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

This medicine is marketed upon doctor's prescription only

DELSTRIGO® FILM-COATED TABLETS

Each film coated tablet contains:
Doravirine 100 mg
Lamivudine 300mg
Tenofovir disoproxil (as fumarate) 245mg

For a list of inactive ingredients see section 6 "Further Informtion". See also section 2.9 **"**Important information about some of the ingredients of the medicine".

Read all of this leaflet carefully before you start using the medicine.

- This leaflet contains concise information about Delstrigo**.** 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 their medical condition seems similar to yours.

1. WHAT DELSTRIGO IS INTENDED FOR?

Delstrigo (doravirine/lamivudine/tenofovir disoproxil fumarate) is indicated as a complete regimen for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults without past or present evidence of viral resistance to doravirine, lamivudine, or tenofovir.

Therapeutic group:

- Doravirine - a non-nucleoside reverse transcriptase inhibitor (NNRTI)
- Lamivudine - a nucleoside analogue reverse transcriptase inhibitor (NRTI)
- Tenofovir disoproxil - a nucleoside analogue reverse transcriptase inhibitor (NRTI)

How Delstrigo works

Delstrigo works by preventing HIV from making more viruses in your body. This will help by:

- reducing the amount of HIV in your blood (this is called your 'viral load').
- increasing the number of white blood cells called 'CD4$^+$ T'. This can make your immune system stronger. This may reduce your risk of early death or catching infections because your immune system is weak.

2. BEFORE USING DELSTRIGO

2.1 Do not use Delstrigo:

- if you are sensitive (allergic) to doravirine, lamivudine or tenofovir disoproxil or any of the other ingredients of this medicine listed in section 6.
- if you are taking any of the following medicines, which are strong cytochrome P450 CYP3A enzyme inducers. These medicines include, but are not limited to the following:
  - carbamazepine, oxcarbazepine, phenobarbital, phenytoin (medicines for seizure)
  - rifampicin, rifapentine (medicines for tuberculosis)
  - St. John's wort (*Hypericum perforatum*, a herbal remedy used for depression and anxiety) or products that contain it
  - mitotane (a medicine to treat cancer)
  - enzalutamide (a medicine to treat prostate cancer)
  - lumacaftor (a medicine to treat cystic fibrosis)

Do not take Delstrigo if the above applies to you. If you are not sure, talk to your doctor, pharmacist, or nurse before taking Delstrigo. See also section "Interactions with other medicines".

2.2 Special warnings regarding the use of Delstrigo
Talk to your doctor, pharmacist, or nurse before taking Delstrigo.

Passing HIV to others
HIV is spread by contact with blood or through sexual contact with a person with HIV. You can still pass on HIV when taking Delstrigo, although effective therapy lowers the risk. Talk to your doctor about what you can do to avoid infecting other people.

Worsening of hepatitis B infection
If you have both HIV and hepatitis B virus infections, your hepatitis B may get worse if you stop taking Delstrigo. You may require blood tests for several months after stopping treatment. Discuss your hepatitis B therapy with your doctor.

New or worsening kidney problems, including kidney failure
This can happen in some people who take Delstrigo. Your doctor will do blood tests to check your kidney function before and during treatment with Delstrigo.

Bone problems
This can happen in some people who take Delstrigo. Bone problems include bone pain, and bone softening or thinning (which may lead to fractures). Joint or muscle pain or muscle weakness may also occur. Your doctor may need to do additional tests to check your bones.

Immune reactivation syndrome
This can happen when you start taking any HIV medicine, including Delstrigo. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your doctor right away if you start having any new symptoms after starting your HIV medicine.

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.

2.3 Children and adolescents
This medicine is not indicated for use in children and adolecents aged less than 18 years. There is no information regarding the safety and efficacy of this medicine in children and adolescents aged less than 18 years.

2.4 Tests and follow-up
If you suffer from Hepatitis B infection, new or worse kidney problems or bone problems, your doctor may need to do additional tests (Please refer to sections 2.2 “Special warnings regarding the use of Delstrigo” and 3 “HOW SHOULD YOU USE DELSTRIGO”?).

2.5 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 the medicines listed below.
This is because other medicines may affect how Delstrigo works, and Delstrigo might affect the way some other medicines work.

There are some medicines you must not take with Delstrigo. See list under section “Do not use Delstrigo”.

