



BlueCross BlueShield
of Alabama

Name of Blue Advantage Policy:

Myocardial Sympathetic Innervation Imaging in Patients with Heart Failure

Policy #: 530
Category: Radiology

Latest Review Date: September 2020
Policy Grade: B

BACKGROUND:

Blue Advantage medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
 - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
 - *Furnished in a setting appropriate to the patient's medical needs and condition;*
 - *Ordered and furnished by qualified personnel;*
 - *One that meets, but does not exceed, the patient's medical need; and*
 - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill **Original Medicare for covered services that are related to **clinical trials** that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Effective for dates of service on or after March 24, 2020:

Blue Advantage will treat myocardial sympathetic innervation imaging with ¹²³Iodine meta-iodobenzylguanidine (MIBG) as a **non-covered benefit** and as **investigational** for patients with heart failure.

Effective for dates for dates of service on or after February 26, 2018, and before March 24, 2020, refer to LCD L34555

Effective for dates of service on or after October 6, 2013 and prior to February 26, 2018:

Blue Advantage will treat myocardial sympathetic innervation imaging with ¹²³Iodine meta-iodobenzylguanidine (MIBG) as a **non-covered benefit** and as **investigational** for patients with heart failure.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

In patients with heart failure, activation of the sympathetic nervous system is an early mechanism to compensate for decreased myocardial function. The concentration of Iodine 123 meta-iodobenzylguanidine (MIBG) over several hours after injection of the agent is a potential marker of sympathetic neuronal activity and may correlate with the severity of heart failure. MIBG activity is proposed as a prognostic marker in patients with heart failure to aid in the identification of patients at risk of 1- and 2- year mortality. The marker could also potentially be used to guide treatment decisions or to monitor the effectiveness of heart failure treatments.

Heart Failure

An estimated 5.7 million adults in the United States have heart failure, and heart failure is the main cause of death for approximately 58,300 Americans each year. Underlying causes of heart failure include coronary artery disease (CAD), hypertension, valvular disorders, and primary cardiomyopathies. These conditions reduce myocardial pump function and decrease left ventricular ejection fraction (LVEF). An early mechanism to compensate for this decreased myocardial function is activation of the sympathetic nervous system. The increased sympathetic activity initially helps compensate for heart failure by increasing heart rate and myocardial contractility in order to maintain blood pressure and organ perfusion. However, over time this places additional strain on the myocardium, increasing coronary perfusion requirements, which can lead to worsening of ischemic heart disease and or myocardial damage. As the ability of the

heart to compensate for reduced myocardial function diminishes, clinical symptoms of heart failure develop. Another detrimental effect of heightened sympathetic activity is an increased susceptibility to potentially fatal ventricular arrhythmias.

Overactive sympathetic innervation associated with heart failure involves increased neuronal release of norepinephrine (NE), the main neurotransmitter of the cardiac sympathetic nervous system. In response to sympathetic stimulation, vesicles containing NE are released into the neuronal synaptic cleft. The released NE binds to post-synaptic beta-1, beta-2 and alpha receptors, enhances adenylyl cyclase activity and brings about the desired cardiac stimulatory effects. NE is then taken back into the presynaptic space for storage or catabolic disposal that terminates the synaptic response by the uptake-1 pathway. The increased release of NE is usually accompanied by decreased NE reuptake, thereby further increase circulating NE levels.

Diagnostic Imaging

Guanethidine is a false neurotransmitter that is an analogue of NE; it is also taken up by the uptake-1 pathway. Iodine 123 meta-iodobenzylguanidine (known as ¹²³I-MIBG or MIBG) is guanethidine that is chemically modified and labeled with radioactive iodine. MIBG moves into the synaptic cleft and then is taken up and stored in the presynaptic nerve space in a manner that is similar to NE. However, unlike NE, MIBG is not catabolized and thus concentrates in myocardial sympathetic nerve endings. This concentrated MIBG can be imaged with a conventional gamma camera. The concentration of MIBG over several hours after injection of the agent is thus a reflection of sympathetic neuronal activity, which in turn may correlate with the severity of heart failure.

MIBG myocardial imaging has been in use in Europe and Japan and standardized procedures for imaging have been proposed by European organizations. Administration of MIBG is recommended by slow (1 to 2 minutes) injection. Planar images of the thorax are acquired 15 minutes (early image) and four hours (late image) after injection. In addition, optional single-photon emission computed tomography (SPECT) imaging can be performed following the early and late planar images. MIBG uptake is semi-quantified by determining the average count per pixel in regions of interest (ROI) drawn over the heart and the upper mediastinum in the planar anterior view. There is no single universally used myocardial MIBG index. The most commonly used myocardial MIBG indices are the early heart to mediastinum (H/M) ratio, late H/M ratio and the myocardial MIBG washout rate. The H/M ratio is calculated by taking the average count per pixel in the myocardium divided by the average count per pixel in the mediastinum. The myocardial washout rate is expressed as the rate of decrease in myocardial counts over time between early and late imaging (normalized to mediastinal activity).

