Pheochromocytoma Medications (Demser®, Dibenzyline®, generics)

Policy # 00626
Original Effective Date: 01/01/2019
Current Effective Date: 01/01/2019

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider Demser®‡ (metyrosine), Dibenzyline®‡ (phenoxybenzamine), or generic phenoxybenzamine for the treatment of pheochromocytoma to be **eligible for coverage** when patient selection criteria are met.

Patient Selection Criteria
Coverage eligibility for Demser (metyrosine), Dibenzyline (phenoxybenzamine), or generic phenoxybenzamine will be considered when the following criteria are met:

- The requested drug is Dibenzyline (phenoxybenzamine); AND
    - The patient has tried and failed (e.g. intolerance or inadequate response) GENERIC phenoxybenzamine unless there is clinical evidence or patient history that suggests the use of GENERIC phenoxybenzamine will be ineffective or cause an adverse reaction to the patient; AND
      *(Note: This specific patient criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
    - The patient has a diagnosis of pheochromocytoma and ONE of the following:
        - Surgical resection of the tumor is planned; OR
        - The patient has tried and failed (e.g. intolerance or inadequate response) ONE of the following alternative agents for a clinically adequate duration: generic doxazosin, generic terazosin, generic prazosin, or a generic calcium channel blocker.
          *(Note: These specific patient criteria are additional company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*
- The requested drug is Demser (metyrosine) or generic phenoxybenzamine; AND
    - The patient has a diagnosis of pheochromocytoma and ONE of the following:
        - Surgical resection of the tumor is planned; OR
        - The patient has tried and failed (e.g. intolerance or inadequate response) ONE of the following alternative agents for a clinically adequate duration: generic doxazosin, generic terazosin, generic prazosin, or a generic calcium channel blocker.

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When Services Are Considered Not Medically Necessary
The use of Demser (metyrosine) when the patient has not tried and failed generic phenoxybenzamine and the use of Demser (metyrosine) or either phenoxybenzamine product when surgery is not planned or the patient has not tried and failed an alternative agent is considered to be **not medically necessary.****

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers Demser (metyrosine), Dibenzyline (phenoxybenzamine), and generic phenoxybenzamine for the treatment of conditions other than pheochromocytoma to be **investigational.***

Background/Overview

Demser (metyrosine) is a tyrosine hydroxylase inhibitor used in the treatment of pheochromocytoma. It works by blocking tyrosine hydroxylase which causes a decrease in the endogenous levels of catecholamines (i.e. epinephrine, norepinephrine, and dopamine). Patients with pheochromocytoma produce excessive amounts of catecholamines, and Demser has been shown to reduce catecholamine synthesis 35-80%. Demser is dosed based on clinical symptoms and catecholamine excretion and should be started at 250 mg orally 4 times daily and increased to a maximum of 4 grams per day in divided doses. The maximum effect usually occurs within 2-3 days and the amount of catecholamines returns to pretreatment levels within 3-4 days after Demser is discontinued. In most patients, the duration of treatment is 2-8 weeks. When it is used for preoperative preparation, the optimally effective dosage of Demser should be given for at least 5-7 days. If patients are not adequately controlled on Demser, an alpha-adrenergic blocking agent such as phenoxybenzamine should be added.

Dibenzyline (phenoxybenzamine) is a non-selective alpha-adrenergic receptor blocker that is indicated to control hypertension and sweating in patients with pheochromocytoma. It is important to note that Dibenzyline-induced alpha-adrenergic blockade leaves beta-adrenergic receptors unopposed and concomitant administration of a beta blocker (e.g. atenolol, metoprolol, or propranolol) may be needed to control excessive tachycardia. Dibenzyline (phenoxybenzamine) should be dosed according to patient response with an initial dose of 10 mg by mouth twice daily increased every other day until the patient's blood pressure is adequately controlled. Long-term use of Dibenzyline (phenoxybenzamine) is not recommended.

Pheochromocytoma is an extremely rare neuroendocrine tumor that produces catecholamines such as epinephrine, norepinephrine, and dopamine. The reported prevalence is 0.2-0.6% of patients with general hypertension. The associated catecholamine secretion may cause hypertension, diaphoresis, headache, palpitations, tachycardia, syncope, and anxiety. Tumors may also be malignant and require surgical

resection, radiation therapy, or chemotherapy. The 2014 Endocrine Society clinical practice guideline recommends pre-operative treatment with alpha-adrenergic receptor blockers as the first choice to control blood pressure and prevent perioperative cardiovascular complications. Both selective (e.g. phenoxybenzamine) and non-selective (e.g. doxazosin, terazosin, prazosin) alpha-blockers have been used and there is insufficient evidence to recommend one over the other. Calcium channel blockers are the most often used add-on drug class to further improve blood pressure control in patients already treated with alpha-adrenergic receptor blockers. Preoperative co-administration of beta-adrenergic receptor blockers (e.g. atenolol, metoprolol, and propranolol) is utilized to control tachycardia after administration of alpha-adrenergic receptor blockers. Demser (metyrosine) may be used in combination with alpha-adrenergic receptor blockers for a short period before surgery to further stabilize blood pressure to reduce blood loss and volume depletion during surgery.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Demser is indicated in the treatment of patients with pheochromocytoma for 1) preoperative preparation of patients for surgery, 2) management of patients when surgery is contraindicated, and 3) chronic treatment of patients with malignant pheochromocytoma. Demser is not recommended for the control of essential hypertension.

Dibenzyline and its generic are indicated in the treatment of pheochromocytoma, to control episodes of hypertension and sweating.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The patient selection criteria presented in this policy take into consideration guideline recommended treatment for pheochromocytoma as well as clinical evidence or patient history that suggest generic equivalents or generic alternative treatments will be ineffective or cause an adverse reaction to the patient. Based on review of available data, in the absence of the above mentioned caveats, there is no advantage of using Demser, Dibenzyline, or generic phenoxybenzamine when surgical resection of the tumor is not planned or the patient has not tried a generic selective alpha-adrenergic blocking agent or calcium channel blocker.

References

1. Demser [package insert]
2. Dibenzyline [package insert]
3. Express Scripts Pheochromocytoma prior authorization policy. Updated August 2017.

4. Lenders JWM, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2014;99(6):1915-1942.
5. Treatment of pheochromocytoma in adults. UpToDate. Oct. 2017

Policy History

Original Effective Date: 01/01/2019
Current Effective Date: 01/01/2019
08/09/2018 Medical Policy Committee review
08/15/2018 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 08/2019

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.