PRIOR AUTHORIZATION POLICY

POLICY: Pheochromocytoma

- Demser® (metyrosine capsules – Pharmaceutics International/Valeant/Aton Pharma)
- Phenoxybenzamine capsules (Dibenzyline® – Concordia Pharmaceuticals, generics)

APPROVAL DATE: 08/28/2019

OVERVIEW

Demser, a tyrosine hydroxylate inhibitor, is indicated in the treatment of 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.[1] Blocking tyrosine hydroxylase results in decreased endogenous levels of catecholamines (e.g., epinephrine, norepinephrine, and dopamine). The recommended initial dose of Desmer for adults and children aged ≥ 12 years is 250 mg four times daily. This may be increased by 250 to 500 mg every day to a maximum of 4.0 grams/day in divided doses. When used for preoperative preparation, the optimally effective dose of Demser should be administered for at least 5 to 7 days. Optimally effective dosages for Demser are usually between 2.0 and 3.0 grams/day, and the dose should be titrated by monitoring clinical symptoms and catecholamine excretion. In those who are hypotensive, the dosage should be titrated to achieve normalization of blood pressure and control of clinical symptoms. In those who are usually normotensive, the dose should be titrated to the amount that will reduce urinary metanephrines and/or vanillylmandelic acid by ≥ 50%. If patients are not adequately controlled by the use of Demser, an alpha-adrenergic blocking agent (e.g., phenoxybenazmine) should be added.

Phenoxybenzamine (Dibenzyline®, generics), a long-acting, adrenergic, alpha-receptor blocking agent, is indicated for the treatment of pheochromocytoma to control episodes of hypertension and sweating. If tachycardia is excessive, it may be necessary to use a beta-blocking agent concomitantly.[2] The dose should be adjusted to meet the needs of each patient. Small initial doses should be slowly increased until the desired effect is achieved or the adverse events (AEs) from blockage become troublesome. After each increase, the patient should be observed on that level before instituting another increase.

Disease Overview

Pheochromocytoma is a tumor that arises from adrenomedullary chromaffin cells that produce catecholamines such as epinephrine, norepinephrine, and dopamine.[3-5] Some of the tumors are malignant. This condition is uncommon and the reported prevalence is up to 0.6% of patients with general hypertension. The catecholamine secretion may cause hypertension, along with other symptoms such as diaphoresis, headache, palpitations, tachycardia, syncope, and anxiety. For some patients measures must be taken to avoid hypertensive crisis.[3-5] Some genetic syndromes associated with phenochromocytoma include multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau syndrome, and neurofibromatosis type 1.[5] Certain foods and beverage contain tyramine which may exacerbate uncontrolled catecholamine release in patients with pheochromocytoma (e.g., chocolate, aged cheese, certain wines). Tumors may also be malignant and require surgical resection, radiation therapy, or chemotherapy.[5] Phenoxybenzamine and Demser are FDA-approved for use in pheochromocytoma.[1-2] Although not indicated, short-acting alpha adrenergic blockers (e.g., doxazosin, prazosin, and terazosin) have also been used.[5-7] Beta-blockers (e.g., atenolol, metoprolol, propranolol) are also utilized, especially in patients with tachycardia or hypertension following alpha-blockade therapy. Dihydropyridine calcium channel blockers (e.g., amlodipine, nifedipine or nicardipine) are also used for preoperative preparation as an adjunctive therapy to alpha-adrenergic blockers).[5] Although only available as an injection, phentolamine, an alpha-adrenergic blocker, is indicated for the prevention and control of hypertensive episodes that may occur in a patient with pheochromocytoma as a result of stress or manipulation during

preoperative preparation and surgical excision.[8] Also, phentolamine injection is indicated for the diagnosis of pheochromocytoma by the phentolamine blocking test.

Guidelines

A clinical practice guideline was published in 2014 from the Endocrine Society regarding from pheochromocytoma and paraganglioma.[3] The guidelines recommend preoperative alpha$_1$-adrenergic receptor blockers as the first choice to control blood pressure and prevent a hypertensive crisis. Both selective and non-selective alpha-blockers have been used (e.g., phenoxybenzamine, doxazosin, prazosin, and terazosin). 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 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.

