- rifampicin (a medicine used to treat some infections such as tuberculosis), as it may decrease your levels of Isentress. Your doctor may consider increasing your dose of Isentress if you are taking rifampicin.

Taking Isentress with food and drink
See section 3.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- Isentress is not recommended in pregnancy because it has not been studied in pregnant women.
- Women with HIV should not breast-feed their infants because babies can be infected with HIV through their breast milk. Talk with your doctor about the best way to feed your baby.

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

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

Isentress film-coated tablets contain lactose
If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

3. How to take Isentress
You should always take this medicine exactly as your doctor, pharmacist or nurse has told you. You should check with your doctor, pharmacist or nurse if you are not sure. Isentress must be used in combination with other medicines for HIV.
- It is very important that this medicine is taken exactly as directed.

How much to take
Adults
The recommended dose is 1 tablet (400 mg) by mouth twice a day.
- Do not change the dose or stop taking this medicine without first talking with your doctor, pharmacist or nurse.

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

Isentress is also available in a chewable tablet for children weighing at least 11 kg and in granules for oral suspension for infants and toddlers from 4 weeks of age and weighing at least 3 kg to less than 20 kg.
- Do not switch between the 400 mg tablet, chewable tablet or granules for oral suspension without first talking with your doctor, pharmacist or nurse.
It is recommended not to chew, crush or split the tablets because it may change the level of medicine in your body. This medicine can be taken with or without food or drink.

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

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

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

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

### 4. Possible side effects

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

**Serious side effects** – these are uncommon (may affect up to 1 in 100 people)

See a doctor immediately, if you notice any of the following:
- herpes infections including shingles
- anaemia including due to low iron
- signs and symptoms of infection or inflammation
- mental disorder
- suicide intention or attempt
- stomach inflammation
- inflammation of liver
- liver failure
- allergic rash
- certain kinds of kidney problems
- drug ingestion in quantities greater than recommended

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

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

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

Additional side effects in children and adolescents
- hyperactivity

Muscle pain, tenderness, or weakness have been reported during treatment with Isentress.

In clinical studies, cancers were observed in patients receiving Isentress at a rate similar to that observed in the patients receiving other HIV treatment that doesn’t contain Isentress.

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

5. **How to store Isentress**

- Keep this medicine out of the sight and reach of children.
- Do not take this medicine after the expiry date which is stated on the bottle after EXP. The expiry date refers to the last day of that month.
- This product does not require any special storage conditions.

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

6. **Contents of the pack and other information**

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

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

**What Isentress looks like and contents of the pack**
The film-coated tablet is oval-shaped, pink, marked with "227" on one side.

Two pack sizes are available: 1 bottle with 60 tablets, and 3 bottles of 60 tablets each.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

**Marketing Authorisation Holder**

Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

**Manufacturer**

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

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

**BE**

MSD Belgium BVBA/SPRL
Tél/Tel: 0800 38 693 (+32(0)27766211)
dpoc_belux@merck.com

**BG**

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

**LT**

UAB Merck Sharp & Dohme
Tel.: +370 5 278 02 47
msd_lietuva@merck.com

**LU**

MSD Belgium BVBA/SPRL
Tél/Tel: +32(0)27766211
dpoc_belux@merck.com
CZ
Merck Sharp & Dohme s.r.o.
Tel.: +420 233 010 111
dpoc_czechslovak@merck.com

HU
MSD Pharma Hungary Kft.
Tel.: +36 1 888 53 00
hungary_msd@merck.com

DK
MSD Danmark ApS
Tel: +45 4482 4000
dkmail@merck.com

MT
Merck Sharp & Dohme Cyprus Limited
Tel: 8007 4433 (+356 99917558)
malta_info@merck.com

DE
MSD SHARP & DOHME GMBH
Tel: 0800 673 673 673 (+49 (0) 89 4561 2612)
e-mail@msd.de

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

EE
Merck Sharp & Dohme OÜ
Tel.: +372 6144 200
msdeesti@merck.com

AT
Merck Sharp & Dohme Ges.m.b.H.
Tel: +43 (0) 1 26 044
msd-medizin@merck.com

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

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

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

HR
Merck Sharp & Dohme d.o.o.
Tel: + 385 1 6611 333
croatia_info@merck.com

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

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

SK
Merck Sharp & Dohme, s. r. o.
Tel.: +421 2 58282010
dpoc_czechslovak@merck.com

