

METOPIRONE- metyrapone capsule, gelatin coated

ESTEVE PHARMACEUTICALS, S.A.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use METOPIRONE safely and effectively. See full prescribing information for METOPIRONE.

METOPIRONE® (metyrapone capsules), for oral use

Initial U.S. Approval: 1961

----- RECENT MAJOR CHANGES -----

Indications and Usage (1)

09/2022

Dosage and Administration, Single-Dose Short Test (2.2)

09/2022

----- INDICATIONS AND USAGE -----

Metopirone is indicated, in combination with other diagnostic tests, for the diagnosis of adrenal insufficiency in adult and pediatric patients. (1)

----- DOSAGE AND ADMINISTRATION -----

- Single-Dose Short Test: 30 mg/kg at midnight (2.2)

----- DOSAGE FORMS AND STRENGTHS -----

Capsules: 250 mg (3)

----- CONTRAINDICATIONS -----

- In patients with adrenal cortical insufficiency (4)
- Hypersensitivity to Metopirone or to any of its excipients (4)

----- WARNINGS AND PRECAUTIONS -----

- Adrenal Insufficiency: May induce acute adrenal insufficiency. Ability of adrenals to respond to exogenous ACTH should be demonstrated before Metopirone is employed as a test (5.1)
- Dizziness and Sedation: May cause dizziness and sedation. Patients should not drive or operate machinery until these effects have passed (5.2)

----- ADVERSE REACTIONS -----

Adverse reactions include: hypotension, nausea, vomiting, abdominal discomfort or pain, headache, dizziness, sedation, allergic rash, leukopenia, anemia, and/or thrombocytopenia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Direct Success Inc. at 844-597-6373 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- DRUG INTERACTIONS -----

- Anticonvulsants, psychotropic, hormone preparations, corticosteroids, antithyroid agents, cyproheptadine: may affect the results of the metyrapone test. (7.1)
- Acetaminophen: Avoid concomitant use with Metopirone. (7.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Important Information Before Conducting Metopirone Testing

2.2 Single-Dose Short Test- Recommended Dose and Interpretation

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Adrenal Insufficiency

5.2 Dizziness and Sedation

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Metopirone

7.2 Effect of Metopirone on Other Drugs

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Metopirone is indicated, in combination with other diagnostic tests, for the diagnosis of adrenal insufficiency in adult and pediatric patients.

2 DOSAGE AND ADMINISTRATION

2.1 Important Information Before Conducting Metopirone Testing

Stop drugs affecting pituitary or adrenocortical function before administration of Metopirone in accordance with half-life of the drugs (consider at least 5 half-lives to avoid any interference with Metopirone testing). *[see Drug Interactions (7.1)]* .

Assess ability of patient's adrenals to respond to exogenous ACTH before Metopirone is employed as a test *[see Warnings and Precautions (5.1)]* .

2.2 Single-Dose Short Test- Recommended Dose and Interpretation

This test, usually given on an outpatient basis, determines plasma 11-desoxycortisol and/or ACTH levels after a single dose of Metopirone. Patients with suspected adrenocortical insufficiency based on the test results previously performed should be hospitalized overnight as a precautionary measure (see *Warnings and Precaution (5.1)*).

Recommended Dose

In adult and pediatric patients, the recommended single dose is 30 mg/kg (maximum 3 grams of Metopirone) administered at midnight with milk/yogurt or snack. The blood sample for the assay is taken early the following morning (7:30-8:00 a.m.). After the blood sample is collected, a prophylactic dose of glucocorticoid may be considered for patients with high risk for acute adrenal insufficiency.

Interpretation of 11-desoxycortisol and ACTH Levels After Metopirone Administration

Approximately 8 hours after administration of Metopirone, evaluate the values of ACTH and 11-desoxycortisol. Normal values will depend on the method used to determine ACTH and 11-desoxycortisol levels. An intact HPA axis function is generally indicated by an increase in 11-desoxycortisol to over 70 mcg/L. Because of an overlap between a normal ACTH response and an abnormal ACTH response, the ACTH response alone cannot be used to distinguish between healthy individuals and those with adrenal insufficiency.

