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

The medicine is dispensed with a doctor's prescription only

Metopirone 250, Capsules

Each capsule contains: Metyrapone 250 mg

Inactive and allergenic ingredients in the preparation - see Section 2 "Important information about some of the ingredients of the medicine" and Section 6 "Further information".

Read the leaflet carefully in its entirety before using the medicine.
This leaflet contains concise information about the medicine. If you have 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.

1. WHAT IS THE MEDICINE INTENDED FOR?

Metopirone 250 acts as a diagnostic preparation that is intended to identify whether you suffer from inadequate production of the hormone ACTH (a hormone secreted by the pituitary gland and which is responsible for cortisol secretion), or as a diagnostic preparation that is intended to help diagnose a specific type of Cushing's syndrome. Cushing's syndrome is a set of symptoms resulting from elevated levels of the cortisol hormone (a hormone produced by the adrenal gland).

Metopirone 250 is also used for treating signs and symptoms of endogenous Cushing's syndrome by lowering elevated levels of cortisol.

Therapeutic group: Metyrapone belongs to the group of endocrine medicines which are also known as diagnostic preparations used to assess pituitary gland function.

2. BEFORE USING THE MEDICINE

☒ Do not take the medicine if:

- You are sensitive (allergic) to the active ingredient or to any of the other ingredients of the medicine (for a list of the inactive ingredients - see Section 6 - "Further information")
- Do not use the medicine as a diagnostic preparation intended to detect whether you suffer from an insufficient level of the hormone ACTH if you suffer from underactive adrenal glands (Addison's disease).

! Special warnings regarding use of the medicine

Before taking Metopirone 250 as a diagnostic preparation, inform the doctor if:

- You have, or think you may have, a condition in which your hormone levels are low (e.g., reduced adrenal gland production of cortisol or severe hypopituitarism). Your doctor will perform a test to make sure the medicine is right for you.

- You have liver disease or damage to the liver, as this may cause the medicine to work more slowly.
- You are taking medicines such as glucocorticoids. Your doctor may decide not to use Metopirone 250 as you will need to stop taking these medicines.

During treatment with Metopirone 250:
Metopirone 250 may temporarily reduce the quantity of hormones produced by the adrenal glands. Your doctor will correct this by prescribing an appropriate hormonal medicine.
If you have Cushing's syndrome, your doctor may give you medicine to prevent infections developing. Contact your doctor as soon as possible if you develop shortness of breath and fever over hours or days, as this may be a serious lung infection.

Tests before and during treatment with Metopirone 250
Blood tests will be performed before you start treatment with Metopirone 250, and regularly during the treatment. This is to detect any possible abnormalities in your potassium levels and to measure cortisol levels. Depending on the results, your doctor may adjust the dosage and/or prescribe a corrective treatment.
Depending on your cardiac risk factors, your doctor may refer you for an ECG before the initiation of or during treatment with Metopirone 250.

Talk to your doctor if you experience any of the following symptoms: weakness, fatigue, dizziness, loss of appetite, nausea or vomiting, diarrhea, abdominal pain. These symptoms and also low blood pressure, high levels of potassium, low levels of sodium or low levels of glucose in the blood may be signs of hypocortisolism (insufficient levels of cortisol in the blood).Your doctor will check your blood pressure and perform a blood test. If you are diagnosed with hypocortisolism, your doctor may decide to temporarily administer a glucocorticoid and/or reduce the dose or interrupt the treatment with Metopirone 250.

Drug interactions:

If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. In particular if you are taking:
- Phenytoin, barbiturates and other anticonvulsants to treat epilepsy
- Amitriptyline, chlorpromazine, alprazolam and other antidepressants, or other medicines used for treating anxiety, depression or mental disorders
- Cortisol, hydrocortisone, ACTH, tetracosactrin, hormones that affect the hypothalamic-pituitary axis which regulate body processes such as stress, emotions, energy levels, hunger and the immune system
- Corticosteroids
- Carbimazole, thyroxine and liothyronine, used for suppressing activity of the thyroid gland
- Cyproheptadine, used for treatment of allergic disorders

Do not take paracetamol together with Metopirone 250 without consulting a doctor.

