

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DUTREBIS 150 mg/300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg of lamivudine and 300 mg of raltegravir (as potassium).

Excipient with known effect: Each tablet contains 39.70 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Green, oval tablet, marked with "144" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DUTREBIS is indicated in combination with other anti-retroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adults, adolescents, and children from the age of 6 years and weighing at least 30 kg without present or past evidence of viral resistance to antiviral agents of the InSTI (Integrase Strand Transfer Inhibitor) and NRTI (Nucleoside Reverse Transcriptase Inhibitor) classes (see sections 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

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

Posology

DUTREBIS should be used in combination with other active anti-retroviral therapy (ART) (see sections 4.4 and 5.1).

Adults, adolescents, and children (6 through 11 years of age weighing at least 30 kg)

The recommended dosage is one tablet (150 mg lamivudine/300 mg raltegravir) twice daily.

Raltegravir 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 SmPCs for additional dosing information.

Lamivudine is also available as an oral solution for children over three months of age and who weigh less than 14 kg or for patients who are unable to swallow tablets.

The maximum dose is one tablet twice daily.

Advice on missed doses

If DUTREBIS is missed within 6 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of DUTREBIS as soon as possible. If this is noticed later than 6 hours of the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule.

Elderly

There is limited information regarding the use of lamivudine and raltegravir in the elderly (see section 5.2). Therefore DUTREBIS should be used with caution in this population. Because lamivudine is substantially excreted by the kidney and older people are more likely to have decreased renal function, renal function should be monitored. A reduction in renal function may necessitate switching DUTREBIS to a regimen of the individual components (lamivudine and raltegravir). Please refer to the SmPC for the individual components of DUTREBIS for dosing instructions.

Renal impairment

DUTREBIS should not be given in patients with a creatinine clearance of <50 ml/min. Renal function should be monitored in patients more likely to have decreased renal function. If creatinine clearance decreases to <50 ml/min, DUTREBIS should be switched to a regimen of the individual components (lamivudine and raltegravir). Please refer to the SmPC for the individual components of DUTREBIS for dosing instructions. Because the extent to which DUTREBIS may be dialyzable is unknown, dosing before a dialysis session should be avoided (see sections 4.2 and 5.2).

Hepatic impairment

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

Paediatric population

DUTREBIS should not be used in children below 6 years of age. Dosing in children less than 6 years of age and those weighting less than 30 kg requires weight based dose adjustments for the individual components of DUTREBIS. Please refer to the SmPC for the individual components of DUTREBIS for dosing instructions. Currently available data are described in sections 5.1 and 5.2.

Method of administration

Oral use.

DUTREBIS tablets can be administered with or without food.

The tablets should be swallowed whole, without crushing or chewing.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

DUTREBIS is not recommended for use as monotherapy.

Depression

Depression, including suicidal ideation and behaviours, has been reported with raltegravir, particularly in patients with a pre-existing history of depression or psychiatric illness. Caution should be used when administering DUTREBIS in patients with a pre-existing history of depression or psychiatric illness.

Renal impairment

DUTREBIS should not be given in patients with a creatinine clearance of <50 ml/min. Renal function should be monitored in patients more likely to have decreased renal function. If creatinine clearance decreases to <50 ml/min, DUTREBIS should be switched to a regimen of the individual components (lamivudine and raltegravir) (see section 4.2). Please refer to the SmPC for the individual components of DUTREBIS for dosing instructions.

Opportunistic infections

Patients receiving lamivudine or any other ART may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

Transmission of HIV

Patients should be advised that current antiretroviral therapy does not cure HIV and has not been proven to prevent the risk of 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.

Virologic failure and development of resistance

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, DUTREBIS should be administered with another active ART to minimise the potential for virological failure and the development of resistance (see section 5.1).

Pancreatitis

Cases of pancreatitis have occurred rarely with lamivudine. However, it is not clear whether these cases were due to the ART or to the underlying HIV disease. Treatment with DUTREBIS should be stopped immediately if clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur.

Lactic acidosis

Lactic acidosis, usually associated with hepatomegaly and hepatic steatosis, has been reported with the use of nucleoside reverse transcriptase inhibitors (NRTIs), such as lamivudine. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness).

Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure, or renal failure.

Lactic acidosis generally occurred after a few or several months of treatment.

Treatment with NRTIs should be discontinued in the setting of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Caution should be exercised when administering NRTIs to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk should be followed closely.

Hepatic impairment

No dosage adjustment for DUTREBIS is required for patients with mild to moderate hepatic impairment. The safety and efficacy of lamivudine and raltegravir have not been established in patients with severe underlying liver disorders. Therefore, DUTREBIS 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 CART 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 HIV and hepatitis B or C virus co-infection

Patients with chronic hepatitis B or C treated with ART are at an increased risk for severe and potentially fatal hepatic adverse reactions. Physicians should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with HBV. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products. If DUTREBIS is discontinued in patients co-infected with hepatitis B virus, periodic monitoring of liver function tests and markers of HBV replication is recommended, as withdrawal of lamivudine may result in an acute exacerbation of hepatitis.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Lipodystrophy

CART has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PIs) and lipodystrophy and NRTIs has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of ART and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral 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 few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis carinii* pneumonia. 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.

Mitochondrial dysfunction

Nucleoside and nucleotide reverse transcriptase inhibitors have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside reverse transcriptase inhibitors. The main adverse reactions reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide reverse transcriptase inhibitors, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms.

Myopathy and rhabdomyolysis

Myopathy and rhabdomyolysis have been reported with raltegravir. DUTREBIS should be used 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).

Co-administration of other medicinal products

DUTREBIS should not be taken with any other medicinal products containing lamivudine, raltegravir or medicinal products containing emtricitabine.

The combination of lamivudine with cladribine is not-recommended (see section 4.5).

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

DUTREBIS should not be co-administered with rifampicin due to reduced plasma concentrations of raltegravir (see section 4.5); the impact on the efficacy of raltegravir is unknown. If rifampicin administration cannot be avoided, DUTREBIS may be switched to a regimen of the individual components (lamivudine and raltegravir). Please refer to the SmPC for the individual components of DUTREBIS for dosing instructions.

In addition, caution should also be used when co-administering DUTREBIS with other strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1.

Severe skin and hypersensitivity reactions

Severe, potentially life-threatening, and fatal skin reactions have been reported in patients taking raltegravir, in most cases concomitantly with other medicinal products associated with these reactions. These include cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. Hypersensitivity reactions have also been reported and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure. Discontinue DUTREBIS 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 DUTREBIS treatment or other suspect agents after the onset of severe rash may result in a life-threatening reaction.

Rash

Rash occurred more commonly in treatment-experienced patients receiving regimens containing raltegravir + darunavir compared to patients receiving raltegravir without darunavir or darunavir without raltegravir (see section 4.8).

Lactose

DUTREBIS 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

As DUTREBIS contains lamivudine and raltegravir, any interactions that have been identified with these agents individually, may occur with DUTREBIS. Interaction studies with these agents have only been performed in adults.

Lamivudine metabolism does not involve CYP3A, making interactions with medicinal products metabolised by this system (e.g. PIs) unlikely.

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.

Lamivudine is eliminated mainly by active renal secretion via the organic cationic transport system. The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when the main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other medicinal products (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine. The NRTIs (e.g. didanosine, zidovudine) are not eliminated by this mechanism and are unlikely to interact with lamivudine.

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.

In a drug interaction study with DUTREBIS and etravirine, there was no clinically meaningful drug interaction between raltegravir and etravirine, with respect to raltegravir. No dosage adjustment is necessary when these agents are given together.