IT
MSD Italia S.r.l.
Tel: +39 06 361911
medicalinformation.it@merck.com

FI
MSD Finland Oy
Puh/Tel: +358 (0) 9 804 650
info@msd.fi
This leaflet was last revised in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.
Package leaflet: Information for the user

Isentress 100 mg chewable tablets
raltegravir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

If you are the parent of a child taking Isentress, please read this information carefully with your child.

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

What is in this leaflet
1. What Isentress is and what it is used for
2. What you need to know before you take Isentress
3. How to take Isentress
4. Possible side effects
5. How to store Isentress
6. Contents of the pack and other information

1. What Isentress is and what it is used for

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

How Isentress works
The virus produces an enzyme called HIV integrase. This helps the virus to multiply in the cells in your body. Isentress stops this enzyme from working. When used with other medicines, Isentress may reduce the amount of HIV in your blood (this is called your "viral load") and increase your CD4-cell count (a type of white blood cells that plays an important role in maintaining a healthy immune system to help fight infection). Reducing the amount of HIV in the blood may improve the functioning of your immune system. This means your body may fight infection better. Isentress may not have these effects in all patients. Isentress is not a cure for HIV infection.

When Isentress should be used
Isentress is used to treat adults, adolescents, children, toddlers and infants 4 weeks of age and older who are infected by HIV. Your doctor has prescribed Isentress to help control your HIV infection.

2. What you need to know before you take Isentress

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

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

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

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

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

**Passing HIV to others**
HIV infection is spread by contact with blood or sexual contact with a person with HIV. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.

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

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

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

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

**Children and adolescents**
Isentress is not for use in infants below 4 weeks of age.
Other medicines and Isentress
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines with or without a prescription.

Isentress might interact with other medicines.
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take:
- antacids. It is not recommended to take Isentress with certain antacids (those containing aluminium and/or magnesium). Talk to your doctor about other antacids you can take.
- rifampicin (a medicine used to treat some infections such as tuberculosis), as it may decrease your levels of Isentress. Your doctor may consider increasing your dose of Isentress if you are taking rifampicin.

Taking Isentress with food and drink
See section 3.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- Isentress is not recommended in pregnancy because it has not been studied in pregnant women.
- Women with HIV should not breast-feed their infants because babies can be infected with HIV through their breast milk. Talk with your doctor about the best way to feed your baby.

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

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

Isentress chewable tablets contain fructose and sorbitol
If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.
Sweeteners contained in this medicine may be harmful to teeth.

Isentress chewable tablets contain aspartame
Isentress contains aspartame, a source of phenylalanine, which may be harmful to people with phenylketonuria.

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

- It is very important that this medicine is taken exactly as directed.
- The 100 mg chewable tablet is orange-banana flavoured and can be split into equal halves if necessary; however, breaking the tablets should be avoided.

How much to take
Dose for children of 2 through 11 years of age
The doctor will work out the right dose of the chewable tablet based on the age and weight of the child. This dose must not exceed 300 mg twice a day. The doctor will tell you how many chewable tablets the child must take.
- Do not change the dose, or stop taking this medicine, or switch between the chewable tablets and the 400 mg tablet, without first talking with your doctor, pharmacist or nurse.

ISENTRESS is also available in a 400 mg tablet for use in adults, adolescents and children weighing
at least 25 kg and able to swallow a tablet; and as granules for oral suspension for use in infants and
toddlers from 4 weeks of age and weighing at least 3 kg to less than 20 kg.

- Do not switch between the chewable tablet, granules for oral suspension or 400 mg tablet
  without first talking with your doctor, pharmacist or nurse.
- Children should keep scheduled doctor’s visits because their Isentress dosage should be adjusted
  as they get older, grow or gain weight. Their doctor may also want to prescribe the 400 mg
  tablet when they are able to swallow a tablet.

You can take this medicine with or without food or drink.