3 DOSAGE FORMS AND STRENGTHS

Capsules: Metopirone 250 mg soft gelatin, white to yellowish-white, oblong, opaque, imprinted with "HRA" on one side in red ink.

4 CONTRAINDICATIONS

Metopirone is contraindicated in patients with adrenal cortical insufficiency or hypersensitivity to Metopirone or to any of its excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Adrenal Insufficiency

Metopirone may induce acute adrenal insufficiency in patients with reduced adrenal secretory capacity, as well as in patients with global pituitary insufficiency. The test should be performed in the hospital with close monitoring in case of suspected adrenal insufficiency.

Ability of adrenals to respond to exogenous ACTH should be demonstrated before Metopirone is employed as a test.

In the presence of hypo- or hyperthyroidism, response to the Metopirone test may be subnormal.

If adrenocortical or anterior pituitary function is more severely compromised than indicated by the results of the test, Metopirone may trigger adrenal insufficiency. This can be corrected by giving appropriate doses of corticosteroids.

5.2 Dizziness and Sedation

Metopirone may cause dizziness and sedation. Patients should not drive or operate machinery until these effects have passed.

6 ADVERSE REACTIONS

The following adverse reactions associated with the use of Metopirone were identified in clinical trials or postmarketing reports. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Cardiovascular System:* Hypotension
- *Gastrointestinal System:* Nausea, vomiting, abdominal discomfort or pain
- *Central Nervous System:* Headache, dizziness, sedation
- *Dermatologic System:* Allergic rash
- *Hematologic System:* Leukopenia, anemia, and/or thrombocytopenia

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Metopirone

Anticonvulsants, psychotropic drugs, hormone preparations, corticosteroids, antithyroid agents and cyproheptadine may affect the results of the Metopirone test.

If these drugs cannot be withdrawn, the necessity of carrying out the Metopirone test should be reviewed.

7.2 Effect of Metopirone on Other Drugs

Acetaminophen

Metopirone inhibits the glucuronidation of acetaminophen, which may decrease elimination of acetaminophen and lead to increased risk of adverse reactions related to acetaminophen.

Avoid concomitant use of Metopirone with acetaminophen.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published case series and reports on Metopirone use in pregnant females are insufficient to identify a drug-associated risk of major birth defects or miscarriage. Metyrapone crosses the placenta and may decrease fetal cortisol production (*see Data*). Animal reproductive studies have not been conducted with metyrapone. Metyrapone can decrease reproductive hormones by targeting adrenal androgenesis.

Data

Human Data

The Metopirone test was administered to pregnant women in their second and third trimester of pregnancy and evidence was found that the fetal pituitary responded to the enzymatic block. Transplacental transfer of Metopirone has been shown in humans and the drug can impair the biosynthesis of fetal and placental steroids. There are a few published reports of low cortisol levels at birth in infants exposed in utero following chronic use of metyrapone in pregnant females.

8.2 Lactation

Risk Summary

Metyrapone and its active metabolite, metyrapol, are present in human milk. There are no available data on the effects of metyrapone on the breastfed infant or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Metopirone and any potential adverse effects on the breastfed infant from Metopirone or from the underlying maternal condition.

8.4 Pediatric Use

Metopirone is indicated, in combination with other diagnostic tests, for the diagnosis of adrenal insufficiency in pediatric patients [*See Dosage and Administration (2.1)*].

8.5 Geriatric Use

Clinical studies of Metopirone did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

Other reported clinical experience has not identified differences in responses between patients 65 years of age and older and younger adult patients.

8.6 Hepatic Impairment

Patients with cirrhosis may have an impaired response to Metopirone.

10 OVERDOSAGE

Death occurred in a child after two doses of Metopirone 2 g.

Signs and Symptoms of Overdosage

The clinical picture of overdosage with Metopirone is characterized by gastrointestinal symptoms and by signs of acute adrenal insufficiency.

