

**PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS'
REGULATIONS (PREPARATIONS) 1986**

This medicine is marketed upon physician's prescription only

ISENTRESS® 400 MG TABLETS

Film-Coated Tablets

Each film-coated tablet contains:

Raltegravir 400 mg (as potassium)

For the list of the inactive ingredients see section 6.1 "What ISENTRESS contains".

See also section 2.7 "Important information about some of the ingredients of the medicine".

Read the entire leaflet carefully before using the medicine.

- This leaflet contains concise information about the medicine. If you have any further questions, refer to the doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.
- This medicine is not intended for children and adolescents under 16 years of age.

1. WHAT ISENTRESS IS INTENDED FOR?

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

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

ISENTRESS may not have these effects in all patients.

ISENTRESS is not a cure for HIV infection.

ISENTRESS is used to treat adults who are infected by HIV.

Your doctor has prescribed ISENTRESS to help control your HIV infection.

Therapeutic group: antivirals for systemic use.

2. BEFORE USING ISENTRESS

2.1 Do not use ISENTRESS if:

- you are hypersensitive (allergic) to raltegravir or any of the other ingredients that this medicine contains. (for a list of inactive ingredients, see section 6.1 "What ISENTRESS contains").

2.2 Special warnings regarding the use of ISENTRESS

Talk to your doctor, pharmacist or nurse before taking ISENTRESS.

Remember that ISENTRESS is not a cure for HIV infection. This means that you may keep getting infections or other illnesses associated with HIV. You should keep seeing your doctor regularly while taking ISENTRESS.

Before starting treatment with ISENTRESS, tell your doctor if:

- Mental Health problems:
you have a history of depression or psychiatric illness. Depression, including suicidal thoughts and behaviors, have been reported in some patients taking **this** medicine, particularly in patients with a prior history of depression or psychiatric illness.
- Bone problems:
Some patients taking combination anti-retroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination anti-retroviral therapy, corticosteroid use, alcohol consumption, severe reduction of the activity of the immune system, higher body mass index (BMI), among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms, please inform your doctor.
- Liver problems:
Tell your doctor, pharmacist or nurse if you have had problems with your liver before, including hepatitis B or C. Your doctor may evaluate how severe your liver disease is before deciding if you can take this medicine.

Additional warnings:

- Passing HIV to others:
HIV infection is spread by contact with blood or sexual contact with a person with HIV. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.
- Infections:
Tell your doctor, pharmacist or nurse immediately if you notice any symptoms of infection, such as fever, and/or feeling unwell. In some patients with advanced HIV infection and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.
In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.
- Muscle problems:
Contact your doctor, pharmacist or nurse immediately, if you experience unexplained muscle pain, tenderness, or weakness while taking this medicine.
- Skin problems:
Contact your doctor promptly if you develop a rash. Severe and life-threatening skin reactions and allergic reactions have been reported in some patients taking this medicine.

2.3 Interactions with other medicines

If you are taking, or have recently taken, other medicines including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. Especially if you are taking, have recently taken or might take:

- **antacids** (an agent that counteracts or neutralises the acid in the stomach to relieve indigestion and heartburn). It is not recommended to take ISENTRESS with certain antacids (those containing aluminium and/or magnesium). Talk to your doctor about other antacids you can take.
- iron salts (to treat and prevent iron deficiency or anemia). You should wait at least two hours between taking iron salts and taking ISENTRESS, as these medicines may reduce ISENTRESS efficacy.
- rifampicin (a medicine used to treat some infections such as tuberculosis), as it may decrease your levels of ISENTRESS. Your doctor may consider increasing your dose of ISENTRESS if you are taking rifampicin.

2.4 Using ISENTRESS with food and drink

ISENTRESS can be taken with or without food or drink.

2.5 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, pharmacist or nurse for advice before taking this medicine.

- 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.

If you are pregnant or breastfeeding, consult the doctor or pharmacist before using any medicine.

2.6 Driving and using machines

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

2.7 Important information about some of the ingredients of the medicine

ISENTRESS contains lactose.

This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

ISENTRESS contains sodium.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. HOW SHOULD YOU USE ISENTRESS?

Always use ISENTRESS according to the doctor's instructions. You should check with the doctor or pharmacist if you are not sure regarding the dosage and treatment regimen.

ISENTRESS must be used in combination with other medicines for HIV.

The dosage and treatment regimen will be determined by the doctor only.

Usually, the acceptable dosage is 1 tablet (400 mg), taken by mouth twice a day.

Do not exceed the recommended dose.

Do not chew, crush or split the tablets because it may change the level of medicine in your body. This medicine can be taken with or without food or drink.

If you have accidentally taken a higher dose than you should

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

If you have taken an overdose, or if a child has accidentally swallowed the medicine, proceed immediately to a doctor or to a hospital emergency room and bring the package of the medicine with you.

If you have forgotten to take ISENTRESS

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

Adhere to the treatment regimen as recommended by the doctor.

Even if there is an improvement in your health, do not discontinue use of ISENTRESS before consulting your doctor.

If you stop taking ISENTRESS

It is important that you take ISENTRESS exactly as your doctor has instructed. Do not change the dose or stop taking this medicine without first talking with your doctor, pharmacist or nurse.