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

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

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

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

4. **Possible side effects**

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

**Serious side effects** – these are uncommon (may affect up to 1 in 100 people)

**See a doctor immediately, if you notice any of the following:**
- herpes infections including shingles
- anaemia including due to low iron
- signs and symptoms of infection or inflammation
- mental disorder
- suicide intention or attempt
- stomach inflammation
- inflammation of liver
- liver failure
- allergic rash
- certain kinds of kidney problems
- drug ingestion in quantities greater than recommended

See a doctor immediately, if you notice any of the side effects above.
Common: the following may affect up to 1 in 10 people
- decreased appetite
- trouble sleeping; abnormal dreams; nightmare; abnormal behaviour; feelings of deep sadness and unworthiness
- feeling dizzy; headache
- spinning sensation
- bloating; abdominal pain; diarrhoea; excessive gas in the stomach or bowel; feeling sick; vomiting; indigestion; belching
- certain kinds of rash (more often when used in combination with darunavir)
- tiredness, unusual tiredness or weakness; fever
- increased liver blood tests; abnormal white blood cells; increased fat levels in blood; increased level of enzyme from salivary glands or pancreas

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

Additional side effects in children and adolescents
- hyperactivity
Muscle pain, tenderness, or weakness have been reported during treatment with Isentress.

In clinical studies, cancers were observed in patients receiving Isentress at a rate similar to that observed in the patients receiving other HIV treatment that doesn’t contain Isentress.

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

5. **How to store Isentress**

- Keep this medicine out of the sight and reach of children.
- Do not take this medicine after the expiry date which is stated on the bottle after EXP. The expiry date refers to the last day of that month.
- Store in the original package with the bottle tightly closed. Keep the drying agent in the bottle to protect from moisture.
- Prior to breaking the seal, this product does not require any special storage conditions.

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

6. **Contents of the pack and other information**

**What Isentress contains**
The active substance is raltegravir. Each chewable tablet contains 100 mg of raltegravir (as potassium).

The other ingredients are: hydroxypropyl cellulose, sacralose, saccharin sodium, sodium citrate dihydrate, mannitol, red iron oxide, yellow iron oxide, monoammonium glycyrrhizinate, sorbitol (E420), fructose, natural and artificial flavours (orange, banana, and masking), aspartame (E951), crospovidone Type A, magnesium stearate, sodium stearyl fumarate, ethylcellulose 20 cP, ammonium hydroxide, medium chain triglycerides, oleic acid, hypromellose 2910/6cP, and macrogol/PEG 400.

**What Isentress looks like and contents of the pack**
The orange-banana flavoured chewable tablet is oval-shaped, pale orange coloured, scored on both sides with the Merck logo and "477" on one side and without inscription on the other side. One pack size is available: 1 bottle with 60 tablets.

**Marketing Authorisation Holder and Manufacturer**

<table>
<thead>
<tr>
<th>Marketing Authorisation Holder</th>
<th>Manufacturer</th>
</tr>
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<tbody>
<tr>
<td>Merck Sharp &amp; Dohme Ltd.</td>
<td>Merck Sharp &amp; Dohme B. V.</td>
</tr>
<tr>
<td>Hertford Road, Hoddesdon</td>
<td>Waarderweg 39</td>
</tr>
<tr>
<td>Hertfordshire EN11 9BU</td>
<td>2031 BN Haarlem</td>
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**BE**
MSD Belgium BVBA/SPRL  
Tel/Tel: 0800 38 693 (+32(0)27766211)  
dpoc_belux@merck.com