Talk to your doctor before taking the following medicines with Delstrigo as your doctor may need to change the dose of your medicines:

- bosentan (a medicine to treat lung disease)
- dabrafenib (a medicine to treat skin cancer)
- lesinurad (a medicine to treat gout)
- modafinil (a medicine to treat excessive sleepiness)
- nafcillin (a medicine to treat some bacterial infections)
- rifabutin (a medicine to treat some bacterial infections such as tuberculosis)
- telotristat ethyl (a medicine to treat diarrhea in people with carcinoid syndrome)
- thioridazine (a medicine to treat psychiatric conditions such as schizophrenia)

If your doctor decides you should take these medicines with Delstrigo, your doctor will prescribe a 100 mg tablet of doravirine to be taken daily, approximately 12 hours after your dose of Delstrigo.

Your doctor may check your blood levels or monitor for side effects if you take the following medicines with Delstrigo:
- ledipasvir/sofosbuvir (medicines used to treat hepatitis C infection)
- sirolimus (a medicine used to control your body's immune response after a transplant)
- sofosbuvir/velpatasvir (medicines used to treat hepatitis C infection)
- tacrolimus (a medicine used to control your body's immune response after a transplant)
- medicines (usually liquids) containing sorbitol and other sugar alcohols (such as xylitol, mannitol, lactitol or maltitol), if taken regularly

2.6 Using Delstrigo with food
This medicine can be taken with food or between meals.

2.7 Pregnancy, breast-feeding and fertility
If you are pregnant or breastfeeding, think you may be pregnant, or are planning to have a baby, talk to your doctor about the risks and benefits of taking Delstrigo. It is preferable to avoid the use of Delstrigo during pregnancy. This is because it has not been studied in pregnancy, and it is not known if Delstrigo will harm your baby while you are pregnant.

Breastfeeding
Women with HIV should not breastfeed because HIV can be passed on to babies through breast milk. Talk with your doctor about the best way to feed your baby.

Fertility
There is no information in human on the effect of Delstrigo on fertility.

2.8 Driving and using machines
Delstrigo may have a minor influence on the ability to drive or ride a bicycle or use machines. A few of the reported side effects such as dizziness, fatigue or somnolence may affect your ability to drive or to operate machinery.

2.9 Important information about some of the ingredients of the medicine
Delstrigo tablets contain lactose
If you have been told by your doctor that you have an intolerance to lactose, talk to your doctor before taking this medicine.

3. HOW SHOULD YOU USE DELSTRIGO?
Always use Delstrigo as instructed by the doctor.
You should check with the doctor or pharmacist if you are not sure regarding the dosage and treatment regimen. Delstrigo is a complete regimen taken as a single tablet for the treatment of HIV infection.

The dosage and treatment regimen will be determined by the doctor only. Usually, the acceptable dosage is 1 tablet once a day. If you take certain medicines, your doctor may need to change the amount of doravirine you take. See section "Interactions with other medicines" for a list of medicines.

Do not exceed the recommended dose.

Method of administration
- Swallow the tablet whole.
- This medicine can be taken with food or between meals.

Crushing/splitting/chewing:
- Do not crush because it may change the level of medicine in your body.
- There is no information regarding splitting/chewing of tablets.

If you have accidentally taken a higher dose than you should
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 Delstrigo
- It is important that you do not miss or skip doses of Delstrigo.
- If you forget a dose, take it as soon as you remember. But if your next dose is due within 12 hours, skip the dose you missed and take the next one at the usual time. Then continue your treatment as before.
- Do not take two doses of Delstrigo at the same time to make up for a missed dose.
- If you are not sure what to do, call your doctor or pharmacist.

If you stop taking Delstrigo
Do not run out of Delstrigo. Refill your prescription or talk to your doctor before your Delstrigo is all gone.

If you stop taking Delstrigo, your doctor will need to check your health often and do blood tests regularly for several months to check your HIV infection. If you have HIV infection and hepatitis B infection, it is especially important not to stop your Delstrigo treatment without talking to your doctor first. Some patients have had blood tests or symptoms indicating that their hepatitis has worsened after stopping lamivudine or tenofovir disoproxil (two of the three active substances of Delstrigo). If Delstrigo is stopped your doctor may recommend that you resume hepatitis B treatment. You may need blood tests to check how your liver is working for 4 months after stopping treatment. In some patients with advanced liver disease or cirrhosis, stopping treatment is not recommended as this may lead to worsening of your hepatitis, which may be life-threatening.

