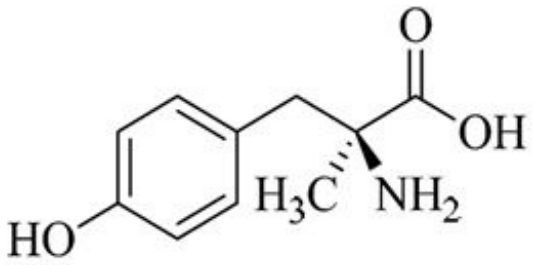
METYROSINE- metyrosine capsule
Amneal Pharmaceuticals NY LLC

Metyrosine Capsules, USP
(250 mg)
Rx Only

DESCRIPTION

Metyrosine is (–)-α-methyl-L-tyrosine or (α-MPT). It has the following structural formula:



Metyrosine, USP is a white to off-white powder of molecular weight 195.22 g/mol and molecular formula $C_{10}H_{13}NO_3$. It is very slightly soluble in methanol and insoluble in chloroform.

Metyrosine, USP is supplied as capsules for oral administration. Each capsule contains 250 mg metyrosine, USP.

Inactive ingredients are colloidal silicon dioxide, D & C yellow 10, FD & C blue 1, FD & C red 3, FD & C red 40, gelatin, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, titanium dioxide and water.

Each capsule is imprinted with black pharmaceutical ink which contains: butyl alcohol, dehydrated alcohol, ferrosoferric oxide, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac and strong ammonia solution.

Meets USP Dissolution Test 2.

CLINICAL PHARMACOLOGY

Metyrosine inhibits tyrosine hydroxylase, which catalyzes the first transformation in catecholamine biosynthesis, i.e. the conversion of tyrosine to dihydroxyphenylalanine (DOPA). Because the first step is also the rate-limiting step, blockade of tyrosine hydroxylase activity results in decreased endogenous levels of catecholamines, usually measured as decreased urinary excretion of catecholamines and their metabolites.

In patients with pheochromocytoma, who produce excessive amounts of norepinephrine and epinephrine, administration of one gram to four grams of metyrosine per day has reduced catecholamine biosynthesis from about 35% to 80% as measured by the total excretion of catecholamines and their metabolites (metanephrine

and vanillylmandelic acid). The maximum biochemical effect usually occurs within two to three days, and the urinary concentration of catecholamines and their metabolites usually returns to pre-treatment levels within three to four days after metyrosine is discontinued. In some patients the total excretion of catecholamines and catecholamine metabolites may be lowered to normal or near normal levels (less than 10 mg/24 hours). In most patients the duration of treatment has been two to eight weeks, but several patients have received metyrosine for periods of 1 to 10 years. Most patients with pheochromocytoma treated with metyrosine experience decreased frequency and severity of hypertensive attacks with their associated headache, nausea, sweating, and tachycardia. In patients who respond, blood pressure decreases progressively during the first two days of therapy with metyrosine; after withdrawal, blood pressure usually increases gradually to pre-treatment values within two to three days.

Metyrosine is well absorbed from the gastrointestinal tract. From 53% to 88% (mean 69%) was recovered in the urine as unchanged drug following maintenance oral doses of 600 mg to 4000 mg/24 hours in patients with pheochromocytoma or essential hypertension. Less than 1% of the dose was recovered as catechol metabolites. These metabolites are probably not present in sufficient amounts to contribute to the biochemical effects of metyrosine. The quantities excreted, however, are sufficient to interfere with accurate determination of urinary catecholamines determined by routine techniques.

Plasma half-life of metyrosine determined over an 8-hour period after single oral doses was 3 to 3.7 hours in three patients.

For further information, refer to: Sjoerdsma A, Engelman K, Waldman TA, Cooperman LH, Hammond WG. *Pheochromocytoma: Current* Concepts of Diagnosis and Treatment: Combined Clinical Staff Conference at the National Institutes of Health. Ann Intern Med. 1966;65:1302-1326.