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

**CZ**
Merck Sharp & Dohme s.r.o.  
Tel.: +420 233 010 111  
dpoc_czechslovak@merck.com

**DK**
MSD Danmark ApS  
Tlf: +45 4482 4000  
dkmail@merck.com

**DE**
MSD SHARP & DOHME GMBH  
Tel: 0800 673 673 673 (+49 (0) 89 4561 2612)  
e-mail@msd.de

**EL**
MSD Α.Φ.Β.ΕΕ.  
Τηλ: + 30 210 98 97 300  
dpoc_greece@merck.com

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

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

**HR**
Merck Sharp & Dohme d.o.o.  
Tel: + 385 1 6611 333  
croatia_info@merck.com

**HU**
MSD Pharma Hungary Kft.  
Tel.: +36 1 888 53 00  
hungary_msd@merck.com

**LT**
UAB Merck Sharp & Dohme  
Tel.: +370 5 278 02 47  
msd_lietuva@merck.com

**LU**
MSD Belgium BVBA/SPRL  
Tel/Tel: +32(0)27766211  
dpoc_belux@merck.com

**MT**
Merck Sharp & Dohme Cypruss Limited  
Tel: 8007 4433 (+356 99917558)  
malta_info@merck.com

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

**NO**
MSD (Norge) AS  
Tlf: +47 32 20 73 00  
msdnorge@msd.no

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

**PT**
Merck Sharp & Dohme, Lda  
Tel: +351 21 4465700  
clic@merck.com

**RO**
Merck Sharp & Dohme Romania S.R.L.  
Tel: + 40 21 529 29 00  
msdromania@merck.com
This leaflet was last revised in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site:
Isentress 25 mg chewable tablets
raltegravir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
If you are the parent of a child taking Isentress, please read this information carefully with your child.

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

What is in this leaflet
1. What Isentress is and what it is used for
2. What you need to know before you take Isentress
3. How to take Isentress
4. Possible side effects
5. How to store Isentress
6. Contents of the pack and other information

1. What Isentress is and what it is used for

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

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

Isentress may not have these effects in all patients.
Isentress is not a cure for HIV infection.

When Isentress should be used
Isentress is used to treat adults, adolescents, children, toddlers and infants 4 weeks of age and older who are infected by HIV. Your doctor has prescribed Isentress to help control your HIV infection.

2. What you need to know before you take Isentress

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

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

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

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

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

Passing HIV to others
HIV infection is spread by contact with blood or sexual contact with a person with HIV. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.

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

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

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

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

Children and adolescents
Isentress is not for use in infants below 4 weeks of age.
Other medicines and Isentress
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines with or without a prescription.

Isentress might interact with other medicines. Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take:
- antacids. It is not recommended to take ISENTRESS with certain antacids (those containing aluminium and/or magnesium). Talk to your doctor about other antacids you can take.
- rifampicin (a medicine used to treat some infections such as tuberculosis), as it may decrease your levels of Isentress. Your doctor may consider increasing your dose of Isentress if you are taking rifampicin.

Taking Isentress with food and drink
See section 3.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- Isentress is not recommended in pregnancy because it has not been studied in pregnant women.
- Women with HIV should not breast-feed their infants because babies can be infected with HIV through their breast milk. Talk with your doctor about the best way to feed your baby.

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

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

Isentress chewable tablets contain fructose and sorbitol
If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.
Sweeteners contained in this medicine may be harmful to teeth.

Isentress chewable tablets contain aspartame
Isentress contains aspartame, a source of phenylalanine, which may be harmful to people with phenylketonuria.

3. How to take Isentress
You should always take this medicine exactly as your doctor, pharmacist or nurse has told you. You should check with your doctor, pharmacist or nurse if you are not sure. Isentress must be used in combination with other medicines for HIV.
- It is very important that this medicine is taken exactly as directed.
- The 25 mg chewable tablet is orange-banana flavoured.

How much to take
Dose for children of 2 through 11 years of age
The doctor will work out the right dose of the chewable tablet based on the age and weight of the child. This dose must not exceed 300 mg twice a day. The doctor will tell you how many chewable tablets the child must take.
- Do not change the dose, or stop taking this medicine, or switch between the chewable tablets and the 400 mg tablet, without first talking with your doctor, pharmacist or nurse.

ISENTRESS is also available in a 400 mg tablet for use in adults, adolescents and children weighing at least 25 kg and able to swallow a tablet; and as granules for oral suspension for use in infants and toddlers from 4 weeks of age and weighing at least 3 kg to less than 20 kg.
Do not switch between the chewable tablet, granules for oral suspension or 400 mg tablet without first talking with your doctor, pharmacist or nurse.

Children should keep scheduled doctor’s visits because their Isentress dosage should be adjusted as they get older, grow or gain weight. Their doctor may also want to prescribe the 400 mg tablet when they are able to swallow a tablet.

