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 $AUC_{0\text{-}24\ hr}$. No development

effects were seen at 3.4-fold human exposure at 400 mg twice daily based on $AUC_{0\text{-}24\ hr}$ (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

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 of 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 raltegravair 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

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

Manufacturer

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

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

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

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

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

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

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

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

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

EL
MSD A.Φ.B.E.E.
Τηλ: + 30 210 98 97 300
dpoc_greece@merck.com

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

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

HR
Merck Sharp & Dohme d.o.o.
Tel: + 385 1 66 11 333
croatia_info@merck.com

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

IS
Vistor hf.
Sími: +354 535 7000

HU
MSD Pharma Hungary Kft.
Tel.: +361 888 53 00
hungary_msd@merck.com

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

NL
Merck Sharp & Dohme B.V.
Tel: 0800 99 99 000 (+31 23 5153153)
medicalinfo.nl@merck.com

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

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

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

PT
Merck Sharp & Dohme, Lda
Tel: +351 21 446 5700
clic@merck.com

RO
Merck Sharp & Dohme Romania S.R.L.
Tel: + 4021 529 29 00
msdromania@merck.com

SI
Merck Sharp & Dohme, inovativna zdravila d.o.o.
Tel: + 386 1 5204201
msd_slovenia@merck.com

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

FI
MSD Finland Oy
Puh/Tel: +358 (0) 9 804 650
info@msd.fi

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

CY
Merck Sharp & Dohme Cyprus Limited
Τηλ: 800 00 673 (+357 22866700)
cyprus_info@merck.com

LV
SIA Merck Sharp & Dohme Latvija
Tel: +371 67364 224
msd_lv@merck.com

SE
Merck Sharp & Dohme (Sweden) AB
Tel: +46 77 5700488
medicinskinfo@merck.com

UK
Merck Sharp & Dohme Limited
Tel: +44 (0) 1992 467272
medicalinformationuk@merck.com

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