- *Cardiovascular System:* Cardiac arrhythmias, hypotension, dehydration.
- *Nervous System and Muscles:* Anxiety, confusion, weakness, impairment of consciousness.
- *Gastrointestinal System:* Nausea, vomiting, epigastric pain, diarrhea.
- *Laboratory Findings:* Hyponatremia, hypochloremia, hyperkalemia.

In patients under treatment with insulin or oral antidiabetics, the signs and symptoms of

acute overdosage with Metopirone may be aggravated or modified.

Treatment and Management of Overdosage

There is no specific antidote for Metopirone overdosage. Immediate treatment is essential in the management of Metopirone overdose.

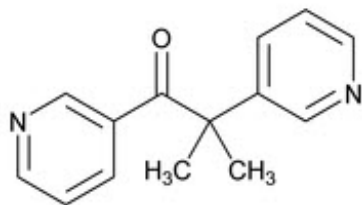
Treatment with activated charcoal may be considered if the overdose has been taken within 1 hour. In addition to general measures, hydrocortisone should be administered at once, together with IV saline and glucose. This should be repeated as necessary in accordance with the patient's clinical condition.

For a few days blood pressure and fluid and electrolyte balance should be monitored.

Consult with a regional poison control center (1-800-222-1222) for additional treatment recommendations.

11 DESCRIPTION

Metopirone (metyrapone capsules) is an adrenal steroid synthesis inhibitor, available as 250-mg capsules for oral administration. Its chemical name is 2-methyl-1,2-di-3-pyridyl-1-propanone, and its structural formula is



Metyrapone is a white to light amber, fine, crystalline powder, having a characteristic odor. It is sparingly soluble in water, and soluble in methanol and in chloroform. It forms water-soluble salts with acids. Its molecular weight is 226.27.

Inactive Ingredients: Ethyl vanillin, gelatin, glycerol, macrogol 400, macrogol 4000, paramethoxy acetophenone, purified water, sodium ethyl parahydroxybenzoate, sodium propyl parahydroxybenzoate, titanium dioxide, + red ink (aluminum chloride hexahydrate, carminic acid, hypromellose, propylene glycol, sodium hydroxide).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The pharmacological effect of Metopirone is to reduce cortisol and corticosterone production by inhibiting the 11-beta-hydroxylation reaction in the adrenal cortex. Removal of the strong inhibitory feedback mechanism exerted by cortisol results in an increase in adrenocorticotrophic hormone (ACTH) production by the pituitary. With continued blockade of the enzymatic steps leading to production of cortisol and corticosterone, there is a marked increase in adrenocortical secretion of their immediate precursors, 11-desoxycortisol and desoxycorticosterone, which are weak suppressors of ACTH release, and a corresponding elevation of these steroids in the plasma and of their metabolites in the urine. These metabolites are readily determined by measuring urinary 17-hydroxycorticosteroids (17-OHCS) or 17-ketogenic steroids (17-KGS).

Because of these actions, Metopirone is used as a diagnostic test, with urinary 17-OHCS measured as an index of pituitary ACTH responsiveness. Metopirone may also suppress biosynthesis of aldosterone, resulting in a mild natriuresis.

12.2 Pharmacodynamics

Metopirone exposure-response relationships and the time course of pharmacodynamic response are unknown.

12.3 Pharmacokinetics

The mean C_{max} of metyrapone following a single 750 mg is 3.7 mcg/mL falling to 0.5 mcg/mL 4 hours after administration.

Absorption

The time to peak plasma concentration of metyrapone is approximately 1 hour after oral administration.

Elimination

The mean ($\pm$ SD) terminal elimination half-lives of metyrapone and its active metabolite metyrapol are 1.9 ($\pm$ 0.7) hours and approximately 4 hours, respectively.

Metabolism

Metyrapone is reduced to metyrapol, an active alcohol metabolite. Both metyrapone and metyrapol are conjugated with glucuronide.