You can take this medicine with or without food or drink.

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

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

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

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

4. **Possible side effects**
Like all medicines, Isentress can cause side effects, although not everybody gets them.

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

See a doctor immediately, if you notice any of the side effects above.
Common: the following may affect up to 1 in 10 people
- decreased appetite
- trouble sleeping; abnormal dreams; nightmare; abnormal behaviour; feelings of deep sadness and unworthiness
- feeling dizzy; headache
- spinning sensation
- bloating; abdominal pain; diarrhoea; excessive gas in the stomach or bowels; feeling sick; vomiting; indigestion; belching
- certain kinds of rash (more often when used in combination with darunavir)
- tiredness, unusual tiredness or weakness; fever
- increased liver blood tests; abnormal white blood cells; increased fat levels in blood; increased level of enzyme from salivary glands or pancreas

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

Additional side effects in children and adolescents
- hyperactivity
Muscle pain, tenderness, or weakness have been reported during treatment with Isentress.

In clinical studies, cancers were observed in patients receiving Isentress at a rate similar to that observed in the patients receiving other HIV treatment that doesn’t contain Isentress.

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

5. **How to store Isentress**

- Keep this medicine out of the sight and reach of children.
- Do not take this medicine after the expiry date which is stated on the bottle after EXP. The expiry date refers to the last day of that month.
- Store in the original package with the bottle tightly closed. Keep the drying agent in the bottle to protect from moisture.
- Prior to breaking the seal, this product does not require any special storage conditions.

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

6. **Contents of the pack and other information**

**What Isentress contains**
The active substance is raltegravir. Each chewable tablet contains 25 mg of raltegravir (as potassium).

The other ingredients are: hydroxypropyl cellulose, sucralose, saccharin sodium, sodium citrate dihydrate, mannitol, yellow iron oxide, monoammonium glycyrrhizinate, sorbitol (E420), fructose, natural and artificial flavours (orange, banana, and masking), aspartame (E951), crospovidone Type A, magnesium stearate, sodium stearyl fumarate, ethylcellulose 20 cP, ammonium hydroxide, medium chain triglycerides, oleic acid, hypromellose 2910/6cP and macrogol/PEG 400

**What Isentress looks like and contents of the pack**
The orange-banana flavoured chewable tablet is round and pale yellow, marked with the Merck logo on one side and 473 on the other side.
One pack size is available: 1 bottle with 60 tablets.

**Marketing Authorisation Holder and Manufacturer**

<table>
<thead>
<tr>
<th>Marketing Authorisation Holder</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td>Merck Sharp &amp; Dohme Ltd.</td>
<td>Merck Sharp &amp; Dohme B. V.</td>
</tr>
<tr>
<td>Hertford Road, Hoddesdon</td>
<td>Waarderweg 39</td>
</tr>
<tr>
<td>Hertfordshire EN11 9BU</td>
<td>2031 BN Haarlem</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>The Netherlands</td>
</tr>
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</table>
For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

