metyrosine (Demser®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP201

Description

Metyrosine (Demser) is an orally administered tyrosine hydroxylase inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
metyrosine (generic Demser)	250 mg capsule	pheochromocytoma	480 capsules/30 days
metyrosine (Demser)			

Initial Evaluation

I. Metyrosine (Demser) may be considered medically necessary when the following criteria are met:
   A. Member is 12 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an endocrinologist; **AND**
   C. A diagnosis of **pheochromocytoma** when the following are met:
      1. Member has a surgical resection planned; **AND**
         i. Treatment with an alpha blocker (e.g., phenoxybenzamine, prazosin, terazosin, doxazosin) in combination with a beta blocker (e.g., propranolol, metoprolol, atenolol) was ineffective, contraindicated, or not tolerated; **OR**
      2. Member has a contraindication to surgery, or has malignant pheochromocytoma; **AND**
         i. Treatment with the following has been ineffective, contraindicated, or not tolerated:
            a. A selective alpha blocker (e.g., doxazosin, terazosin or prazosin); **AND**
            b. Generic phenoxybenzamine

II. Metyrosine (Demser) is considered investigational when used for all other conditions, including but not limited to:
   A. Velocardiofacial syndrome-associated psychosis

B. Bipolar disorder
C. Schizophrenia
D. Gilles de la Tourette's syndrome
E. Sarcoma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member requires long-term pharmacologic treatment following surgery or has malignant pheochromocytoma; **AND**
IV. Treatment with the following has been ineffective, contraindicated, or not tolerated:
    A. A selective alpha blocker (e.g., doxazosin, terazosin or prazosin); **AND**
    B. Generic phenoxybenzamine; **AND**
V. Member has exhibited improvement or stability of disease symptoms [e.g., hypertension, diaphoresis, headache, palpitations, tachycardia, syncope, anxiety] while on therapy

Supporting Evidence

I. Pheochromocytoma is a rare neuroendocrine tumor that hypersecrete one or more catecholamines (epinephrine, norepinephrine, and dopamine) and ff left untreated, cardiovascular morbidity and mortality are high. Once diagnosed, patients should undergo surgical resection of the pheochromocytoma following appropriate medical preparation. Preop medications are used for volume expansion and to control hypertension and preventing a hypertensive crisis during surgery. Patients with undiagnosed pheochromocytomas who undergo surgery for other reasons (and therefore have not undergone preoperative medical therapy), have an increased surgical mortality rate due to lethal hypertensive crises, malignant arrhythmias, and multiorgan failure. No randomized, controlled trials have compared the different approaches, and there is no universally accepted method of preparation for surgery in patients with pheochromocytoma.
II. Guidelines recommend preoperative combined alpha and beta blockade to prevent perioperative cardiovascular complications. Both selective (e.g. phenoxybenzamine) and non-selective (e.g. doxazosin, terazosin, prazosin) alpha-blockers have been used, there is insufficient evidence to recommend one over the other. After adequate alpha blockade has

been achieved, beta blockade is initiated, which typically occurs two to three days preoperatively. Metyrosine can then be considered in patients who cannot be treated with the typical combined alpha and beta blockade protocol because of intolerance or cardiopulmonary reasons. Preoperative medical treatment is recommended for 7 to 14 days to allow adequate time to normalize blood pressure and heart rate.

III. Metyrosine (Demser) is FDA approved for preoperative preparation of patients for surgery, management of patients when surgery is contraindicated, or chronic treatment of patients with malignant pheochromocytoma.

IV. The recommended initial dose of metyrosine (Demser) for adults and children 12 years of age or older is 250 mg four times daily. Treatment is dosed based on clinical symptoms and catecholamine excretion and may be increased by 250 to 500 mg every day to a maximum of 4.0 grams per day in divided doses.

V. There are no curative treatments for metastatic pheochromocytoma, unless the sites of disease are surgically resectable. Even in the metastatic setting standard treatment consists of surgery and palliative care. If all identifiable disease is resectable, including a limited number of distant metastases, surgery can provide occasional long-term remission. If disease is unresectable, surgical debulking will not improve survival; however, it is occasionally indicated for symptom relief. Per UptoDate, selective alpha-1-adrenergic blocking agents (e.g., prazosin, terazosin, or doxazosin) are utilized in many centers or are preferred to phenoxybenzamine when long-term pharmacologic treatment is indicated (e.g., for metastatic pheochromocytoma), due to their more favorable side-effect profiles and lower financial cost.

VI. Most patients with pheochromocytoma treated with Demser experience decreased frequency and severity of hypertensive attacks with their associated headache, nausea, sweating, and tachycardia

VII. The maximum biochemical effect usually occurs within two to three days, and the urinary concentration of catecholamines and their metabolites usually returns to pretreatment levels within three to four days after treatment 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 (Demser) for periods of 1 to 10 years. Per the package insert, the total human experience with the drug is quite limited and few patients have been studied long term.

Investigational or Not Medically Necessary Uses

I. Metyrosine (Demser) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Velocardiofacial syndrome-associated psychosis

i. Clinical evidence available is limited to case reports. There was a phase 2 trial (N=2) sponsored by Bausch Health (NCT01127503). However, results were not completed as the study was terminated due to enrollment, study-design and execution challenges.

B. Bipolar disorder
   i. Ten patients with psychotic diseases were given metyrosine, up to 4 grams/day. Of the 7 patients with mania, 5 improved while receiving metyrosine and 3 continued to improve after the metyrosine was discontinued. All 3 patients who were being treated for depression became worse and later improved after the metyrosine was discontinued. Further evidence is needed to further evaluate and support this off label use in a space with several treatment options.

C. Schizophrenia
   i. In a double-blind, crossover, placebo study severe schizophrenic symptoms could not be managed by metyrosine (2.75 grams/day). Use in this setting is not supported by available clinical evidence.

D. Gilles de la Tourette's syndrome
   i. Metyrosine (Demser) in doses of 1750 to 3000 milligrams/day was not an effective treatment for Giles de la Gilles de la Tourette's syndrome. In only 2 out of 6 patients were movements greatly diminished with high doses of metyrosine. Use in this setting is not supported by available clinical evidence.

E. Sarcoma
   i. Combination therapy with a metyrosine (Demser) derivative is subject of ongoing trials, currently recruiting, in this setting.

References

1. Demser [package insert]. Bridgewater, NJ. Valeant Pharmaceuticals International, Inc. December 2017
2. Uptodate. Treatment of pheochromocytoma in adults. Updated 11/25/2019
3. Uptodate. Paraganglioma and pheochromocytoma: Management of malignant disease. Updated 09/12/2019
4. Lenders JWM, Duh Q-Y, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(6):1915-1942.
5. PDQ® Adult Treatment Editorial Board. PDQ Pheochromocytoma and Paraganglioma Treatment. Bethesda, MD: National Cancer Institute. Updated 10/16/2020. Available at: https://www.cancer.gov/types/pheochromocytoma/hp/pheochromocytoma-treatment-pdq. [PMID: 26389312]
6. Metyrosine. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Available at: http://www.micromedexsolutions.com.
7. Carandang CG, Scholten MC. Metyrosine in psychosis associated with 22q11.2 deletion syndrome: case report. J Child Adolesc Psychopharmacol. 2007;17(1):115-120.

8. Bausch Health Americas, Inc. Metyrosine (Demser®) for the Treatment of Psychotic Disorders in Patients with Velocardiofacial Syndrome. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01127503. NLM identifier: NCT01127503.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020