Administration of trimethoprim/sulfamethoxazole 160 mg/800 mg results in a 40 % increase in lamivudine exposure, because of the trimethoprim component; the sulfamethoxazole component did not interact. However, unless the patient has renal impairment, no dosage adjustment of DUTREBIS is necessary (see section 4.2). Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. When concomitant administration of DUTREBIS is warranted, patients should be monitored clinically. Co-administration of DUTREBIS with high doses of co-trimoxazole for the treatment of *Pneumocystis carinii* pneumonia (PCP) and toxoplasmosis should be avoided.

A modest increase in C_{max} (28 %) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) is not significantly altered. Zidovudine has no effect on the pharmacokinetics of lamivudine (see section 5.2).

In vitro lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine. Therefore, the concomitant use of DUTREBIS with cladribine is not recommended (see section 4.4).

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

DUTREBIS should not be used when co-administered with rifampicin. Rifampicin reduces plasma levels of raltegravir; the impact on the efficacy of raltegravir is unknown. However, if co-administration with rifampicin is unavoidable, DUTREBIS may be switched to a regimen of the individual components (lamivudine and raltegravir). Please refer to the SmPC for the individual components of DUTREBIS for dosing instructions. Given that raltegravir is metabolised primarily via UGT1A1, caution should also be used when co-administering DUTREBIS with other strong inducers of UGT1A1. 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 DUTREBIS.

Co-administration of DUTREBIS 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 studies, 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 of DUTREBIS is required.

Co-administration of DUTREBIS with antacids containing divalent metal cations may reduce raltegravir absorption by chelation, resulting in a decrease of raltegravir plasma levels. Taking an aluminium and magnesium antacid within 6 hours of raltegravir administration significantly decreased raltegravir plasma levels. Therefore, co-administration of DUTREBIS with aluminium and/or magnesium containing antacids is not recommended. Co-administration of raltegravir with a calcium carbonate antacid decreased raltegravir plasma levels; however, this interaction is not considered clinically meaningful. Therefore, when DUTREBIS is co-administered with calcium carbonate containing antacids no dose adjustment is required.

Co-administration of DUTREBIS 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 studies taking proton pump inhibitors or H2 antagonists were comparable with those who were not taking these antacids. Therefore no dose adjustment of DUTREBIS is required with use of proton pump inhibitors or H2 antagonists.

Interactions between the components of DUTREBIS and co-administered medicinal products are listed in Table 1 below.

Table 1
Pharmacokinetic Interaction Data between the Individual Components of DUTREBIS and Other Medicinal Products

Medicinal products by therapeutic area	Interaction (mechanism, if known)	Recommendations concerning co-administration with DUTREBIS
ANTI-RETROVIRAL		
<i>Protease inhibitors (PI)</i>		
atazanavir /ritonavir /raltegravir (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 41 % raltegravir C _{12hr} ↑ 77 % raltegravir C _{max} ↑ 24 % (UGT1A1 inhibition)	No dose adjustment required for DUTREBIS.
atazanavir /ritonavir /lamivudine	Interaction not studied	
tipranavir /ritonavir /raltegravir (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 24 % raltegravir C _{12hr} ↓ 55 % raltegravir C _{max} ↓ 18 % (UGT1A1 induction)	No dose adjustment required for DUTREBIS.
tipranavir /ritonavir /lamivudine	Interaction not studied	

Medicinal products by therapeutic area	Interaction (mechanism, if known)	Recommendations concerning co-administration with DUTREBIS
<i>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</i>		
efavirenz /raltegravir (raltegravir 400 mg Single Dose)	raltegravir AUC ↓ 36 % raltegravir C _{12hr} ↓ 21 % raltegravir C _{max} ↓ 36 % (UGT1A1 induction)	No dose adjustment required for DUTREBIS.
efavirenz /lamivudine	Interaction not studied	
etravirine /raltegravir (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 DUTREBIS or etravirine.
etravirine /DUTREBIS (DUTREBIS 150 mg lamivudine/300 mg raltegravir)	raltegravir AUC ↑ 8 % raltegravir C _{max} ↑ 20 % raltegravir C _{12hr} ↓ 14 %	
<i>Nucleoside/tide reverse transcriptase inhibitors (NRTIs)</i>		
emtricitabine	DDI not studied	DUTREBIS is not recommended for use in combination with emtricitabine containing products, since both lamivudine (in DUTREBIS) and emtricitabine are cytidine analogues (i.e. risk for intracellular interactions, (see section 4.4).
tenofovir /raltegravir (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 DUTREBIS or tenofovir disoproxil fumarate.
tenofovir /lamivudine	Interaction not studied	
zidovudine /lamivudine	lamivudine PK ↔ zidovudine C _{max} ↑ 28 % zidovudine AUC ↔	No dose adjustment required for DUTREBIS or zidovudine.
zidovudine /raltegravir	Interaction not studied	
cladribine /raltegravir	Interaction not studied	

Medicinal products by therapeutic area	Interaction (mechanism, if known)	Recommendations concerning co-administration with DUTREBIS
cladribine /lamivudine	Possible interaction between lamivudine and cladribine due to inhibition of intracellular phosphorylation of cladribine by lamivudine.	DUTREBIS with cladribine is not recommended.
<i>CCR5 inhibitors</i>		
maraviroc /raltegravir (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 37 % raltegravir C _{12hr} ↓ 28 % raltegravir C _{max} ↓ 33 % (mechanism of interaction unknown) maraviroc AUC ↓ 14 % maraviroc C _{12hr} ↓ 10 % maraviroc C _{max} ↓ 21 %	No dose adjustment required for DUTREBIS or maraviroc.
maraviroc /lamivudine	Interaction not studied	
HCV ANTIVIRALS		
<i>NS3/4A protease inhibitors (PI)</i>		
boceprevir /raltegravir (raltegravir 400 mg Single Dose)	raltegravir AUC ↑ 4 % raltegravir C _{12hr} ↓ 25 % raltegravir C _{max} ↑ 11 % boceprevir AUC ↓ 2 % boceprevir C _{8hr} ↓ 26 % boceprevir C _{max} ↓ 4 % (mechanism of interaction unknown)	No dose adjustment required for DUTREBIS or boceprevir.
boceprevir /lamivudine	Interaction not studied	
ANTIMICROBIALS		
<i>Antimycobacterial</i>		
rifampicin /raltegravir (raltegravir 400 mg Single Dose)	raltegravir AUC ↓ 40 % raltegravir C _{12hr} ↓ 61 % raltegravir C _{max} ↓ 38 % (UGT1A1 induction)	Co-administration of rifampicin with DUTREBIS is not recommended. If co-administration with rifampicin is unavoidable, DUTREBIS may be switched to a regimen of the individual components (lamivudine and raltegravir). Please refer to the SmPC for the individual components of DUTREBIS for dosing instructions (see section 4.4).
rifampicin /lamivudine	Interaction not studied	
trimethoprim /sulfamethoxazole /raltegravir	Interaction not studied	No dosage adjustment of DUTREBIS or trimethoprim

Medicinal products by therapeutic area	Interaction (mechanism, if known)	Recommendations concerning co-administration with DUTREBIS
trimethoprim /sulfamethoxazole /lamivudine	lamivudine AUC ↑40 % trimethoprim PK ↔ sulfamethoxazole PK ↔	/sulfamethoxazole is necessary, unless the patient has renal impairment (see section 4.2). Co-administration of DUTREBIS with high doses of co-trimoxazole for the treatment of <i>Pneumocystis carinii</i> pneumonia (PCP) and toxoplasmosis should be avoided.
SEDATIVE		
midazolam /raltegravir (raltegravir 400 mg Twice Daily)	midazolam AUC ↓ 8 % midazolam C _{max} ↑ 3 %	No dosage adjustment required for DUTREBIS or midazolam.
midazolam /lamivudine	Interaction not studied	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 (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 49 % raltegravir C _{12 hr} ↓ 63 % raltegravir C _{max} ↓ 44 % <u>2 hours before raltegravir</u> raltegravir AUC ↓ 51 % raltegravir C _{12 hr} ↓ 56 % raltegravir C _{max} ↓ 51 % <u>2 hours after raltegravir</u> raltegravir AUC ↓ 30 % raltegravir C _{12 hr} ↓ 57 % raltegravir C _{max} ↓ 24 % <u>6 hours before raltegravir</u> raltegravir AUC ↓ 13 % raltegravir C _{12 hr} ↓ 50 % raltegravir C _{max} ↓ 10 % <u>6 hours after raltegravir</u> raltegravir AUC ↓ 11 % raltegravir C _{12 hr} ↓ 49 % raltegravir C _{max} ↓ 10 % (chelation of metal cations)	Aluminium and magnesium containing antacids reduce raltegravir plasma levels. Co-administration of DUTREBIS with aluminium and/or magnesium containing antacids is not recommended.