**BE**
MSD Belgium BVBA/SPRL
Tél/Tel: 0800 38 693 (+32(0)27766211)
d poc_belux@merck.com

**BG**
Мерк Шарп и Доум България ЕООД
Tel.: +359 2 819 3737
info-msdbg@merck.com

**CZ**
Merck Sharp & Dohme s.r.o.
Tel.: +420 233 010 111
d poc_czechslovak@merck.com

**DK**
MSD Danmark ApS
Tlf: +45 4482 4000
dkmail@merck.com

**DE**
MSD SHARP & DOHME GMBH
Tel: 0800 673 673 673 (+49 (0) 89 4561 2612)
e-mail@msd.de

**EE**
Merck Sharp & Dohme OÜ
Tel.: +372 6144 200
msdeesti@merck.com

**EL**
MSD Α.Φ.Β.Ε.Ε.
Τηλ: + 30 210 98 97 300
d poc_greece@merck.com

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

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

**HR**
Merck Sharp & Dohme d.o.o.
Tel: + 385 1 6611 333
croatia_info@merck.com

**HU**
MSD Pharma Hungary Kft.
Tel.: +36 1 888 53 00
hungary_msd@merck.com

**MT**
Merck Sharp & Dohme Cyprus Limited
Tel: 8007 4433 (+356 99917558)
malta_info@merck.com

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

**NO**
MSD (Norge) AS
Tlf: +47 32 20 73 00
msdnorge@msd.no

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

**PT**
Merck Sharp & Dohme, Lda
Tel: +351 21 4465700
clic@merck.com

**UK**
UAB Merck Sharp & Dohme
Tel.: +370 5 278 02 47
msd_lietuva@merck.com

**BE**
MSD Belgium BVBA/SPRL
Tél/Tel: +32(0)27766211
d poc_belux@merck.com

**BG**
Мерк Шарп и Доум България ЕООД
Tel.: +359 2 819 3737
info-msdbg@merck.com

**CZ**
Merck Sharp & Dohme s.r.o.
Tel.: +420 233 010 111
d poc_czechslovak@merck.com

**DK**
MSD Danmark ApS
Tlf: +45 4482 4000
dkmail@merck.com

**DE**
MSD SHARP & DOHME GMBH
Tel: 0800 673 673 673 (+49 (0) 89 4561 2612)
e-mail@msd.de

**EE**
Merck Sharp & Dohme OÜ
Tel.: +372 6144 200
msdeesti@merck.com

**EL**
MSD Α.Φ.Β.Ε.Ε.
Τηλ: + 30 210 98 97 300
d poc_greece@merck.com

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

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

**HR**
Merck Sharp & Dohme d.o.o.
Tel: + 385 1 6611 333
croatia_info@merck.com

**HU**
MSD Pharma Hungary Kft.
Tel.: +36 1 888 53 00
hungary_msd@merck.com

**MT**
Merck Sharp & Dohme Cyprus Limited
Tel: 8007 4433 (+356 99917558)
malta_info@merck.com

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

**NO**
MSD (Norge) AS
Tlf: +47 32 20 73 00
msdnorge@msd.no

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

**UK**
UAB Merck Sharp & Dohme
Tel.: +370 5 278 02 47
msd_lietuva@merck.com
This leaflet was last revised in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.
Package leaflet: Information for the user

Isentress 100 mg granules for oral suspension
raltegravir

If you are the parent or carer of a child taking Isentress, please read this information carefully. Read all of this leaflet carefully before you start giving this medicine to your child because it contains important information.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet
1. What Isentress is and what it is used for
2. What you need to know before you take Isentress
3. How to take Isentress
4. Possible side effects
5. How to store Isentress
6. Contents of the pack and other information
7. Instructions for use – see the end of this Package Leaflet for how to prepare and give the medicine

1. What Isentress is and what it is used for

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

How Isentress works
The virus produces an enzyme called HIV integrase. This helps the virus to multiply in the cells in your body. Isentress stops this enzyme from working. When used with other medicines, Isentress may reduce the amount of HIV in your blood (this is called your "viral load") and increase your CD4-cell count (a type of white blood cells that plays an important role in maintaining a healthy immune system to help fight infection). Reducing the amount of HIV in the blood may improve the functioning of your immune system. This means your body may fight infection better. Isentress may not have these effects in all patients.

Isentress is not a cure for HIV infection.

When Isentress should be used
Isentress is used to treat adults, adolescents, children, toddlers and infants 4 weeks of age and older who are infected by HIV. Your doctor has prescribed Isentress to help control your HIV infection.

2. What you need to know before you take Isentress

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

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

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

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

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

Passing HIV to others
HIV infection is spread by contact with blood or sexual contact with a person with HIV. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.

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

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

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

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

Children and adolescents
Isentress is not for use in infants below 4 weeks of age.
Other medicines and Isentress
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines with or without a prescription.

Isentress might interact with other medicines.
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take:
- antacids. It is not recommended to take Isentress with certain antacids (those containing aluminum and/or magnesium). Talk to your doctor about other antacids you can take.
- rifampicin (a medicine used to treat some infections such as tuberculosis), as it may decrease your levels of Isentress. Your doctor may consider increasing your dose of Isentress if you are taking rifampicin.

