BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

DEMSER® (metyrosine)
DIBENZYLINE® (phenoxybenzamine)
Metyrosine
Phenoxybenzamine

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for DEMSER (metyrosine) and generic Metyrosine

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by an Oncologist or Endocrinologist, or in consultation with one

Indication
- Diagnosis of pheochromocytoma with **ANY** of the following:

  - Short-term (5 to 7 days) preoperative management
  - Surgery contraindicated
  - Chronic treatment of malignant pheochromocytoma
- Other oncologic direct treatment use listed in National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

Age Requirement

- 12 years or older

Baseline Clinical Evaluation

- Symptoms consistent with pheochromocytoma: hypertension, episodic headache, nausea, tachycardia, sweating, syncope
- **ONE** of the following baseline tests completed before initiation and continued monitoring as clinically appropriate:
  - Free metanephrine in plasma
  - 24-hour urine fractionated metanephrines and normetanephrines with or without serum and/or 24-hour urine fractionated catecholamines

Alternative Therapies

- Failure, contraindication, intolerance to **ALL** the following:
  - ONE selective alpha 1 blocker: terazosin, doxazosin, prazosin
  - Phenoxybenzamine (brand or generic)
  - Beta-adrenergic blockade (only after adequate alpha blocker control of blood pressure)

Brand Specific Criteria

- **For Demser:** Have failure, contraindication, or intolerance to **THREE** generic equivalents (if available) of **metyrosine** for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- Use is not intended for treatment of essential hypertension

Documentation Requirements

- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (include all related lab values from above criteria)
  - Supporting clinical documentation

Initial Therapy Approval Duration:

- 6 months OR end of plan year

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Criteria for Continuation of Therapy (renewal therapy)

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualification

- Continues to be seen by or in consultation with an Oncologist or Endocrinologist

Clinical Response

- Positive clinical response defined as **ALL** of the following:
  - No evidence of disease progression
  - Normalization of blood pressure and control of other symptoms (e.g., episodic headache, nausea, tachycardia, sweating, syncope) **OR** at least 50% reduction in urinary metanephrines and/or vanillylmandelic acid in an individual with normal blood pressure

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- **For Demser**: Have failure, contraindication, or intolerance to **THREE** generic equivalents (if available) of **metyrosine** for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No significant adverse drug effects such as:
  - Significant hypotension
  - Life-threatening arrhythmia
  - Crystalluria and urolithiasis

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values that confirm safe use from above criteria

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Medical Necessity Requirements for DIBENZYLINE (phenoxybenzamine) and Phenoxybenzamine generic

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Criteria for Initial Therapy:

Indication
- Diagnosis of pheochromocytoma with episodes of headache, sweating, and tachycardia with or without paroxysmal hypertension (if tac tachycardia is excessive, a beta-blocker such as metoprolol may be added after alpha-blockade
- Other oncologic direct treatment use listed in National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

Age Requirement
- 18 years or older

Alternative Therapies
- Failure, contraindication, intolerance to ALL the following:
  - **ONE** selective alpha 1 blocker: doxazosin, prazosin, terazosin
  - **ONE** calcium channel blocker: nicardipine, amlodipine

Brand Specific Criteria
- **For Dibenzyline:** Have failure, contraindication, or intolerance to **THREE** generic equivalents (if available) of **phenoxybenzamine** for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Documentation Requirements
- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (include all related lab values from above criteria)
  - Supporting clinical documentation

Initial Therapy Approval Duration:
- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy)
Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Clinical Response
- Blood pressure is controlled
- No significant sweating, tachycardia, and episodic headaches

Adherence
- Adherence to the prescribed therapy regimen has been documented

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Brand Specific Criteria

- **For Dibenzyline:** Have failure, contraindication, or intolerance to **THREE** generic equivalents (if available) of **phenoxybenzamine** for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No significant adverse drug effects such as:
  - Significant episodes of postural hypotension
  - Significant tachycardia
  - Significant episodes of dizziness or fainting

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values that confirm safe use from above criteria

Continuation Therapy Approval Duration:

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications

2. Off-Label Use of Cancer Medications

Description:

Phenoxybenzamine, a long-acting, adrenergic, *alpha*-receptor-blocking agent, is indicated in the treatment of pheochromocytoma, to control episodes of hypertension and sweating. Alpha-adrenergic blockade leaves beta-adrenergic receptors unopposed and if tachycardia is excessive, it may be necessary to use a *beta*-blocking agent simultaneously. The long-acting alpha-blockade produces and maintains a chemical sympathectomy. It also increases blood flow to the skin, mucosa, and abdominal viscera, and lowers both supine and erect blood pressures. It has no effect on the parasympathetic system.