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 further questions on the use of the medicine, consult with a doctor or a pharmacist.

4. SIDE EFFECTS
As with any medicine, Delstrigo 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.
Do not stop taking this medicine without first talking to your doctor.

Common: may affect up to 1 in 10 people:
- abnormal dreams, difficulty in sleeping (insomnia)
- headache, dizziness, sleepiness
- cough, nasal symptoms
- feeling sick (nausea), diarrhoea, stomach pain, vomiting, wind (flatulence)
- hair loss, rash
- muscle symptoms (pain, stiffness)
- feeling tired, fever

Blood tests may also show:
- increased levels in liver enzymes (ALT)

Uncommon: may affect up to 1 in 100 people:

- nightmares, depression, anxiety, irritability, confusion, suicidal thoughts
- trouble concentrating, memory problems, tingling of hands and feet, stiff muscles, poor quality of sleep
- high blood pressure
- constipation, stomach discomfort, swollen or bloated stomach (abdominal distention), indigestion, soft stools, stomach spasms, frequent bowel movements, inflammation of the pancreas (pancreatitis) (causing stomach pain, vomiting)
- itchiness
- joint pain, breakdown of muscle tissue, muscular weakness
- feeling weak, general feeling of being unwell

Blood tests may also show:

- decreased number of white blood cells in your blood (neutropenia)
- decreased number of red blood cells in your blood (anaemia)
- decreased levels of platelets in your blood (you may bleed more easily)
- decreased levels phosphate
- decreased levels of potassium in your blood
- increased levels of creatinine in your blood
- increased levels in liver enzymes (AST)
- increased levels of lipase
- increased levels of amylase
- decreased levels of haemoglobin

The muscle pain, muscle weakness and decreases in potassium or phosphate in the blood may occur due to damage to kidney tubule cells.

Rare: may affect up to 1 in 1,000 people

- aggression, hallucinations, difficulty adjusting to changes, mood changes, sleep walking
- difficulty breathing, enlarged tonsils
- feeling of incomplete defecation
- enlarged liver or fatty liver, yellow skin or eyes, pain in the belly (abdomen) caused by inflammation of the liver
- inflammation of the skin due to allergy, redness on the cheeks, nose, chin or forehead, bumps or pimples on the face, swelling of the face, lips, tongue or throat
- muscle weakness, weakening of the bones (with bone pain and sometimes resulting in fractures)
- kidney damage, kidney stones, kidney failure, damage to kidney tubule cells, kidney injury, passing a lot of urine and feeling thirsty
- pain in the chest, feeling cold, pain, thirst

Blood tests may also show:

- decreased levels of magnesium
- lactic acidosis (excess lactic acid in the blood)
- increased levels of creatine phosphokinase

Very rare: may affect up to 1 in 10,000 people
Blood tests may also show:

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

If a side effect appears, if any of the side effects worsens 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 home page of the Ministry of Health's web site (www.health.gov.il) which refers to the online side effects reporting form, or by using the link: https://sideeffects.health.gov.il

5. HOW TO STORE DELSTRIGO?

- Avoid Poisoning! This medicine and 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**:
  - Do not store above 30ºC.
  - Keep the tablets and desiccant in the original package and keep the bottle tightly closed in order to protect from moisture.
  - The bottle contains a desiccant protecting the tablets from moisture. Keep the desiccant inside the bottle and do not throw away until you have finished taking all of the medicine.
- 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

In addition to the active ingredients Delstrigo also contains:
Hypromellose acetate succinate; microcrystalline cellulose E460; croscarmellose sodium E468; magnesium stearate E470b; silica, colloidal anhydrous E551; sodium stearyl fumarate.
The tablets are film-coated with a coating material containing the following ingredients: Hypromellose E464; titanium dioxide E171; lactose monohydrate; triacetin E1518; iron oxide yellow E172; and carnauba wax E903.

What Delstrigo looks like and contents of the pack
Delstrigo is available as a yellow, oval-shaped, film-coated tablet, and is debossed with the corporate logo and 776 on one side and plain on the other side.

Pack size: 1 bottle with 30 film-coated tablets.

Marketing Authorization Holder:
Merck Sharp & Dohme (Israel-1996) Company Ltd., P.O.Box 7121, Petah-Tikva 49170

Manufacturer:
Merck Sharp & Dohme Corp., New Jersey, USA

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Drug registration no. listed in the official Registry of the Ministry of Health: 165.35.36061