Taking Isentress with food and drink
See section 3.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- Isentress is not recommended in pregnancy because it has not been studied in pregnant women.
- Women with HIV should not breast-feed their infants because babies can be infected with HIV through their breast milk. Talk with your doctor about the best way to feed your baby.

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

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

Isentress granules for oral suspension contain fructose, sorbitol and sucrose
If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.
Sweeteners contained in this medicine may be harmful to teeth.

3. How to take Isentress
You should always give this medicine to your child exactly as their doctor, pharmacist or nurse has told you. You should check with your child’s doctor, pharmacist or nurse if you are not sure. Isentress must be used in combination with other medicines for HIV.
- It is very important that this medicine is taken exactly as directed.
- See the “Instructions for Use” section at the end of this Package Leaflet for how to prepare and give a dose of Isentress granules for oral suspension.
- Granules for oral suspension should be given to your child within 30 minutes of mixing.

How much to take
Dose for infants and toddlers from 4 weeks of age and weighing at least 3 kg
The doctor will work out the right dose of granules for oral suspension based on the age and weight of the infant or toddler. The doctor will tell you how much of the oral suspension the infant or toddler must take.
- Do not change the dose or stop giving this medicine to your child without first talking to their doctor, pharmacist or nurse.

Isentress is also available in a 400 mg tablet for use in adults, adolescents and children weighing at least 25 kg and able to swallow a tablet; and a chewable tablet for children weighing at least 11 kg.
- Do not switch between the granules for oral suspension, chewable tablet or 400 mg tablet without first talking to your child’s doctor, pharmacist or nurse.
• Children should keep scheduled doctor’s visits because their Isentress dosage should be adjusted as they get older, grow or gain weight. Their doctor may also want to prescribe the chewable tablet when they are able to chew a tablet.

You can take this medicine with or without food or drink.

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

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

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

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

### 4. Possible side effects
Like all medicines, Isentress can cause side effects, although not everybody gets them.

**Serious side effects** – these are uncommon (may affect up to 1 in 100 people)

See a doctor immediately, if you notice any of the following:
• herpes infections including shingles
• anaemia including due to low iron
• signs and symptoms of infection or inflammation
• mental disorder
• suicide intention or attempt
• stomach inflammation
• inflammation of liver
• liver failure
• allergic rash
• certain kinds of kidney problems
• drug ingestion in quantities greater than recommended

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

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

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

Additional side effects in children and adolescents
- hyperactivity

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In clinical studies, cancers were observed in patients receiving Isentress at a rate similar to that observed in the patients receiving other HIV treatment that doesn’t contain Isentress.
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If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Isentress

- Keep this medicine out of the sight and reach of children.
- Do not take this medicine after the expiry date which is stated on the carton and sachet after EXP. The expiry date refers to the last day of that month.
- Granules for oral suspension should be given to the patient within 30 minutes of mixing.
- Store in the original package in order to protect from moisture.
- This product does not require any special storage conditions.

See the Instructions for use section of this Patient Leaflet for the right way to dispose of your leftover medicine.

6. Contents of the pack and other information

What Isentress contains
The active substance is raltegravir. Each single-use sachet of granules for oral suspension contains 100 mg of raltegravir (as potassium).

The other ingredients are: hydroxypropyl cellulose, sucralose, mannitol, monoammonium glycyrrhizinate, sorbitol (E420), fructose, banana flavour, sucrose, crospovidone Type A, magnesium stearate, ethylcellulose 20 cP, ammonium hydroxide, medium chain triglycerides, oleic acid, hypromellose 2910/6cP, macrogol/PEG 400, microcrystalline cellulose and carmellose sodium.