Metyrosine is indicated in the treatment of individuals with pheochromocytoma for: 1) preoperative preparation of individuals for surgery; 2) management of individuals when surgery is contraindicated; and 3) chronic treatment of

individuals with malignant pheochromocytoma. Metyrosine is not recommended for the control of essential hypertension.

Metyrosine inhibits tyrosine hydroxylase, the enzyme that 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.

Pheochromocytomas are neoplasms of the chromaffin cells of the adrenal medulla in 80-90% of cases. Ectopic or extra-adrenal pheochromocytomas that come from sympathetic and para-aortic sympathetic ganglia are called paragangliomas. Approximately 10-15% of pheochromocytomas and paragangliomas are malignant. Some suggest it could be up to 40%. Malignant pheochromocytomas are histologically and biochemically the same as benign ones. The only consistent indication to the presence of a malignant pheochromocytoma is local invasion into surrounding tissues and organs (e.g., kidney, liver) or distant metastases. Some experts have suggested that all pheochromocytomas have some metastatic potential. The diagnosis of pheochromocytoma is made based upon biochemical confirmation of catecholamine hypersecretion, followed by identifying the tumor with imaging studies. Once a pheochromocytoma is diagnosed, all patients should undergo a resection of the pheochromocytoma following appropriate medical preparation.

Pheochromocytomas release catecholamines (epinephrine and norepinephrine) and their metabolites metanephrine and normetanephrine, resulting in hypertension, arrhythmia, and/or hyperglycemia. Symptoms are present in approximately 50% of patients with pheochromocytoma, and when present, they are typically paroxysmal. The classic triad of symptoms in patients with a pheochromocytoma consists of episodic headache, sweating, and tachycardia. However, most patients with pheochromocytoma do not have the three classic symptoms.

Surgical resection is the mainstay of treatment for both benign and malignant pheochromocytomas and paragangliomas Surgery (or stress) can cause a sudden release of large amounts of catecholamines, causing very significant and sometimes life-threatening hypertension. Treatment of pheochromocytoma consist of alpha-1 selective blockers (terazosin, doxazosin, prazosin) or non-selective alpha blockade (phenoxybenzamine) 7-14 days prior to surgery. After adequate alpha blockade is achieved, a beta blocker is started 2-3 days prior to surgery. Intravenous phentolamine can be used intraoperatively. Alpha blockade is first-line therapy for all hormonally secreting pheochromocytomas. After alpha blockade, if further blood pressure control is needed, the addition of a dihydropyridine calcium channel blocker can be used. Metyrosine can also be used with alpha blockers for blood pressure control. Beta blockers can be added to alpha blockers for tachycardia. Beta-1 selective agents or non-selective beta blockers can be used.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

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Resources:

Demser (metyrosine) product information, revised by Bausch Health US, LLC. 07-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 28, 2025.

Metyrosine product information, revised by Oceanside Pharmaceuticals. 07-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 28, 2025.

Dibenzyline (phenoxybenzamine) product information, revised by Advanz Pharma (US) Corp. 11-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 28, 2025.

Phenoxybenzamine product information, revised by Burel Pharmaceuticals, LLC. 07-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 28, 2025.

Young WF, Kebebew E. Treatment of pheochromocytoma in adults. In: UpToDate, Nieman LK, Carty SE, Rubinow K, Chen W (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through April 2025. Topic last updated October 18, 2024. Accessed May 28, 2025.

Young WF. Clinical presentation and diagnosis of pheochromocytoma. In: UpToDate, Nieman LK, Rubinow K (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through April 2025. Topic last updated July 29, 2024. Accessed May 28, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Neuroendocrine and Adrenal Tumors Version 2.2025 – Updated May 28, 2025. Available at https://www.nccn.org. Accessed May 28, 2025.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.