Use of the medicine and food
Metopirone 250 is to be swallowed whole with milk or after a meal. This will reduce the chance of nausea caused by the capsules.

Pregnancy, breastfeeding and fertility
Metopirone 250 is not recommended for women of childbearing age who are not using contraception.
If you are pregnant, think you are pregnant or are planning to become pregnant, talk to your doctor as soon as possible to know if you should stop or continue Metopirone 250.

If you have to continue taking the medicine during pregnancy, your doctor will need to monitor your baby's cortisol levels for the first week of its life.

Do not breastfeed during treatment, as the active ingredient may be passed to your baby through breast milk.

Driving and using machines
Taking Metopirone 250 may make you feel dizzy or tired. If you feel these effects, do not drive or operate machinery until these effects have passed.

Taking Metopirone 250 for a long time
Could cause increased blood pressure.

Important information about some of the ingredients of the medicine
Metopirone 250 contains:

- Sodium ethyl parahydroxybenzoate and sodium propyl parahydroxybenzoate (preservatives from the paraben group) that may cause allergic reactions (sometimes delayed).
- As this medicine contains less than 1 millimole of sodium (23 mg) per dose, it is considered to be essentially 'sodium free'.

Monitoring and supervision
When used as a diagnostic agent, the medicine will be given only in the presence of a healthcare professional.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the preparation according to the doctor’s instructions.

Check with the doctor or pharmacist if you are not sure about the dosage and treatment regimen of the preparation.

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

The usual dosage is generally:

Use in Adults

1) As a diagnostic agent

- If you are undergoing a short single-dose test (for testing pituitary gland function):

  You will be asked to swallow the capsule(s) with yogurt or with milk at around midnight. The next morning, a blood sample will be taken from you and then checked by the doctor.
  The recommended dosage is 30 mg/kg.

- If you are undergoing a multiple-dose test (for testing function of the pituitary gland or for aiding in the diagnosis of a specific type of Cushing’s syndrome):

  Urine samples will be collected from you 24 hours before taking Metopirone 250. You will then receive 2-3 capsules (500-750 mg) every 4 hours over the next 24 hours. Take the capsules with milk or after a meal.
  Over the following 24 hours additional urine samples will be collected from you.

2) For treatment of signs and symptoms of endogenous Cushing’s syndrome
The dose given to you will be specific for you, and may range from one capsule (250 mg) to up to 24 capsules (6 g) per day, in 3 or 4 divided doses during the course of the day. The doctor may change the dosage from time to time in order to attain normal cortisol levels.

Always follow the doctor's instructions and never alter the dose, unless instructed to do so by the doctor.

Use in Children

1) As a diagnostic agent

- In the case of a short single-dose test (for testing pituitary gland function):

  The capsule(s) are to be swallowed with yogurt or with milk at around midnight. The next morning, a blood sample will be taken from the child and then checked by the doctor.
  The recommended dosage for children is 30 mg/kg, the same as the adult dosage.

- With regard to multiple-dose tests, the recommended dosage in children is 15 mg/kg or a minimum dose of 250 mg (one capsule), every 4 hours.

2) For treatment of signs and symptoms of Cushing's syndrome
The dosage will be adjusted individually according to cortisol levels and tolerability.

Do not exceed the recommended dose.

Child-resistant caps have significantly reduced the number of poisoning incidents caused by medicines each year. However, if you find it difficult to open the container, you can ask the pharmacist to remove the cap's safety mechanism and turn it into a regular easy-to-open cap.

Crushing/splitting/chewing
Swallow the capsules whole. Do not chew the capsules. No information is available regarding opening and dispersal of the capsule content.

If you have accidentally taken a higher dosage
If you have taken an overdose, or if a child or other person has accidentally swallowed the medicine, refer immediately to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you. If you have accidentally taken more capsules than you should have, you may experience nausea, abdominal pain and/or diarrhea. There may also be dizziness, tiredness, headache, sweating and an increase in blood pressure. You may need to take activated charcoal and be given hydrocortisone.