What Isentress looks like and contents of the pack
The banana flavoured granules for oral suspension is a white to off-white powder that may contain yellow or beige to tan particles in a single-use sachet.
One pack size is available: 1 carton with 60 sachets, two 5 ml dosing syringes and two mixing cups.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Merck Sharp & Dohme Ltd.
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

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

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BE
MSD Belgium BVBA/SPRL
Tél/Tel: 0800 38 693 (+32(0)27766211)
d poc_belux@merck.com

LT
UAB Merck Sharp & Dohme
Tel.: +370 5 278 02 47
msd_lietuva@merck.com

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

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| HU      | MSD Pharma Hungary Kft.  
Tel.: +36 1 888 53 00  
hungary_msd@merck.com |
| DK      | MSD Danmark ApS  
Tel: +45 4482 4000  
dkmail@merck.com |
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Tel: 0800 673 673 673 (+49 (0) 89 4561 2612)  
e-mail@msd.de |
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Tel: 0800 9999000 (+31 23 5153153)  
medicalinfo.nl@merck.com |
| EE      | Merck Sharp & Dohme OÜ  
Tel.: +372 6144 200  
msdeesti@merck.com |
| NO      | MSD (Norge) AS  
Tel: +47 32 20 73 00  
msdnorge@msd.no |
| EL      | Merck Sharp & Dohme de España, S.A.  
Tel: +34 91 321 06 00  
msd_info@merck.com |
| AT      | Merck Sharp & Dohme Ges.m.b.H.  
Tel: +43 (0) 1 26 044  
msd-medizin@merck.com |
| ES      | Merck Sharp & Dohme de España, S.A.  
Tel: +34 91 321 06 00  
msd_info@merck.com |
| FR      | MSD France  
Tél: + 33 (0) 1 80 46 40 40 |
| HR      | Merck Sharp & Dohme d.o.o.  
Tel: + 385 1 6611 333  
croatia_info@merck.com |
| IE      | Merck Sharp & Dohme Ireland (Human Health) Limited  
Tel: +353 (0)1 2998700  
medinfo_ireland@merck.com |
| IS      | Vistor hf.  
Sími: +354 535 7000 |
| IT      | MSD Italia S.r.l.  
Tel: +39 06 3619111  
medicalinformation.it@merck.com |
| FI      | MSD Finland Oy  
Puh/Tel: +358 (0) 9 804 650  
info@msd.fi |
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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.
Instructions for Use

In each pack

Mixing cups (2) Dosing syringes (2)

Medicine (60 sachets)

Dosing syringe

Tip Barrel Plunger
These instructions show you how to prepare and give a dose of Isentress. Make sure that you read and understand these instructions before giving this medicine to your child. Your child’s doctor will decide the right dose based on your child’s age and weight.

Always give your child the medicine within 30 minutes of mixing.

What is in each Isentress pack:
- 2 mixing cups with joined lids – which are to be used more than once
- 2 dosing syringes (5 ml) – which are to be used more than once
- 60 sachets - each sachet contains medicine for a single dose.

For each dose of Isentress you will need the following:
- 1 mixing cup with joined lid
- 1 dosing syringe (5 ml)
- 1 sachet containing the medicine
- drinking water (not included in the pack).

Preparing the medicine
1. Fill the mixing cup with drinking water.
2. Pull 5 ml of water into the dosing syringe:
   - put the syringe tip into the water in the mixing cup
   - pull back the plunger to the 5 ml mark.
3. Pour away the remaining water from the mixing cup.
4. Add the 5 ml of water from the dosing syringe back into the mixing cup by pushing the plunger down.
5. Open 1 sachet of the medicine and pour the entire contents into the mixing cup.
6. Close the lid to seal the mixing cup. It will snap shut.
7. Swirl the mixing cup gently to mix for 30 to 60 seconds. Do not turn the mixing cup upside down. The liquid should look cloudy.

8. Open the mixing cup. Put the syringe tip into the liquid and pull back the plunger to the amount (ml) of your child’s dose.

Giving the medicine
9. Place the dosing syringe in your child’s mouth towards the cheek and gently push the plunger down to release the medicine.
   - Always give the medicine within 30 minutes of mixing.
Throwing away leftover medicine
10. Pour any leftover medicine from the mixing cup into a rubbish bag.

Cleaning the cup and syringe
11. Wash the mixing cup and dosing syringe under the tap with warm water and dishwashing soap. Rinse with water and leave to dry in the air. Once they are dry, place the mixing cup and dosing syringe back in the carton containing the sachets.

If you have any questions on how to prepare or give a dose of Isentress, talk to your doctor, pharmacist or nurse.