The National Comprehensive Cancer Network guidelines for Neuroendocrine and Adrenal Tumors (Version 1.2019 – March 5, 2019) address pheochromocytoma and paragangliomas.[9] Alpha blockade (e.g., terazosin, doxazosin, and prazosin) is recommended first-line for all hormonally-secreting pheochromocytomas and paragangliomas. After alpha blockade, if additional blood pressure support is required, the additional of dihydropyridine calcium channel blockers can be considered. Metyrosine can be used in addition to alpha blockage to stabilize blood pressure.

Safety

Demser is associated with AEs that include severe central nervous system (CNS) changes (e.g., sedation [moderate to severe], changes in sleep pattern with medication withdrawal), extrapyramidal effects (e.g., dropping, speech difficulty, and tremor), anxiety, psychic disturbances (e.g., hallucinations, depression, confusion), diarrhea, and crystalluria. User Demser cautiously if the patient is receiving phenothiazines or haloperidol because the extrapyramidal effects of these medications may be potentiated by inhibition of catecholamine synthesis. Also, use of Demser with alcohol or other CNS depressants may increase the sedative effects. The safety and effectiveness of Demser is pediatric patients below the age of 12 years have not been established. Demser is rated in Pregnancy Category C. AEs associated with phenoxybenzamine include those of the autonomic nervous system (e.g., postural hypotension, tachycardia, nasal congestion and miosis).

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Demser and phenoxybenzamine. All approvals are provided for the duration noted below. Due to the specialized skills required for evaluation and diagnosis of patients treated with Demser and phenoxybenzamine, as well as the monitoring required for AEs and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a prescriber who specializes in the condition being treated.

Automation: None.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, and prescription receipts.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of phenoxybenzamine is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Pheochromocytoma.** Approve phenoxybenzamine for 1 year if the patient meets the following criteria (A and B):
   - **A)** The agent is prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the management of pheochromocytoma; AND
   - **B)** If brand Dibenzyline is requested, the patient has tried AND cannot take generic phenoxybenzamine due to a formulation difference in the inactive ingredient(s) (e.g., difference in dyes, fillers, preservatives) between the brand and the bioequivalent generic product which, according to the prescriber, would result in a significant allergy or a serious adverse reaction **[documentation required]**.

II. Coverage of Demser is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Pheochromocytoma.**
   - **A)** Initial therapy. Approve Demser for 1 year if the patient meets all of the following criteria (i, ii, and iii):
     - **i.** The patient has tried a selective alpha blocker (e.g., doxazosin, terazosin or prazosin); AND
     - **ii.** The patient has tried phenoxybenzamine (brand or generic); AND
     - **iii.** Demser is prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the management of pheochromocytoma.
   - **B)** Patient is currently receiving Demser or has received Demser in the past. Approve for 1 year if Demser is prescribed by, or in consultation with, an endocrinologist or a physician who specializes in the management of pheochromocytoma.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Demser and phenoxybenzamine have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below.

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Demser® capsules [prescribing information]. Hunt Valley, MD and Bridgewater, NJ: Pharmaceutics International and Aton Pharma/Valeant; December 2017.
2. Dibenzyline® capsules [prescribing information]. St. Michael, Barbados: Concordia Pharmaceuticals; December 2018.
3. 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.
4. Fishbein L. Pheochromocytoma and paraganglioma: genetics, diagnosis and treatment. *Hematol Oncol Clin N Am*. 2016;30:135-150.
5. Hodin R, Lubitz C, Phitayakorn R, Stephen A. Diagnosis and management of pheochromocytoma. *Curr Prob Surg*. 2014;51(4):151-187.

6. Van der Zee PA, De Boer A. Pheochromocytoma: a review on preoperative treatment with phenoxybenzamine or doxazosin. *Neth J Med*. 2014;72(4):190-201.
7. Lenders JWM, Eisenhofer G. Update on modern management of pheochromocytoma and paraganglioma. *Endocrinol Metab (Seoul)*. 2017;32(2):152-161.
8. Phentolamine injection. Bedford, OH: Bedford Laboratories; May 1999.
9. The NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (Version 1.2019 – March 5, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 29, 2019.