Medicinal products by therapeutic area	Interaction (mechanism, if known)	Recommendations concerning co-administration with DUTREBIS
aluminium and magnesium hydroxide antacid /lamivudine	Interaction not studied	
calcium carbonate antacid /raltegravir (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 DUTREBIS.
calcium carbonate antacid /lamivudine	Interaction not studied	
H2 BLOCKERS AND PROTON PUMP INHIBITORS		
omeprazole /raltegravir (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 37 % raltegravir C _{12 hr} ↑ 24 % raltegravir C _{max} ↑ 51 % (increased solubility)	No dose adjustment required for DUTREBIS.
omeprazole /lamivudine	Interaction not studied	
famotidine /raltegravir (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 44 % raltegravir C _{12 hr} ↑ 6 % raltegravir C _{max} ↑ 60 % (increased solubility)	No dose adjustment required for DUTREBIS.
famotidine /lamivudine	Interaction not studied	
HORMONAL CONTRACEPTIVES		
Ethinyl Estradiol Norelgestromin /raltegravir (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 DUTREBIS or hormonal contraceptives (oestrogen- and/or progesterone-based).
Ethinyl Estradiol Norelgestromin /lamivudine	Interaction not studied	
OPIOID ANALGESICS		
methadone /raltegravir (raltegravir 400 mg Twice Daily)	methadone AUC ↔ methadone C _{max} ↔	No dose adjustment required for DUTREBIS or methadone.
methadone /lamivudine	Interaction not studied	

4.6 Fertility, pregnancy and lactation

Pregnancy

DUTREBIS should not be used during pregnancy.

There are no adequate data from the use of raltegravir in pregnant women; however, a large amount of data on pregnant women who were administered lamivudine (more than 1,000 exposed outcomes) indicate no malformative toxicity. Studies with raltegravir in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

For patients co-infected with hepatitis who are being treated with DUTREBIS and subsequently become pregnant, consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of DUTREBIS.

Mitochondrial dysfunction

Nucleoside and nucleotide reverse transcriptase inhibitors have been demonstrated in vitro and in vivo to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in infants exposed in utero and/or post-natally to nucleoside reverse transcriptase inhibitors (see section 4.4).

Anti-retroviral Pregnancy Registry

To monitor maternal-foetal outcomes in patients inadvertently administered DUTREBIS 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 anti-retroviral 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

Breastfeeding is not recommended while taking DUTREBIS. 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.

Following oral administration, lamivudine was excreted in breast milk at similar concentrations to those found in serum.

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.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Clinical studies in patients have not been specifically performed with DUTREBIS. The safety profile of DUTREBIS is based on the safety data from the individual components of DUTREBIS (lamivudine and raltegravir).

The most common adverse reactions reported during treatment with lamivudine are headache, nausea, malaise, fatigue, nasal signs and symptoms, diarrhoea and cough. The most frequently reported adverse reactions during treatment with raltegravir were headache and nausea.

Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues (see section 4.4).

Cancers were reported in treatment-experienced and treatment-naïve patients who initiated raltegravir in conjunction with other antiretroviral agents. The types and rates of specific cancers were those expected in a highly immunodeficient population. The risk of developing cancer in these studies was similar in the groups receiving raltegravir and in the groups receiving comparators.

Grade 2-4 creatine kinase laboratory abnormalities were observed in subjects treated with raltegravir. Myopathy and rhabdomyolysis have been reported. Use DUTREBIS 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).

CART has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

CART has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (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 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 CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. 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 (see section 4.4).

Tabulated list of adverse reactions

The following adverse reactions have been reported during therapy for HIV disease with lamivudine and/or raltegravir (alone or in combination with other ART).

The adverse reactions seen in clinical studies and in post-marketing experience are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$).

System Organ Class	Frequency	Lamivudine and/or Raltegravir (alone or in combination with other ART)*
Infections and infestations	uncommon	genital herpes, folliculitis, gastroenteritis, herpes simplex, herpes virus infection, herpes zoster, influenza, lymph node abscess, molluscum contagiosum, nasopharyngitis, upper respiratory tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	uncommon	skin papilloma
Blood and lymphatic system disorders	uncommon	iron deficiency anaemia, lymph node pain, lymphadenopathy, neutropenia and anaemia (both occasionally severe), thrombocytopenia
	very rare	pure red cell aplasia
Immune system disorders	uncommon	immune reconstitution syndrome, drug hypersensitivity, hypersensitivity
Metabolism and nutrition disorders	common	decreased appetite
	uncommon	cachexia, diabetes mellitus, dyslipidaemia, hypercholesterolaemia, hyperglycaemia, hyperlipidaemia, hyperphagia, increased appetite, polydipsia, body fat disorder

System Organ Class	Frequency	Lamivudine and/or Raltegravir (alone or in combination with other ART)*
Psychiatric disorders	common	abnormal dreams, insomnia, nightmare, abnormal behaviour, depression
	uncommon	mental disorder, suicide attempt, anxiety, confusional state, depressed mood, major depression, middle insomnia, mood altered, panic attack, sleep disorder, suicidal ideation, suicidal behaviour (particularly in patients with a pre-existing history of psychiatric illness)
Nervous system disorders	common	dizziness, headache, psychomotor hyperactivity
	uncommon	amnesia, carpal tunnel syndrome, cognitive disorder, disturbance in attention, dizziness postural, dysgeusia, hypersomnia, hypoesthesia, lethargy, memory impairment, migraine, neuropathy peripheral, paraesthesia, somnolence, tension headache, tremor, poor quality sleep
Eye disorders	uncommon	visual impairment
Ear and labyrinth disorders	common	vertigo
	uncommon	tinnitus
Cardiac disorders	uncommon	palpitations, sinus bradycardia, ventricular extrasystoles
Vascular disorders	uncommon	hot flush, hypertension
Respiratory, thoracic and mediastinal disorders	common	cough, nasal congestion
	uncommon	dysphonia, epistaxis
Gastrointestinal disorders	common	abdominal distention, diarrhoea, flatulence, nausea, vomiting, dyspepsia, abdominal pain or cramps
	uncommon	gastritis, abdominal discomfort, abdominal pain upper, abdominal tenderness, anorectal discomfort, constipation, dry mouth, epigastric discomfort, erosive duodenitis, eructation, gastroesophageal reflux disease, gingivitis, glossitis, odynophagia, pancreatitis, peptic ulcer, rectal haemorrhage
Hepato-biliary disorders	uncommon	hepatitis, hepatic steatosis, hepatitis alcoholic, hepatic failure
Skin and subcutaneous	common	rash, alopecia