Do not stop taking it because:

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

Do not take medicines in the dark! Check the label and the dose each time you take a medicine. Wear glasses if you need them.

If you have any further questions on the use of this medicine, consult with a doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, ISENTRESS may cause side effects, in some users.

Do not be alarmed by reading the list of side effects, you may not suffer from any of them.

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

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

- herpes infections including shingles
- anaemia including due to low iron
- signs and symptoms of infection or inflammation
- mental disorder
- suicide intention or attempt
- stomach inflammation
- inflammation of liver
- liver failure
- allergic rash
- certain kinds of kidney problems

- drug ingestion in quantities greater than recommended

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

Common side effects (may affect up to 1 in 10 people):

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

Uncommon side effects (may affect up to 1 in 100 people):

- infection of the hair roots; influenza; skin infection due to virus; vomiting or diarrhoea due to an infectious agent; upper respiratory tract infection; lymph node abscess
- wart
- lymph node pain; low count of white blood cells that fight infection; swollen glands in the neck, armpit and groin
- allergic reaction
- increased appetite; diabetes; increased blood cholesterol and lipids; high sugar levels in the blood; excessive thirst; severe weight loss; high levels of fat (such as cholesterol and triglycerides) in the blood; body fat disorder
- feeling anxious; feeling of confusion; depressed mood; mood changes; panic attack
- loss of memory; pain in the hand due to nerve compression; disturbance in attention; dizziness with rapid changes in posture; abnormal taste; increased sleepiness; lack of energy; forgetfulness; migraine headache; loss of feeling, numbness or weakness of the arms and/or legs; tingling; sleepiness; tension headache; tremors; poor quality sleep
- visual disturbance
- buzzing, hissing, whistling, ringing or other persistent noise in the ears
- palpitations; slow heart rates; fast or irregular heart beats
- hot flush; high blood pressure
- harsh, raspy, or strained voice; nosebleed; nasal congestion
- abdominal pain upper; rectal discomfort; constipation; dry mouth; heartburn; pain when swallowing; inflammation of the pancreas; ulcer or sore in stomach or upper intestine; bleeding at anus; stomach discomfort; inflammation of the gums; swollen, red sore tongue
- accumulation of fat in the liver
- acne; unusual hair loss or thinning; redness of skin; unusual distribution of fat on the body, this may include loss of fat from legs, arms, and face, and increase in abdomen fat; excessive sweating; night sweats; thickening and itching of the skin due to repeated scratching; skin lesion; dry skin
- joint pain; painful joint disease; back pain; pain in bone/muscle; muscle tenderness or weakness; neck pain; pain in arms or legs; inflammation of the tendons; decrease in the amount of minerals in the bone
- kidney stones; urination at night; kidney cyst

- erectile dysfunction; breast enlargement in men; menopausal symptoms
- chest discomfort; chills; swelling of face; feeling jittery; generally feeling unwell; neck mass; swelling of hands, ankles or feet; pain
- decreased white blood cell count; decreased count of platelets in blood (a kind of cell that helps blood clot); blood test showing reduced kidney function; high blood sugar level; increased muscle enzyme in blood; sugar present in urine; red blood cells present in urine; weight gain; increase in waist size; decreased blood protein (albumin); increase in time for blood to clot.

If a side effect appears, if any of the side effects gets serious or if you suffer from a side effect not mentioned in this leaflet, consult with the doctor.

Side effects can be reported to the Ministry of Health by using the link "Adverse Drug Reactions Report" at the homepage of the Ministry of Health's website (www.health.gov.il) that refers to the online side effects reporting form, or by using the link: <https://sideeffects.health.gov.il/>

5. HOW TO STORE ISENTRESS?

- Avoid Poisoning! This medicine as any other medicine must be stored in a safe place out of the reach and sight of children and/or infants, in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Do not use the medicine after the expiry date (exp. date) which is stated on the pack. The expiry date refers to the last day of the indicated month.
- **Storage conditions:** Store below 30°C.
- The bottle contains a desiccant. Do not swallow it.
- Medicines should not be disposed of via wastewater or household waste. Ask the pharmacist how to dispose of medicines you no longer use. These measures will help to protect the environment.

6. FURTHER INFORMATION

6.1 What ISENTRESS contains

- In addition to the active ingredient ISENTRESS also contains:
Microcrystalline cellulose, poloxamer 407, calcium phosphate dibasic anhydrous, hypromellose 2208, lactose monohydrate, magnesium stearate and sodium stearyl fumarate.
In addition, the film coating contains:
polyvinyl alcohol, macrogol/polyethylene glycol 3350, talc, titanium dioxide, red iron oxide and black iron oxide.

6.2 What ISENTRESS looks like and contents of the pack

The tablet is oval-shaped, pink, marked with "227" on one side and plain on the other.
Pack size: a bottle with 60 tablets and desiccant.

Marketing authorization holder:

Merck Sharp & Dohme (Israel-1996) Ltd., P.O.Box 7121, Petah-Tikva 49170.

Manufacturer: Merck Sharp & Dohme, B.V., Haarlem, Holland.

Revised in December 2021 according to MOHs' guidelines.

Drug registration no. listed in the official registry of the Ministry of Health:
140-33-31793