INDICATIONS AND USAGE

Metyrosine capsules are indicated in the treatment of patients with pheochromocytoma for:

1. Preoperative preparation of patients for surgery.
2. Management of patients when surgery is contraindicated.
3. Chronic treatment of patients with malignant pheochromocytoma.

Metyrosine capsules are not recommended for the control of essential hypertension.

CONTRAINDICATIONS

Metyrosine capsules are contraindicated in persons known to be hypersensitive to this compound.

WARNINGS

Maintain Fluid Volume During and After Surgery

When metyrosine is used preoperatively, alone or especially in combination with alpha-

adrenergic blocking drugs, adequate intravascular volume must be maintained intraoperatively (especially after tumor removal) and postoperatively to avoid hypotension and decreased perfusion of vital organs resulting from vasodilatation and expanded volume capacity. Following tumor removal, large volumes of plasma may be needed to maintain blood pressure and central venous pressure within the normal range.

In addition, life-threatening arrhythmias may occur during anesthesia and surgery, and may require treatment with a beta-blocker or lidocaine. During surgery, patients should have continuous monitoring of blood pressure and electrocardiogram.

Intraoperative Effects

While the preoperative use of metyrosine in patients with pheochromocytoma is thought to decrease intraoperative problems with blood pressure control, metyrosine does not eliminate the danger of hypertensive crises or arrhythmias during manipulation of the tumor, and the alpha-adrenergic blocking drug, phentolamine, may be needed.

Interaction with Alcohol

Metyrosine may add to the sedative effects of alcohol and other CNS depressants, e.g., hypnotics, sedatives, and tranquilizers (see **PRECAUTIONS, Information for Patients** and **Drug Interactions**).

PRECAUTIONS

General

Metyrosine Crystalluria

Crystalluria and urolithias is have been found in dogs treated with metyrosine at doses similar to those used in humans, and crystalluria has also been observed in a few patients.

To minimize the risk of crystalluria, patients should be urged to maintain water intake sufficient to achieve a daily urine volume of 2000 mL or more, particularly when doses greater than 2 g per day are given. Routine examination of the urine should be carried out. Metyrosine will crystallize as needles or rods. If metyrosine crystalluria occurs, fluid intake should be increased further. If crystalluria persists, the dosage should be reduced or the drug discontinued.

Relatively Little Data Regarding Long-Term Use

The total human experience with the drug is quite limited and few patients have been studied long-term. Chronic animal studies have not been carried out. Therefore, suitable laboratory tests should be carried out periodically in patients requiring prolonged use of metyrosine and caution should be observed in patients with impaired hepatic or renal function.

Information for Patients

When receiving metyrosine, patients should be warned about engaging in activities requiring mental alertness and motor coordination, such as driving a motor vehicle or

operating machinery. Metyrosine may have additive sedative effects with alcohol and other CNS depressants, e.g., hypnotics, sedatives, and tranquilizers.

Patients should be advised to maintain a liberal fluid intake (see **PRECAUTIONS, General**).

Drug Interactions

Caution should be observed in administering metyrosine to patients receiving phenothiazines or haloperidol because the extrapyramidal effects of these drugs can be expected to be potentiated by inhibition of catecholamine synthesis.

Concurrent use of metyrosine with alcohol or other CNS depressants can increase their sedative effects (see **WARNINGS** and **PRECAUTIONS, Information for Patients**).

Laboratory Test Interference

Spurious increases in urinary catecholamines may be observed in patients receiving metyrosine due to the presence of metabolites of the drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenic studies in animals and studies on mutagenesis and impairment of fertility have not been performed with metyrosine.