System Organ Class	Frequency	Lamivudine and/or Raltegravir (alone or in combination with other ART)*
tissue disorders	uncommon	acne, dermatitis acneiforme, dry skin, erythema, facial wasting, hyperhidrosis, lipoatrophy, lipodystrophy acquired, lipohypertrophy, night sweats, prurigo, pruritus, pruritus generalised, rash macular, rash maculo-papular, rash pruritic, skin lesion, urticaria, xeroderma, Stevens Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS)
	rare	angioedema
Musculoskeletal and connective tissue disorders	common	arthralgia, muscle disorders
	uncommon	arthritis, back pain, flank pain, musculoskeletal pain, myalgia, neck pain, osteopenia, pain in extremity, tendonitis, rhabdomyolysis
Renal and urinary disorders	uncommon	renal failure, nephritis, nephrolithiasis, nocturia, renal cyst, renal impairment, tubulointerstitial nephritis
Reproductive system and breast disorders	uncommon	erectile dysfunction, gynaecomastia, menopausal symptoms
General disorders and administration site conditions	common	asthenia, fatigue, malaise, fever
	uncommon	chest discomfort, chills, face oedema, fat tissue increased, feeling jittery, submandibular mass, oedema peripheral, pain
Investigations	common	atypical lymphocytes, elevations in liver enzymes (AST, ALT), blood triglycerides increased, lipase increased, blood pancreatic amylase increased
	uncommon	absolute neutrophil count decreased, alkaline phosphatase increased, blood albumin decreased, blood amylase increased, blood bilirubin increased, blood cholesterol increased, blood creatinine increased, blood glucose increased, blood urea nitrogen increased, creatine phosphokinase increased, fasting blood glucose increased, glucose urine present, high density lipoprotein increased, international normalised ratio increased, low density lipoprotein increased, platelet count decreased, red blood cells urine positive, waist circumference increased, weight increased, white blood cell count decreased
Injury, poisoning and procedural complications	uncommon	accidental overdose

*The adverse reaction data was collected based on each individual component of DUTREBIS.

Description of selected adverse reactions

For each of the following clinical adverse reactions reported for raltegravir 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 receiving raltegravir, rash, irrespective of causality, was more commonly observed with regimens containing raltegravir and darunavir compared to those containing raltegravir without darunavir or darunavir without raltegravir. Rash considered by the investigator to be drug-related occurred at similar rates. The exposure-adjusted rates of rash (all causality) were 10.9, 4.2, and 3.8 per 100 patient-years (PYR), respectively; and for drug-related rash were 2.4, 1.1, and 2.3 per 100 PYR, respectively. The rashes observed in clinical studies were mild to moderate in severity and did not result in discontinuation of therapy (see section 4.4).

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

In Phase III studies with raltegravir, 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 raltegravir in patients with hepatitis B and/or hepatitis C virus co-infection was similar to that in patients without hepatitis B and/or hepatitis C virus co-infection, although the rates of AST and ALT abnormalities were somewhat higher in the subgroup 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 raltegravir as compared to 11 %, 10 % and 9 % of all other subjects treated with raltegravir. At 240-weeks, in treatment-naïve patients, Grade 2 or higher laboratory abnormalities that represent a worsening Grade from baseline of AST, ALT or total bilirubin occurred in 22 %, 44 % and 17 %, respectively, of co-infected subjects treated with raltegravir as compared to 13 %, 13 % and 5 % of all other subjects treated with raltegravir.

The following adverse reactions were identified through post-marketing surveillance of raltegravir: 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

DUTREBIS should not be used in children below 6 years of age or in patients weighing less than 30 kg due to weight based dosing requirements in this patient population (see section 5.2).

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

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

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

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

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

Administration of lamivudine at very high dose levels in acute animal studies did not result in any organ toxicity. Limited data are available on the consequences of ingestion of acute overdoses in humans. No fatalities occurred, and the patients recovered. No specific signs or symptoms have been identified following such overdose.

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.

Since lamivudine is dialysable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied.

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

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; antivirals for treatment of HIV infections, combinations, ATC code: J05AR16

Mechanism of action

Lamivudine is a nucleoside reverse transcriptase inhibitor (NRTI) which has activity against human immunodeficiency virus (HIV) and hepatitis B virus (HBV).

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

Antiviral activity *in vitro*

In vitro data tend to suggest that the continuation of lamivudine in anti-retroviral regimen despite the development of M184V might provide residual anti-retroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established.

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

HIV-1 resistance to lamivudine involves the development of a M184V amino acid change close to the active site of the viral reverse transcriptase (RT). This variant arises both *in vitro* and in HIV-1 infected patients treated with lamivudine-containing antiretroviral therapy. M184V mutants display greatly reduced susceptibility to lamivudine and show diminished viral replicative capacity *in vitro*. *In vitro* studies indicate that zidovudine-resistant virus isolates can become zidovudine sensitive when they simultaneously acquire resistance to lamivudine. The clinical relevance of such findings remains, however, not well defined.

Cross-resistance conferred by the M184V RT is limited within the nucleoside inhibitor class of antiretroviral agents. Zidovudine and stavudine maintain their antiretroviral activities against lamivudine-resistant HIV-1. Abacavir maintains its antiretroviral activities against lamivudine resistant HIV-1 harbouring only the M184V mutation. The M184V RT mutant shows a <4-fold decrease in susceptibility to didanosine; the clinical significance of these findings is unknown. *In vitro* susceptibility testing has not been standardised and results may vary according to methodological factors.

Lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells *in vitro*.

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 efficacy with lamivudine

In clinical studies, lamivudine in combination with zidovudine has been shown to reduce HIV-1 viral load and increase CD4 cell count. Clinical end-point data indicate that lamivudine in combination with zidovudine, results in a significant reduction in the risk of disease progression and mortality.

Evidence from clinical studies shows that lamivudine plus zidovudine delays the emergence of zidovudine resistant isolates in individuals with no prior antiretroviral therapy.

Lamivudine has been widely used as a component of antiretroviral combination therapy with other antiretroviral agents of the same class (NRTIs) or different classes (PIs, non-nucleoside reverse transcriptase inhibitors, integrase inhibitors).

Multiple drug antiretroviral therapy containing lamivudine has been shown to be effective in antiretrovirally-naïve patients as well as in patients presenting with viruses containing the M184V mutations.

The relationship between *in vitro* susceptibility of HIV to lamivudine and clinical response to lamivudine-containing therapy remains under investigation.

Lamivudine has not been specifically investigated in HIV patients co-infected with HBV.

Clinical efficacy with raltegravir

The evidence of efficacy of raltegravir was based on the analyses of 96-week data from two randomised, double-blind, placebo-controlled studies, (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-naïve HIV-1 infected adult patients.

Treatment-experienced adult patients

BENCHMRK 1 and BENCHMRK 2 (multi-centre, randomised, double-blind, placebo-controlled studies) evaluated the safety and anti-retroviral activity of raltegravir 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 medicinal product 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 raltegravir 400 mg twice daily and placebo. Patients had prior exposure to a median of 12 anti-retrovirals for a median of 10 years. A median of 4 ARTs was used in OBT.

Results 48 week and 96 week analyses

Durable outcomes (Week 48 and Week 96) for patients on the recommended dose raltegravir 400 mg twice daily from the pooled studies BENCHMRK 1 and BENCHMRK 2 are shown in Table 2.