If you forget to take the medicine
If you forget to take this medicine at the appointed time, take it as soon as possible unless it is almost time to take the next dose. Do not take a double dose in order to make up for the forgotten dose. Go on taking the medicine as usual.

Adhere to the treatment regimen as recommended by the doctor.

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

If you have further questions regarding use of the medicine, consult with the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, the use of Metopirone 250 may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.

Serious side effects

- Tell your doctor immediately if you have two or more of these symptoms: weakness, light-headedness, fatigue, lack of appetite, nausea, vomiting, abdominal pain, diarrhea. This may indicate that you have adrenal insufficiency (low cortisol levels). Adrenal insufficiency occurs when metyrapone lowers cortisol levels too much. It is more likely to occur during periods of metyrapone dosage increase or increased stress. Your doctor will correct this by using a hormone medicine to compensate for the lack of cortisol and/or by adjusting the dose of metyrapone.
- Tell your doctor immediately if you have bleeding or bruising lasting longer than normal, bleeding from your gums, nose or skin, or if you feel tired most of the time. This may indicate that you have a decreased amount of red blood cells and/or white blood cells and/or platelets in your blood.

See also section 2 “During treatment with Metopirone 250”

Additional side effects

Very common side effects - effects that occur in more than 1 in 10 users:

- Adrenal insufficiency (low cortisol levels)
- Loss of appetite
- Headache
- Dizziness (light-headedness)
- High blood pressure (hypertension)
- Nausea
- Abdominal (stomach) pain
- Diarrhea
- Skin allergic reaction (urticaria, rash (skin redness), itching)
- Joint pain
- Swelling of limbs, hands or feet
- Asthenic conditions (tiredness, fatigue)

Common side effects - effects that occur in 1-10 users in 100:

- Low level of potassium (hypokalemia)
- Feeling sleepy or tired
- Low blood pressure
- Vomiting
- Acne
- Excessive body hair growth
- Muscular pain

Side effects of unknown frequency (effects having a frequency yet to be determined):

- Abnormal liver function (hepatic enzymes increased)
- Leukopenia, anemia, thrombocytopenia (decreased amount of red blood cells, white blood cells or platelets in blood)
- Hair loss
- Pulmonary infection

If a side effect occurs, if one of the side effects worsens or if you suffer from a side effect not mentioned in the leaflet, consult with the doctor.

Side effects can be reported to the Ministry of Health by clicking on the link “Report Side Effects of Drug Treatment” found on the Ministry of Health homepage

(www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il/

5. HOW SHOULD THE MEDICINE BE STORED?

Avoid poisoning! This medicine and any other medicine should be kept 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 the doctor.

Do not use the medicine after the expiry date (EXP) that appears on the package and bottle. The expiry date refers to the last day of that month.

Storage conditions:
Store below a temperature of 25°C in a tightly closed bottle to protect against moisture.

6. FURTHER INFORMATION

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

Capsule core:
Polyethylene Glycol 400, Glycerol 85%, Purified Water, Polyethylene Glycol 4000

Capsule shell:
Gelatin, Glycerol 85%, Titanium Dioxide, Sodium Ethyl Parahydroxybenzoate, Ethyl Vanillin, Sodium Propyl Parahydroxybenzoate, Paramethoxyacetophenone, Phosal 53MCT

What does the medicine look like and what are the contents of the package:
A plastic bottle containing 50 capsules.
The capsules are oblong, opaque, white to yellowish-white, with the inscription “HRA” printed in red on one side.

License holder name and address: CTS Ltd., 4 Haharash St., Hod Hasharon, 4524075.

Manufacturer name and address:
HRA Pharma Rare Diseases
200, Avenue De Paris, 92320 Chatillon, France

This leaflet was revised in 08/2022 according to the Ministry of Health guidelines.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 068-34-23659-01