Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986
This medicine is dispensed with a doctor's prescription only

Isturisa 1 mg film-coated tablets
Isturisa 5 mg film-coated tablets
Isturisa 10 mg film-coated tablets

Active ingredient and its quantity:

Isturisa 1 mg film-coated tablets:
Each film-coated tablet contains osilodrostat phosphate corresponding to 1 mg osilodrostat

Isturisa 5 mg film-coated tablets:
Each film-coated tablet contains osilodrostat phosphate corresponding to 5 mg osilodrostat

Isturisa 10 mg film-coated tablets:
Each film-coated tablet contains osilodrostat phosphate corresponding to 10 mg osilodrostat

Inactive ingredients and allergens - see section 6 "Additional information".

Read the entire leaflet carefully before you start using this medicine.
This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.
This medicine has been prescribed to treat your illness. Do not pass it on to others. It may harm them, even if it seems to you that their illness is similar to yours.

1. What is the medicine intended for?

Isturisa is indicated for the treatment of endogenous Cushing's syndrome in adult patients for whom surgery is not an option or has not been curative. Cushing's syndrome is a condition in which the body produces too much of a hormone called cortisol. Too much cortisol may lead to a variety of symptoms such as weight gain (particularly around the waist), a moon-shaped face, bruising easily, irregular periods, excessive body and facial hair, and generally feeling weak, tired or unwell.

How Isturisa works
Isturisa blocks the main enzyme that makes cortisol in the adrenal glands. The effect of this is to decrease the over-production of cortisol and improve the symptoms of endogenous Cushing's syndrome.

Therapeutic group: Anti-corticosteroids

2. Before using the medicine

X Do not use this medicine if:

- You are sensitive (allergic) to osilodrostat or to any of the other ingredients of this medicine (see section 6 "Additional information").

Special warnings about using this medicine

Talk to your doctor before taking Isturisa:

- if you have a heart disorder or a heart rhythm disorder, such as an irregular heartbeat, including a condition called prolonged QT syndrome (QT interval prolongation).
- if you have a liver disease; your doctor may need to change your dose of Isturisa.

Contact your doctor immediately if you have two or more of these symptoms during your

treatment with Isturisa. This may indicate that you have adrenal insufficiency (low cortisol levels):

- weakness
- light-headedness
- tiredness
- lack of appetite
- nausea (feeling sick)
- vomiting

Children and adolescents
This medicine is not intended for patients aged under 18 years. There is no information regarding the safety and efficacy of the medicine in children and adolescents.

Tests and follow-up
Your doctor will test your blood and/or urine before you start treatment and regularly during treatment. This is to detect any possible abnormalities in your magnesium, calcium and potassium levels and also to measure the levels of cortisol. Depending on the results, your doctor may change your dose.

This medicine may have an unwanted effect (called QT prolongation) on the function of the heart. Your doctor will therefore also check for this effect by performing an electrocardiogram (ECG) before you start treatment and during treatment.

If your Cushing's syndrome is caused by a benign tumour (called adenoma) in the pituitary gland, your doctor may consider stopping your treatment if a pituitary scan shows that the adenoma has expanded into neighbouring regions.

Drug interactions
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including non-prescription medications and nutritional supplements. It is particularly important that you mention any of the following medicines:

- medicines that may have an unwanted effect (called QT prolongation) on the function of the heart. These include medicines used for abnormal heart rhythm such as quinidine, sotalol and amiodarone; medicines used for allergies (antihistamines); antidepressants such as amitriptyline and drugs for mental health disorders (antipsychotics); antibiotics, including the following types: macrolides, fluoroquinolones or imidazole; and other medicines for Cushing's disease (pasireotide, ketoconazole)
- theophylline (used to treat breathing problems) or tizanidine (used to treat muscle pain and muscle cramps)

Pregnancy and breast-feeding
This medicine may cause foetal harm when administered to pregnant women.
This medicine should not be used during pregnancy or breast-feeding, unless your doctor has advised you to do so. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Breast-feeding
It is unknown whether the active ingredient or its metabolites are excreted in human milk. Breast-feeding should be discontinued during treatment with Isturisa and for at least one week after treatment.

Contraception
A pregnancy test before initiating treatment is recommended in women of childbearing potential. Women who could become pregnant should use an effective method of contraception during treatment and for at least one week after the last dose. Ask your doctor about the need for contraception before you start taking Isturisa.

Driving and using machines
Dizziness and tiredness may occur during treatment with Isturisa. Do not drive or operate machines if you get these symptoms.

3. How to use this medicine?

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure about the dose or how to take this medicine.

The dose and the method of administration will be determined only by your doctor. The usual starting dose is two 1 mg tablets twice a day (about every 12 hours). Patients of Asian ancestry and patients with liver disease may need a lower starting dose (one 1 mg tablet twice a day).