Table 2
Efficacy Outcome at Weeks 48 and 96

BENCHMRK 1 and 2 Pooled Parameter	48 Weeks		96 Weeks	
	Raltegravir400 mg twice daily + OBT (N = 462)	Placebo + OBT (N = 237)	Raltegravir400 mg twice daily + OBT (N = 462)	Placebo + OBT (N = 237)
Percent HIV-RNA < 400 copies/ml (95 % CI)				
All patients [†]	72 (68, 76)	37 (31, 44)	62 (57, 66)	28 (23, 34)
Baseline Characteristic [‡]				
HIV-RNA > 100,000 copies/ml	62 (53, 69)	17 (9, 27)	53 (45, 61)	15 (8, 25)
HIV-RNA ≤ 100,000 copies/ml	82 (77, 86)	49 (41, 58)	74 (69, 79)	39 (31, 47)
CD4-count ≤ 50 cells/mm ³	61 (53, 69)	21 (13, 32)	51 (42, 60)	14 (7, 24)
> 50 and ≤ 200 cells/mm ³	80 (73, 85)	44 (33, 55)	70 (62, 77)	36 (25, 48)
> 200 cells/mm ³	83 (76, 89)	51 (39, 63)	78 (70, 85)	42 (30, 55)
Sensitivity score (GSS) [§]				
0	52 (42, 61)	8 (3, 17)	46 (36, 56)	5 (1, 13)
1	81 (75, 87)	40 (30, 51)	76 (69, 83)	31 (22, 42)
2 and above	84 (77, 89)	65 (52, 76)	71 (63, 78)	56 (43, 69)
Percent HIV-RNA < 50 copies/ml (95 % CI)				
All patients [†]	62 (57, 67)	33 (27, 39)	57 (52, 62)	26 (21, 32)
Baseline Characteristic [‡]				
HIV-RNA > 100,000 copies/ml	48 (40, 56)	16 (8, 26)	47 (39, 55)	13 (7, 23)
HIV-RNA ≤ 100,000 copies/ml	73 (68, 78)	43 (35, 52)	70 (64, 75)	36 (28, 45)
CD4-count ≤ 50 cells/mm ³	50 (41, 58)	20 (12, 31)	50 (41, 58)	13 (6, 22)
> 50 and ≤ 200 cells/mm ³	67 (59, 74)	39 (28, 50)	65 (57, 72)	32 (22, 44)
> 200 cells/mm ³	76 (68, 83)	44 (32, 56)	71 (62, 78)	41 (29, 53)
Sensitivity score (GSS) [§]				
0	45 (35, 54)	3 (0, 11)	41 (32, 51)	5 (1, 13)
1	67 (59, 74)	37 (27, 48)	72 (64, 79)	28 (19, 39)
2 and above	75 (68, 82)	59 (46, 71)	65 (56, 72)	53 (40, 66)
Mean CD4 Cell Change (95 % CI), cells/mm³				
All patients [†]	109 (98, 121)	45 (32, 57)	123 (110, 137)	49 (35, 63)
Baseline Characteristic [‡]				
HIV-RNA > 100,000 copies/ml	126 (107, 144)	36 (17, 55)	140 (115, 165)	40 (16, 65)
HIV-RNA ≤ 100,000 copies/ml	100 (86, 115)	49 (33, 65)	114 (98, 131)	53 (36, 70)
CD4-count ≤ 50 cells/mm ³	121 (100, 142)	33 (18, 48)	130 (104, 156)	42 (17, 67)
> 50 and ≤ 200 cells/mm ³	104 (88, 119)	47 (28, 66)	123 (103, 144)	56 (34, 79)

BENCHMRK 1 and 2 Pooled Parameter	48 Weeks		96 Weeks	
	Raltegravir 400 mg twice daily + OBT (N = 462)	Placebo + OBT (N = 237)	Raltegravir 400 mg twice daily + OBT (N = 462)	Placebo + OBT (N = 237)
> 200 cells/mm ³	104 (80, 129)	54 (24, 84)	117 (90, 143)	48 (23, 73)
Sensitivity score (GSS) §				
0	81 (55, 106)	11 (4, 26)	97 (70, 124)	15 (-0, 31)
1	113 (96, 130)	44 (24, 63)	132 (111, 154)	45 (24, 66)
2 and above	125 (105, 144)	76 (48, 103)	134 (108, 159)	90 (57, 123)

† Non-completer is failure imputation: patients who discontinued prematurely are imputed as failure thereafter. Percent of patients with response and associated 95 % confidence interval (CI) are reported.

‡ For analysis by prognostic factors, virologic failures were carried forward for percent < 400 and 50 copies/ml. For mean CD4 changes, baseline-carry-forward was used for virologic failures.

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

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

Switch to raltegravir

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

Treatment-naïve adult patients

STARTMRK (multi-centre, randomised, double-blind, active-control study) evaluated the safety and anti-retroviral activity of raltegravir 400 mg twice daily vs. efavirenz 600 mg at bedtime, in a combination with emtricitabine (+) tenofovir, 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 raltegravir 400 mg twice daily and the group receiving efavirenz 600 mg at bedtime.

Results 48-week and 240-week analyses

With respect to the primary efficacy endpoint, the proportion (%) of patients achieving HIV RNA < 50 copies/ml at Week 48 was 241/280 (86.1 %) in the group receiving raltegravir and 230/281 (81.9 %) in the group receiving efavirenz. The treatment difference (raltegravir– efavirenz) was 4.2 % with an associated 95 % CI of (-1.9, 10.3) establishing that raltegravir is non-inferior to efavirenz (p-value for non-inferiority < 0.001). At Week 240, the treatment difference (raltegravir – efavirenz) was 9.5 % with an associated 95 % CI of (1.7, 17.3). Week 48 and Week 240 outcomes for patients on the recommended dose of raltegravir 400 mg twice daily from STARTMRK are shown in Table 3.

Table 3
Efficacy Outcome at Weeks 48 and 240

STARTMRK Study Parameter	48 Weeks		240 Weeks	
	Raltegravir 400 mg twice daily (N = 281)	Efavirenz 600 mg at bedtime (N = 282)	Raltegravir 400 mg twice daily (N = 281)	Efavirenz 600 mg at bedtime (N = 282)
Percent HIV-RNA < 50 copies/ml (95 % CI)				
All patients [†]	86 (81, 90)	82 (77, 86)	71 (65, 76)	61 (55, 67)
Baseline Characteristic [‡]				
HIV-RNA > 100,000 copies/ml	91 (85, 95)	89 (83, 94)	70 (62, 77)	65 (56, 72)
≤ 100,000 copies/ml	93 (86, 97)	89 (82, 94)	72 (64, 80)	58 (49, 66)
CD4-count ≤ 50 cells/mm ³	84 (64, 95)	86 (67, 96)	58 (37, 77)	77 (58, 90)
> 50 and	89 (81, 95)	86 (77, 92)	67 (57, 76)	60 (50, 69)
≤ 200 cells/mm ³				
> 200 cells/mm ³	94 (89, 98)	92 (87, 96)	76 (68, 82)	60 (51, 68)
Viral Subtype Clade B	90 (85, 94)	89 (83, 93)	71 (65, 77)	59 (52, 65)
Non-Clade B	96 (87, 100)	91 (78, 97)	68 (54, 79)	70 (54, 82)
Mean CD4 Cell Change (95 % CI), cells/mm³				
All patients [‡]	189 (174, 204)	163 (148, 178)	374 (345, 403)	312 (284, 339)
Baseline Characteristic [‡]				
HIV-RNA > 100,000 copies/ml	196 (174, 219)	192 (169, 214)	392 (350, 435)	329 (293, 364)
≤ 100,000 copies/ml	180 (160, 200)	134 (115, 153)	350 (312, 388)	294 (251, 337)
CD4-count ≤ 50 cells/mm ³	170 (122, 218)	152 (123, 180)	304 (209, 399)	314 (242, 386)
> 50 and	193 (169, 217)	175 (151, 198)	413 (360, 465)	306 (264, 348)
≤ 200 cells/mm ³				
> 200 cells/mm ³	190 (168, 212)	157 (134, 181)	358 (321, 395)	316 (272, 359)
Viral Subtype Clade B	187 (170, 204)	164 (147, 181)	380 (346, 414)	303 (272, 333)
Non-Clade B	189 (153, 225)	156 (121, 190)	332 (275, 388)	329 (260, 398)

[†] Non-completer is failure imputation: patients who discontinued prematurely are imputed as failure thereafter. Percent of patients with response and associated 95 % confidence interval (CI) are reported.