Eight hours after a single oral dose, the ratio of metyrapone to its active metabolite metyrapol in plasma is 1:1.5.

Excretion

Following administration of metyrapone 750 mg every 4 hours, approximately 5.3% of the dose was excreted in urine as unchanged and 38.5% as its active metabolite metyrapol within 72 hours after the first dose.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term animal carcinogenicity studies have not been conducted with Metopirone.

Mutagenesis

Metyrapone was not mutagenic with or without metabolic activation in bacterial mutagenicity tests.

Impairment of Fertility

No studies have been conducted to assess the effect of Metopirone on fertility.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Metopirone (metyrapone capsules) are supplied as 250 mg soft gelatin, white to yellowish-white, oblong, opaque capsules, imprinted with "HRA" on one side in red ink.

Bottle of 18 capsules: NDC 76336-455-18

Storage and Handling

Store Metopirone bottles at room temperature 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

Keep container tightly closed and protect from heat and moisture.

17 PATIENT COUNSELING INFORMATION

Advise patient to read the FDA-approved labeling (Patient Information).

Advise patient that Metopirone may induce acute adrenal insufficiency (nausea, vomiting, abdominal pain, hypotension) [see *Warnings and Precautions* (5.1)] .

Advise patient that Metopirone may cause dizziness and sedation. Advise patients not to drive or operate machinery until these effects have passed [see *Warnings and Precautions* (5.2)] .

Manufactured by:
Catalent Germany Eberbach GmbH
Eberbach, Germany

For:
HRA Pharma Rare Diseases
CHATILLON, France

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Fax: 1-855-674-6767

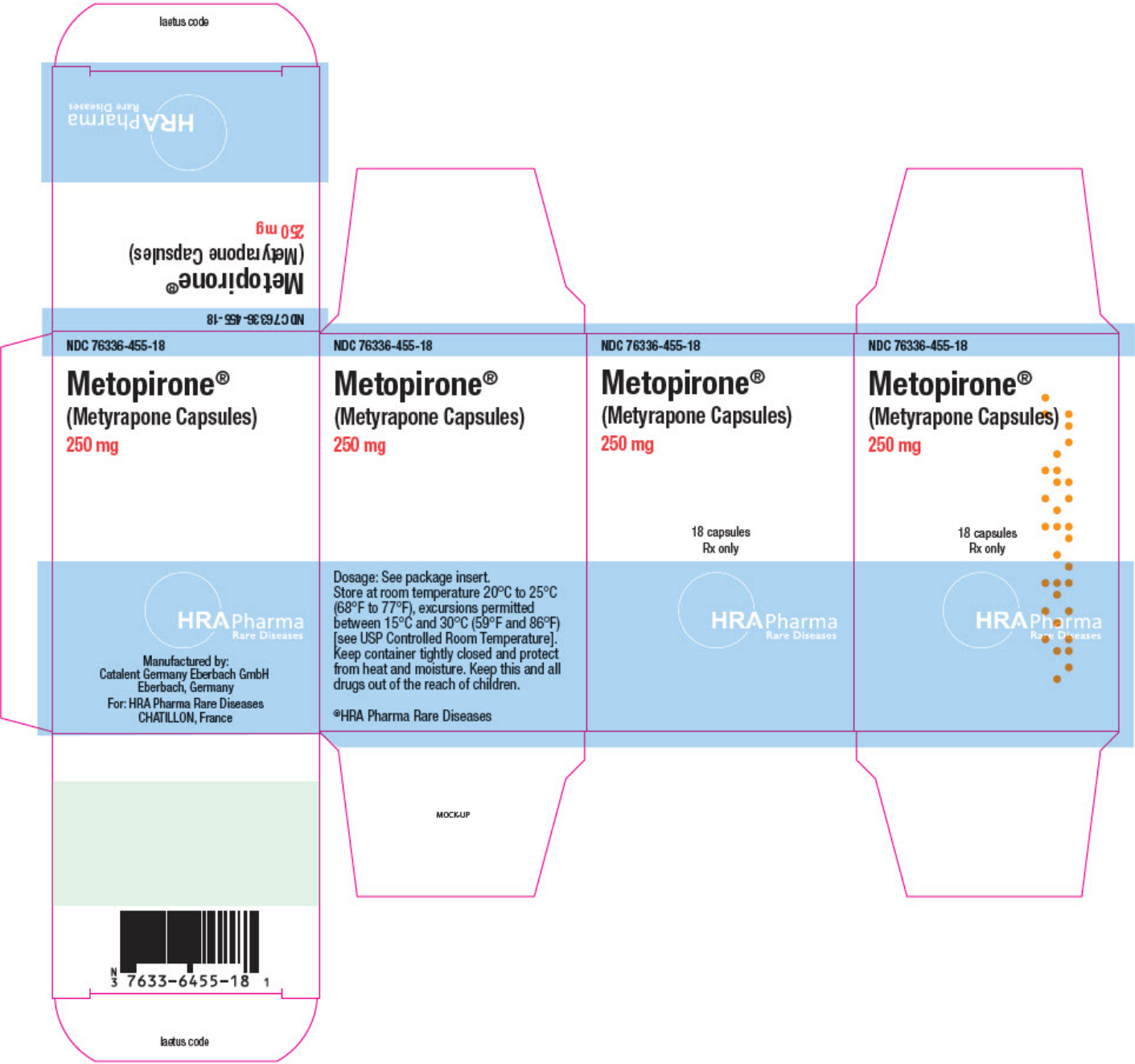
PRINCIPAL DISPLAY PANEL - 250 mg Bottle Carton