After you have started treatment, your doctor may change your dose. This will depend on how you respond to the treatment. The highest recommended dose is 30 mg twice a day.

Do not exceed the recommended dose.

Isturisa tablets are taken by mouth and can be taken with or without food.

Do not crush/divide/chew the tablets because the tablets are film-coated.

If you take more Isturisa than you should
If you have taken an overdose and you feel unwell (for example if you feel weak, light-headed, tired or sick, or if you have to vomit), or if a child has accidentally swallowed your medicine, proceed immediately to a doctor or a hospital emergency room and bring the package of the medicine with you.

If you forget to take Isturisa
Do not take a double dose to make up for a forgotten dose. Instead, just wait until it is time for your next dose and take that at the scheduled time.

If you stop taking Isturisa
Do not stop taking Isturisa unless your doctor tells you to. If you stop your treatment with Isturisa, your symptoms may come back.

The treatment should be continued as recommended by your doctor. Even if there is an improvement in your health, do not stop treatment with the medicine without consulting your doctor.

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 regarding the use of the medicine, consult a doctor or pharmacist.

4. Side effects

Like with all medicines, this medicine may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

Some side effects may be serious. Please take particular note of the following:

- Tell your doctor immediately if you experience a heart disorder or heart rhythm disorder, such as a fast and irregular heartbeat, even when you are at rest, heart palpitations, blackouts or fainting (this could be a sign of a condition called QT prolongation, a side effect that may affect up to 1 in 10 people).
- Tell your doctor immediately if you have two or more of these symptoms: weakness, light-headedness, tiredness (fatigue), lack of appetite, nausea (feeling sick), vomiting. This may

indicate that you have adrenal insufficiency (low cortisol levels), a side effect that may affect more than 1 in 10 people. Adrenal insufficiency occurs when Isturisa lowers the amount of cortisol too much. It is more likely to occur during periods of increased stress. Your doctor will correct this by using a hormone medicine or by adjusting the dose of Isturisa.

Additional side effects

Very common side effects (may affect more than 1 in 10 people):
- vomiting
- nausea (feeling sick)
- diarrhoea
- abdominal pain
- tiredness (fatigue)
- build-up of fluid leading to swelling (oedema), particularly of your ankles
- abnormal blood tests (increased levels of testosterone, increased levels of adrenocorticotrophic hormone, also known as ACTH, low levels of potassium)
- decreased appetite
- dizziness
- headache
- rash
- low blood pressure (hypotension)

Common side effects (may affect up to 1 in 10 people):
- fast heartbeat (tachycardia)
- general feeling of being unwell (malaise)
- abnormal results of liver function tests
- fainting (syncope)
- excessive facial or body hair growth (hirsutism)
- acne

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

Reporting of side effects
You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects, or by the following link:
https://sideeffects.health.gov.il

5. How to store the medicine?

- Avoid poisoning! This medicine and any other medicine should be kept in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting without explicit instructions from the doctor.

- Do not use this medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.

- Storage Conditions:
  Do not store above 25°C.

  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. Additional information

In addition to the active ingredient, this medicine also contains:

- In the tablet core:

microcrystalline cellulose, mannitol, croscarmellose sodium, magnesium stearate, colloidal anhydrous silica.

- In the film coating:

hypromellose, titanium dioxide (E171), macrogol 4000, talc and iron oxides (E172, see below).

- Isturisa 1 mg film-coated tablets contain iron oxide yellow and iron oxide red.
- Isturisa 5 mg film-coated tablets contain iron oxide yellow.
- Isturisa 10 mg film-coated tablets contain iron oxide yellow, iron oxide red and iron oxide black.

What the medicine looks like and contents of the pack:
Isturisa is marketed in packs containing 60 film-coated tablets.

The 1 mg tablets are pale yellow, round and marked “Y1” on one side and “NVR” on the other side.

The 5 mg tablets are yellow, round and marked “Y2” on one side and “NVR” on the other side.

The 10 mg tablets are pale orange brown, round and marked “Y3” on one side and “NVR” on the other side.

Registration holder’s name and address:
Medison Pharma Ltd., 10 Hashiloach St., POB 7090, Petach Tikva.

Manufacturer’s name and address:

Recordati Rare Diseases
Immeuble Le Wilson
70 avenue du Général de Gaulle
92800 Puteaux
France

Approved in December 2022

Registration number of the medicine in the Ministry of Health’s National Drug Registry:

Isturisa 1 mg film-coated tablets: 171-12-37207
Isturisa 5 mg film-coated tablets: 171-13-37208
Isturisa 10 mg film-coated tablets: 171-14-37209

Isturisa 1 mg, 5 mg, 10 mg-PIL-1122-V1