[‡] For analysis by prognostic factors, virologic failures were carried forward for percent < 50 and 400 copies/ml. For mean CD4 changes, baseline-carry-forward was used for virologic failures.

Notes: The analysis is based on all available data.
Raltegravir and efavirenz were administered with emtricitabine (+) tenofovir.

Paediatric population

DUTREBIS should not be used in children below 6 years of age or in patients weighing less than 30 kg due to weight based dosing requirements in this patient population (see section 5.2).

IMPAACT P1066 is a Phase I/II open label multicentre study 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 raltegravir (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)

Parameter	Final dose population	
	N=96	
Demographics		
Age (years), median [range]	13 [2 – 18]	
Male Gender	49 %	
Race		
Caucasian	34 %	
Black	59 %	
Baseline Characteristics		
Plasma HIV-1 RNA (\log_{10} copies/ml), mean [range]	4.3 [2.7 – 6]	
CD4 cell count (cells/mm ³), median [range]	481 [0 – 2361]	
CD4 percent, median [range]	23.3 % [0 – 44]	
HIV-1 RNA >100,000 copies/ml	8 %	
CDC HIV category B or C	59 %	
Prior ART Use by Class		
NNRTI	78 %	
PI	83 %	
Response	Week 24	Week 48
Achieved $\geq 1 \log_{10}$ HIV RNA drop from baseline or <400 copies/ml	72 %	79 %
Achieved HIV RNA <50 copies/ml	54 %	57 %
Mean CD4 cell count (%) increase from baseline	119 cells/mm ³ (3.8 %)	156 cells/mm ³ (4.6 %)

5.2 Pharmacokinetic properties

The comparative bioavailability of DUTREBIS (150 mg lamivudine/300 mg raltegravir) fixed-dose combination tablet was assessed relative to individual components administered concomitantly (150 mg of lamivudine and 400 mg of raltegravir) in 108 healthy subjects. Lamivudine in the fixed-dose combination tablet was bioequivalent with the lamivudine (single agent) after administration of the individual component. Raltegravir in the fixed-dose combination tablet was not bioequivalent with respect to C₁₂, however, based on PK/PD modelling, no clinically meaningful differences in raltegravir exposure are expected following administration of the fixed-dose combination tablet compared to administration of raltegravir as a single agent.

Absorption

When DUTREBIS is administered, raltegravir is absorbed with a T_{max} of approximately 1 hour in the fasted state. This is slightly faster than the raltegravir poloxamer formulation, which has a T_{max} of approximately 3 hours. The bioavailability of the raltegravir component of DUTREBIS in the fasted state is approximately 60 %, which is higher than the bioavailability of raltegravir in the raltegravir poloxamer formulation, and accounts for the difference in raltegravir dose. Once absorbed the lamivudine and raltegravir distribution, metabolism, and excretion are similar to those of the reference components administered individually as described in the following paragraphs.

Lamivudine is well absorbed from the gastrointestinal tract, and the bioavailability of oral lamivudine in adults is normally between 80 and 85 %. Following oral administration, the mean time (t_{max}) to maximal serum concentrations (C_{max}) is about an hour. Based on data derived from a study in healthy volunteers, at a therapeutic dose of 150 mg twice daily, mean (CV) steady-state C_{max} and C_{min} of lamivudine in plasma are 1.2 $\mu\text{g/ml}$ (24 %) and 0.09 $\mu\text{g/ml}$ (27 %), respectively. The mean (CV) AUC over a dosing interval of 12 hours is 4.7 $\mu\text{g}\cdot\text{h/ml}$ (18 %). At a therapeutic dose of 300 mg once daily, the mean (CV) steady-state C_{max} , C_{min} and 24h AUC are 2.0 $\mu\text{g/ml}$ (26 %), 0.04 $\mu\text{g/ml}$ (34 %) and 8.9 $\mu\text{g}\cdot\text{h/ml}$ (21 %), respectively.

Co-administration of zidovudine with lamivudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. This is not considered to be of significance to patient safety and therefore no dosage adjustments are necessary.

As demonstrated in healthy volunteers administered single oral doses of raltegravir in the fasted state, raltegravir AUC and C_{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 of raltegravir, pharmacokinetic steady state is achieved rapidly, within approximately the first 2 days of dosing. There is little to no accumulation in AUC and C_{max} and evidence of slight accumulation in $C_{12\text{ hr}}$.

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 within the BENCHMRK study may include differences in co-administration with food and concomitant medicines. Overall, the results of the clinical pharmacology studies with DUTREBIS demonstrate similar drug exposures compared to the individual components of lamivudine and raltegravir, including similar variability in raltegravir $C_{12\text{hr}}$ and C_{max} . The pharmacokinetic properties, use in special populations and drug-drug interactions for each of the individual components (lamivudine and raltegravir) are applicable to DUTREBIS.

An open-label, single-dose, randomized, two-period crossover study assessed the effect of a high fat meal on DUTREBIS administered to 20 healthy male and female subjects. Similar AUC values for fed vs. fasted and somewhat lower C_{max} values (23 % for raltegravir and 21 % for lamivudine) were observed with DUTREBIS. In addition, higher $C_{12\text{h}}$ levels (20 % for raltegravir and 53 % for lamivudine) were observed. These changes are not considered clinically meaningful; therefore, DUTREBIS may be administered with or without food.

Distribution

In intravenous studies with lamivudine, the mean volume of distribution is 1.3 l/kg. The observed half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/h/kg, with predominantly renal clearance (> 70 %) via the organic cationic transport system.

Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (< 16 % - 36 % to serum albumin in *in vitro* studies).

Limited data show that lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The mean ratio CSF/serum lamivudine concentration 2-4 hours after oral administration was approximately 0.12. The true extent of penetration or relationship with any clinical efficacy is unknown.

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 active moiety, intracellular lamivudine triphosphate, has a prolonged terminal half-life in the cell (16 to 19 hours) compared to the plasma lamivudine half-life (5 to 7 hours).

Lamivudine is predominately cleared unchanged by renal excretion. The likelihood of metabolic interactions of lamivudine with other medicinal products is low due to the small extent of hepatic metabolism (5-10 %) and low plasma protein binding.

Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction. DUTREBIS should not be given in patients with a creatinine clearance of <50 ml/min (see section 4.2).

An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine exposure at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment (see sections 4.5 and 4.2). Administration of co-trimoxazole with lamivudine in patients with renal impairment should be carefully assessed.

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 receiving raltegravir 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

The pharmacokinetics of DUTREBIS in the paediatric patient population has not been studied in clinical studies. DUTREBIS should not be used in children below 6 years of age or in patients weighing less than 30 kg due to weight based dosing requirements in this patient population.

The dosing regimen of the lamivudine component of DUTREBIS in the paediatric population is the same as the dosing regimen of the individual component (EPIVIR).

The raltegravir component in DUTREBIS (300 mg raltegravir) fixed-dose combination tablet was not bioequivalent with respect to C₁₂, however, based on PK/PD modelling, no clinically meaningful differences in raltegravir exposure are expected. Based on modelling and simulation using raltegravir pharmacokinetic data in adults, the pharmacokinetics of raltegravir in DUTREBIS in children was projected to result in exposures that have been previously shown to be safe and efficacious in adults.

The pharmacokinetics of DUTREBIS in children under 6 years of age has not been established.