NDC 76336-455-18

Metopirone[®]
(Metyrapone Capsules)
250 mg

18 capsules
Rx only

HRA Pharma



METOPIRONE

metyrapone capsule, gelatin coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:68118-455
Route of Administration	ORAL		
Active Ingredient/Active Moiety			
Ingredient Name		Basis of Strength	Strength

METYRAPONE (UNII: ZS9KD92H6V) (METYRAPONE - UNII:ZS9KD92H6V)	METYRAPONE	250 mg
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Inactive Ingredients

Ingredient Name	Strength
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POLYETHYLENE GLYCOL 4000 (UNII: 4R4HFI6D95)	
GLYCERIN (UNII: PDC6A3C0OX)	
SODIUM ETHYLPARABEN (UNII: Z0D00IVA10)	
4-ACETYLANISOLE (UNII: 0IRH2BR587)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
PROPYLPARABEN SODIUM (UNII: 625NNB0G9N)	
ETHYL VANILLIN (UNII: YC9ST449YJ)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
WATER (UNII: 059QF0KO0R)	

Product Characteristics

Color	white (white to yellowish-white)	Score	no score
Shape	CAPSULE (soft gelatin; oblong; opaque)	Size	19mm
Flavor		Imprint Code	HRA
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68118-455-18	18 in 1 BOTTLE; Type 0: Not a Combination Product	01/25/1962	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA012911	01/25/1962	

Labeler - ESTEVE PHARMACEUTICALS, S.A. (460023922)

Establishment

Name	Address	ID/FEI	Business Operations
Minakem Beuvry Production		265413258	analysis(68118-455) , api manufacture(68118-455)

Establishment

Name	Address	ID/FEI	Business Operations
Minakem Dunkerque Production		277412599	analysis(68118-455)

Establishment			
Name	Address	ID/FEI	Business Operations
DELPHARM LILLE SAS		283582547	pack(68118-455) , analysis(68118-455)

Establishment			
Name	Address	ID/FEI	Business Operations
Catalent Germany Eberbach GmbH		318612223	manufacture(68118-455) , analysis(68118-455)

Establishment			
Name	Address	ID/FEI	Business Operations
Piramal Pharma Limited		919067108	analysis(68118-455) , api manufacture(68118-455)

Revised: 10/2025

ESTEVE PHARMACEUTICALS, S.A.