Pregnancy

Animal reproduction studies have not been conducted with metyrosine. It is also not known whether metyrosine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Metyrosine should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether metyrosine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when metyrosine is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Geriatric Use

Clinical studies of metyrosine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Central Nervous System

Sedation

The most common adverse reaction to metyrosine is moderate to severe sedation, which has been observed in almost all patients. It occurs at both low and high dosages. Sedative effects begin within the first 24 hours of therapy, are maximal after two to three days, and tend to wane during the next few days. Sedation usually is not obvious after one week unless the dosage is increased, but at dosages greater than 2000 mg/day some degree of sedation or fatigue may persist.

In most patients who experience sedation, temporary changes in sleep pattern occur following withdrawal of the drug. Changes consist of insomnia that may last for two or three days and feelings of increased alertness and ambition. Even patients who do not experience sedation while on metyrosine may report symptoms of psychic stimulation when the drug is discontinued.

Extrapyramidal Signs

Extrapyramidal signs such as drooling, speech difficulty, and tremor have been reported in approximately 10% of patients. These occasionally have been accompanied by trismus and frank parkinsonism.

Anxiety and Psychic Disturbances

Anxiety and psychic disturbances such as depression, hallucinations, disorientation, and confusion may occur. These effects seem to be dose-dependent and may disappear with reduction of dosage.

Diarrhea

Diarrhea occurs in about 10% of patients and may be severe. Anti-diarrheal agents may be required if continuation of metyrosine is necessary.

Miscellaneous

Infrequently, slight swelling of the breast, galactorrhea, nasal stuffiness, decreased salivation, dry mouth, headache, nausea, vomiting, abdominal pain, and impotence or failure of ejaculation may occur. Crystalluria (see **PRECAUTIONS**) and transient dysuria and hematuria have been observed in a few patients. Hematologic disorders (including eosinophilia, anemia, thrombocytopenia, and thrombocytosis), increased SGOT levels, peripheral edema, and hypersensitivity reactions such as urticaria and pharyngeal edema have been reported rarely.

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE

Signs of metyrosine overdosage include those central nervous system effects observed in some patients even at low dosages.

At doses exceeding 2000 mg/day, some degree of sedation or feeling of fatigue may persist. Doses of 2000 mg/day to 4000 mg/day can result in anxiety or agitated

depression, neuromuscular effects (including fine tremor of the hands, gross tremor of the trunk, tightening of the jaw with trismus), diarrhea, and decreased salivation with dry mouth.

Reduction of drug dose or cessation of treatment results in the disappearance of these symptoms.

The acute toxicity of metyrosine was 442 mg/kg and 752 mg/kg in the female mouse and rat respectively.

DOSAGE AND ADMINISTRATION

The recommended initial dosage of metyrosine capsules for adults and children 12 years of age and older is 250 mg orally four times daily. This may be increased by 250 mg to 500 mg every day to a maximum of 4 g/day in divided doses. When used for preoperative preparation, the optimally effective dosage of metyrosine capsules should be given for at least five to seven days.

Optimally effective dosages of metyrosine capsules usually are between 2 g/day and 3 g/day, and the dose should be titrated by monitoring clinical symptoms and catecholamine excretion. In patients who are hypertensive, dosage should be titrated to achieve normalization of blood pressure and control of clinical symptoms. In patients who are usually normotensive, dosage should be titrated to the amount that will reduce urinary metanephrines and/or vanillylmandelic acid by 50% or more.

If patients are not adequately controlled by the use of metyrosine capsules, an alpha-adrenergic blocking agent (phenoxybenzamine) should be added.

Use of metyrosine capsules in children under 12 years of age has been limited and a dosage schedule for this age group cannot be given.

HOW SUPPLIED

Metyrosine Capsules USP, **250 mg** are supplied as size “0”, hard gelatin capsules with dark blue opaque cap imprinted with “AA” and light blue opaque body imprinted with “05A” with black ink. Each capsule is filled with white to off-white granular powder. They are available as follows:

Bottles of 100:	NDC 69238-1621-1
Bottles of 30:	NDC 69238-1621-3

Storage

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Package is not child-resistant.

Dispense in a tight, child-resistant container as defined in the USP.