Elderly

No dosage adjustment is necessary for DUTREBIS based on age. The pharmacokinetics of lamivudine after administration to patients over 65 years of age have not been studied; however, 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

No dosage adjustment is necessary for DUTREBIS based on gender, race, or BMI. There were no clinically important pharmacokinetic differences due to gender, race or body mass index (BMI) for raltegravir in adults.

Renal impairment

No study has been performed with DUTREBIS in subjects with renal insufficiency. Recommendations are based on available data from the individual components. DUTREBIS should not be given in patients with a creatinine clearance of <50 ml/min. Renal function should be monitored in patients more likely to have decreased renal function. If the creatinine clearance decreases to <50 ml/min, DUTREBIS should be switched to a regimen of the individual components (lamivudine and raltegravir). Please refer to the SmPC for the individual components of DUTREBIS for dosing instructions. Because the extent to which DUTREBIS may be dialyzable is unknown, dosing before a dialysis session should be avoided (see section 4.2).

The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-1-infected adults with impaired renal function.

Exposure (AUC_∞), C_{max}, and half-life increased with diminishing renal function (as expressed by creatinine clearance). Apparent total oral clearance (Cl/F) of lamivudine decreased as creatinine clearance decreased. T_{max} was not significantly affected by renal function.

For raltegravir, renal clearance of unchanged drug is a minor pathway of elimination. A study of the pharmacokinetics of raltegravir was performed in adult patients with severe renal insufficiency. Additionally, renal insufficiency was evaluated in the composite pharmacokinetic analysis. There were no clinically important pharmacokinetic differences between patients with severe renal insufficiency and healthy subjects.

Hepatic impairment

No study has been performed with DUTREBIS in subjects with hepatic insufficiency. Recommendations are based on available data from the individual components. No dosage adjustment for DUTREBIS is required for patients with mild to moderate hepatic insufficiency.

The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function; therefore, no dose adjustment for lamivudine is required for patients with impaired hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

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).

Pharmacokinetics in pregnancy

Following oral administration, lamivudine pharmacokinetics in late pregnancy were similar to non-pregnant women.

5.3 Preclinical safety data

No animal studies have been conducted with DUTREBIS. The following data are based on findings in separate studies with the individual components of DUTREBIS (lamivudine and raltegravir).

Administration of lamivudine in animal toxicity studies at high doses was not associated with any major organ toxicity. At the highest dosage levels, minor effects on indicators of liver and kidney function were seen together with occasional reductions in liver weight. The clinically relevant effects noted were a reduction in red blood cell count and neutropenia.

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

Lamivudine was not mutagenic in bacterial tests but, like many nucleoside analogues, showed activity in an *in vitro* cytogenetic assay and the mouse lymphoma assay. Lamivudine was not genotoxic *in vivo* at doses that gave plasma concentrations around 40-50 times higher than the anticipated clinical plasma levels. As the *in vitro* mutagenic activity of lamivudine could not be confirmed in *in vivo* tests, it is concluded that lamivudine should not represent a genotoxic hazard to patients undergoing treatment.

A transplacental genotoxicity study conducted in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at human-equivalent exposures. The study demonstrated that foetuses exposed *in utero* to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple foetal organs, and showed evidence of more telomere shortening than in those exposed to zidovudine alone. The clinical significance of these findings is unknown.

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 conducted with raltegravir.

Carcinogenicity

The results of long-term carcinogenicity studies with lamivudine in rats and mice did not show any carcinogenic potential relevant for humans.

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

Hypromellose, 2910
Croscarmellose sodium
Lactose monohydrate
Silicon dioxide, colloidal
Magnesium stearate
Microcrystalline cellulose

Film-coating

Hypromellose
Lactose monohydrate
Triacetin
Yellow iron oxide
Indigo Carmine (E132) Aluminium Lake
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

After first opening of the medicinal product, the in-use shelf life is 30 days, below 30°C.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a child-resistant closure (HDPE) with foil induction seal liner.

Pack size: 1 bottle containing 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/1/15/995/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

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.ema.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 AUTHORISATION**
- 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(s) responsible for batch release

Merck Sharp & Dohme B.V.
Waarderweg 39
NL-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 marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

DUTREBIS 150 mg/300 mg film-coated tablets
lamivudine/raltegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg of lamivudine and 300 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

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

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/1/15/995/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

DUTREBIS

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle label

1. NAME OF THE MEDICINAL PRODUCT

DUTREBIS 150 mg/300 mg film-coated tablets
lamivudine/raltegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg of lamivudine and 300 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

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

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 + logo

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/995/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the user

DUTREBIS 150 mg/300 mg film-coated tablets lamivudine/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 DUTREBIS, 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 DUTREBIS is and what it is used for
2. What you need to know before you take DUTREBIS
3. How to take DUTREBIS
4. Possible side effects
5. How to store DUTREBIS
6. Contents of the pack and other information

1. What DUTREBIS is and what it is used for

What DUTREBIS is

DUTREBIS is an antiretroviral medicine used to treat infection with human immunodeficiency virus (HIV). It contains the active substances lamivudine and raltegravir:

- Lamivudine belongs to a group of medicines called nucleoside analogue reverse transcriptase inhibitors (NRTIs)
- Raltegravir belongs to a group of medicines called HIV integrase strand transfer inhibitors

What DUTREBIS is used for

DUTREBIS is used to treat HIV (Human Immunodeficiency Virus). HIV is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

DUTREBIS is used in combination with other medicines to treat adults, adolescents, and children 6 years of age and older and weighing at least 30 kg who are infected by HIV. Your doctor has prescribed DUTREBIS to help control your HIV infection.

How DUTREBIS works

When used with other medicines, DUTREBIS may:

- reduce the amount of HIV in your blood (this is called your "viral load")
- increase your CD4-cell count (a type of white blood cell 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.

DUTREBIS also helps stop the production of an enzyme called "HIV integrase". This enzyme is needed for HIV to make more virus.

DUTREBIS is not a cure for HIV infection.

2. What you need to know before you take DUTREBIS

Do not take DUTREBIS:

- If you are allergic to lamivudine, raltegravir or any of the other ingredients in this medicine listed in section 6.

If you are not sure, talk to your doctor, pharmacist or nurse before taking DUTREBIS.

Warnings and precautions

Remember that DUTREBIS is not a cure for HIV infection. This means that you may keep getting infections or other illnesses associated with HIV, if you don't take DUTREBIS as your doctor has instructed you.

Talk to your doctor, pharmacist or nurse before taking DUTREBIS if:

- you have a history of depression or psychiatric illness. Depression, including suicidal thoughts and behaviours, has been reported in some patients taking raltegravir (one of the medicines in DUTREBIS), particularly in patients with a prior history of depression or psychiatric illness.
- you have kidney problems - Your doctor may decide to change your dose by using the medicines in DUTREBIS separately.
- 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. Do not stop taking DUTREBIS without your doctor's advice.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking DUTREBIS.

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 therapy. Discuss with your doctor the precautions needed to avoid infecting other people.

Look out for side effects

DUTREBIS can cause some side effects that you need to talk to your doctor, pharmacist or nurse about. See section 4 for more information about side effects.

Skin problems

Talk to your doctor immediately if you develop a rash. Severe and life-threatening skin reactions and allergic reactions have been reported in some patients taking raltegravir (one of the medicines in DUTREBIS).

Muscle problems

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

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 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.

Tell your doctor, pharmacist or nurse immediately 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.

Lactic acidosis

Some people taking DUTREBIS, or similar medicines, may get a side effect called “lactic acidosis” and a swollen liver. Lactic acidosis is caused by a build-up of lactic acid in the body. It is rare (may affect up to 1 in 1,000 people) and if it does happen, it usually happens after a few months of treatment. It can be life-threatening, and cause internal organs to fail.

- Lactic acidosis is more likely to happen in people who have liver problems, or in people who are very overweight, especially women.

During your treatment, your doctor will check you for signs of lactic acidosis.

Tell your doctor immediately if you have any of the following signs of lactic acidosis, or any other symptoms that worry you:

- deep, fast, difficult breathing, feeling drowsy, numb or weak arms or legs, feeling or being sick (nausea or vomiting), stomach pain.

Bone problems

Some patients taking combination treatment for HIV may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). This may be more likely with long-term HIV treatment, more severe damage to the immune system, overweight, or the use of alcohol or other medicines called corticosteroids.

Tell your doctor if you notice any of the following signs of osteonecrosis:

- joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty moving.

Changes in body shape

Talk to your doctor if you notice changes in your body shape. People taking anti-retroviral medicines may find that their body shape changes. This is because of changes in fat distribution:

- fat may be lost from the legs, arms or face; extra fat may build up around the tummy, breasts or internal organs; fatty lumps (sometimes called buffalo hump) may appear on the back of the neck. It is not yet known what causes these changes, or whether they have any long-term effects.

Some people taking DUTREBIS or other antiretroviral medicines may have other effects show up in their blood tests:

- increased levels of lactic acid in the blood, which on rare occasions can lead to lactic acidosis; increased levels of sugar and fats (triglycerides and cholesterol) in the blood; resistance to insulin (so if you are diabetic, you may have to change your insulin dose to control your blood sugar).

Children and adolescents

DUTREBIS is not for use in children below 6 years of age.

Other medicines and DUTREBIS

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. This is because DUTREBIS might interact with other medicines.

DUTREBIS must not be used with the following medicines. Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take:

- medicines containing lamivudine – used to treat HIV or hepatitis B.
- medicines containing raltegravir or emtricitabine – used to treat HIV.
- high doses of co-trimoxazole – used to treat infections.
- trimethoprim – used to treat infections.
- interferons taken with or without ribavirin – used to treat hepatitis.
- cladribine – used to treat hairy cell leukaemia.
- antacids containing aluminium and/or magnesium – used for heartburn. Talk to your doctor about other medicines you can take.

- rifampicin – used to treat some infections such as tuberculosis. Rifampicin may decrease your levels of raltegravir (one of the medicines in DUTREBIS). Your doctor may decide to change your dose by using the medicines in DUTREBIS separately, if you are taking rifampicin.

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.

- DUTREBIS is not recommended in pregnancy.
- 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.

DUTREBIS 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 DUTREBIS

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure. DUTREBIS must be used in combination with other medicines for HIV.

How much to take

Adults, children, and adolescents

The recommended dose is 1 tablet twice a day.

Taking this medicine

- Swallow the tablet whole (do not crush or chew).
- This medicine can be taken with or without food or drink.

If you take more DUTREBIS 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 DUTREBIS

If you forget to take a dose, take it as soon as you remember it. If you notice within 6 hours, you must take the tablet immediately. If you notice after 6 hours, then skip the intake and take the next doses as usual.

If you stop taking DUTREBIS

It is important that you take DUTREBIS 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 DUTREBIS 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 DUTREBIS 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, this medicine can cause side effects, although not everybody gets them.

DUTREBIS contains two medicines: lamivudine and raltegravir. The side effects for the two individual medicines contained in DUTREBIS are presented below.

Serious side effects

See a doctor immediately, if you notice any of the following:

These are uncommon (may affect up to 1 in 100 people)

- 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 (hepatitis); When hepatitis causes symptoms, they can include: belly pain; nausea and vomiting; not feeling hungry; jaundice, which is when the skin or white part of the eye turns yellow
- liver failure (the liver stops working , which may cause heavy bleeding, swelling, and breathing problems)
- allergic rash (including red spots or blotches sometimes with blistering and swelling of the skin)
- certain kinds of kidney problems, including conditions in which the kidneys lose the ability to remove waste and excess water from the bloodstream. As waste and fluids accumulate, other body systems are affected, potentially leading to complications
- taking drug in quantities greater than recommended

These are rare (may affect up to 1 in 1,000 people)

- lactic acidosis – signs include deep, fast, difficult breathing, feeling drowsy, numb or weak arms or legs, feeling or being sick (nausea or vomiting), stomach pain

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

Other side effects

Common (may affect up to 1 in 10 people)

- headache; feeling dizzy
- feeling or being sick (nausea or vomiting), diarrhoea, stomach pain
- feeling tired, lack of energy, difficulty in sleeping (insomnia)
- fever, general feeling of being unwell
- muscle pain and discomfort, joint pain
- cough, irritated or runny nose
- rash, hair loss (alopecia)
- decreased appetite
- abnormal dreams; nightmare; abnormal behaviour; feelings of deep sadness and unworthiness
- spinning sensation
- bloating; excessive gas in the stomach or bowel; indigestion; belching
- rash (more often when used in combination with darunavir)
- increased liver blood tests; abnormal white blood cells; increased fat levels in blood (such as cholesterol and triglycerides); increased level of enzyme from salivary glands or pancreas

Uncommon (may affect up to 1 in 100 people)

- infection of the hair roots; influenza; skin infection due to virus; upper respiratory tract infection (such as inflammation of the nasal cavity or sinuses located around the nose; common cold); infection in the lymph node (gland in the neck, armpit, or groin)
- wart
- low count of white blood cells that fight infection; pain or swollen glands (lymph nodes) in the neck, armpit and groin
- allergic reaction
- increased appetite; diabetes; high sugar levels in the blood; excessive thirst; severe weight loss; 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; reduced sense of touch, 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 rate; fast or irregular heart beats
- hot flush; high blood pressure
- harsh, raspy, or strained voice; nosebleed; nasal congestion
- pain in the upper part of the belly; rectal discomfort; constipation; dry mouth; heartburn; pain when swallowing; inflammation of the pancreas (pancreatitis); ulcer or sore in stomach or upper intestine; bleeding from 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
- 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; lump in the neck; swelling of hands, ankles or feet; pain
- blood test showing decreased count of platelets in blood (a kind of cell that helps blood clot); blood test showing reduced kidney function; 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; blood test showing low red blood cell count (anaemia)

Rare (may affect up to 1 in 1,000 people)

- serious allergic reaction causing swelling of the face, tongue or throat which may cause difficulty in swallowing or breathing
- breakdown of muscle tissue
- liver problems, such as yellowing of the skin or whites of the eyes, swollen or fatty liver
- blood test showing an increase in an enzyme called amylase

Very rare (may affect up to 1 in 10,000 people)

- blood test showing failure of the bone marrow to produce new red blood cells (pure red cell aplasia)

Additional side effects in children and adolescents

- hyperactivity

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

Patients with HIV are at higher risk of developing cancer than patients without the disease. In clinical studies, the number of HIV patients taking raltegravir who developed cancer was similar to that of patients taking other HIV medicines.

Tell your doctor, pharmacist or nurse if you notice any of the side effects above.

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 DUTREBIS

- 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 in order to protect from moisture.
- 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 DUTREBIS contains

- The active substances are lamivudine and raltegravir. Each film-coated tablet contains 150 mg of lamivudine and 300 mg of raltegravir (as potassium).
- The other ingredients are: hypromellose (2910), croscarmellose sodium, lactose monohydrate, silicon dioxide (colloidal), magnesium stearate, and microcrystalline cellulose. In addition, the film coating contains the following inactive ingredients: hypromellose, lactose monohydrate, triacetin, yellow iron oxide, Indigo Carmine (E132) Aluminium Lake, and titanium dioxide.

What DUTREBIS looks like and contents of the pack

The film-coated tablet is oval-shaped, green, marked with "144" on one side. One pack size is available: 1 bottle with 60 tablets.

Marketing Authorisation Holder

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Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.