Manufactured by:
Amneal Pharmaceuticals Pvt. Ltd.
Oral Solid Dosage Unit
Ahmedabad 382213, INDIA

Distributed by:

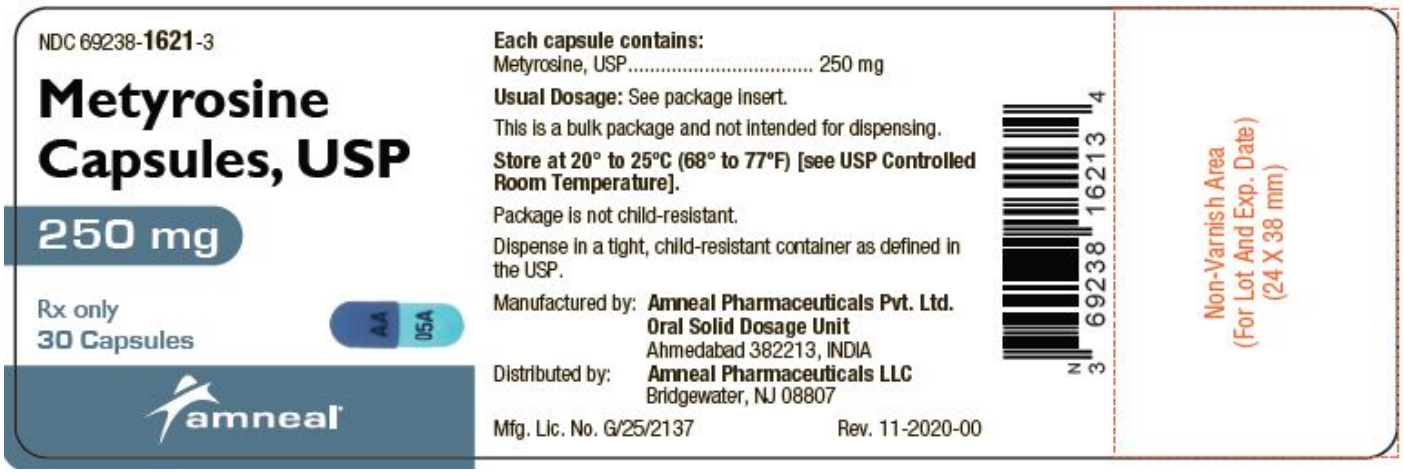
Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807

Rev. 11-2020-02

PRINCIPAL DISPLAY PANEL

NDC 69238-1621-1
Metyrosine Capsules USP, 250 mg
Rx Only
100 Capsules
Amneal Pharmaceuticals LLC

NDC 69238-1621-3
Metyrosine Capsules USP, 250 mg
Rx Only
30 Capsules
Amneal Pharmaceuticals LLC



METYROSINE

metyrosine capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:69238-1621

Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
METYROSINE (UNII: DOQ0J0TPF7) (METYROSINE - UNII:DOQ0J0TPF7)	METYROSINE	250 mg

Inactive Ingredients

Ingredient Name	Strength
ALCOHOL (UNII: 3K9958V90M)	
AMMONIA (UNII: 5138Q19F1X)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 3 (UNII: PN2ZH5LOQY)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
GELATIN (UNII: 2G86QN327L)	
HYDROXYPROPYL CELLULOSE, LOW SUBSTITUTED (UNII: 2165RE0K14)	
HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 9XZ8H6N6OH)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46N107B71O)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
WATER (UNII: 059QF0KO0R)	

Product Characteristics

Color	BLUE (dark blue opaque cap and light blue opaque body)	**Score**	no score
Shape	CAPSULE	**Size**	21mm
Flavor		**Imprint Code**	AA;05A
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69238-1621-1	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	07/24/2020	
2	NDC:69238-1621-3	30 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	12/15/2020	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA213734	07/24/2020	

Labeler - Amneal Pharmaceuticals NY LLC (123797875)

Revised: 2/2021 Amneal Pharmaceuticals NY LLC