MIBG activity is proposed as a prognostic marker in patients with heart failure, to be used in conjunction with established markers or prognostic models to identify heart failure patients at increased risk of short-term mortality. MIBG activity could also potentially be used to guide treatment decisions or to monitor the effectiveness of heart failure treatments.

KEY POINTS:

The most recent literature update was performed through July 8, 2020.

Summary of Evidence

For individuals with heart failure who receive imaging with MIBG for prognosis, the evidence includes numerous studies that findings on cardiac imaging with MIBG predict outcomes in patients with heart failure. Relevant outcomes are overall survival, disease-specific survival, functional outcomes, health status measures, quality of life, hospitalizations, and medication use. While the available studies vary in their patient inclusion criteria and methods for analyzing MIBG parameters, the highest quality studies demonstrate a significant association of MIBG results with adverse cardiac events, including cardiac death. Moreover, MIBG findings have been shown to improve the ability of the Seattle Heart Failure Model and other risk prediction models to predict mortality. However, there is no direct published evidence on the clinical utility of MIBG (i.e., whether findings of the test would lead to patient management changes that improve health outcomes) and no chain of evidence can be constructed to support clinical utility. Management changes made as a result of MIBG imaging are uncertain, and it is not possible to determine whether management changes based on MIBG results lead to improved health outcomes compared with management without MIBG imaging. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

National Heart, Lung and Blood Institute

In 2011, a working group of the National Heart, Lung, and Blood Institute published a report on translation of cardiovascular molecular imaging. In regard to imaging the heart with MIBG, the report cited the ADMIRE-HF trial [discussed earlier] and stated that additional clinical trials are needed to determine the efficacy of heart failure management strategies with MIBG compared to usual care without MIBG imaging.

American College of Cardiology Foundation et al

The American College of Cardiology Foundation and the American Heart Association updated its 2013 joint guidelines (2017) on the management of heart failure with the Heart Failure Association of America. These guidelines did not address the use of MIBG imaging in heart failure management.

U.S. Preventive Services Task Force Recommendations

Not applicable

KEY WORDS:

Heart failure, Sympathetic innervation, ¹²³Iodine meta-iodobenzylguanidine, ¹²³I-MIBG, MIBG, Myocardial Imaging, AdreView, SPECT, I-123

APPROVED BY GOVERNING BODIES:

In 2008, AdreView® (Iobenguane I 123) Injection (GE Healthcare) was approved by the Food and Drug Administration new drug application process (22-290) for the detection of primary or metastatic pheochromocytoma or neuroblastoma as an adjunct to other diagnostic tests.

In 2013, the Food and Drug Administration approved a supplemental new drug application (22-290/S001) for AdreView® and expanded the labeled indication to include scintigraphic assessment of sympathetic innervation of the myocardium by measurement of the H/M ratio of radioactivity uptake in patients with New York Heart Association class II or class III heart failure and left ventricular ejection fraction less than 35%.

BENEFIT APPLICATION:

Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

CODING:

CPT Codes:

0331T	Myocardial sympathetic innervations imaging, planar qualitative and quantitative assessment;
0332T	; with tomographic SPECT

HCPCS:

A9582	Iodine I- ¹²³ iobenguane, diagnostic, per study dose, up to 15 millicuries
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REFERENCES:

1. Akutsu Y, Kaneko K, Kodama Y, et al. Iodine-123 mIBG Imaging for predicting the development of atrial fibrillation. JACC Cardiovasc Imaging. Jan 2011; 4(1):78-86.
2. Al Badarin FJ, Wimmer AP, Kennedy KF, et al. The utility of ADMIRE-HF risk score in predicting serious arrhythmic events in heart failure patients: incremental prognostic benefit of cardiac 123I-mIBG scintigraphy. J Nucl Cardiol. Aug 2014; 21(4):756-762; quiz 753-755, 763-755.
3. Armstrong L, Sharif JA, Galloway P et al. Evaluating the use of metabolite measurement in children receiving treatment with a thiopurine. Aliment Pharmacol Ther 2011; 34(9):1106-14.

4. Buxton DB, Antman M, Danthi N et al. Report of the National Heart, Lung, and Blood Institute working group on the translation of cardiovascular molecular imaging. *Circulation* 2011; 123(19):2157-63.
5. Centers for Disease Control and Prevention (CDC). Heart Failure Fact Sheet. Available online at: www.cdc.gov/dhdsdp/data_statistics/fact_sheets/fs_heart_failure.htm. Last accessed August 2018.
6. Chirumamilla A, Travin MI. Cardiac applications of ¹²³I-mIBG imaging. *Semin Nucl Med*. Sept 2011; 41(5):374-87.
7. Doi T, Nakata T, Hashimoto A et al. Synergistic prognostic values of cardiac sympathetic innervation with left ventricular hypertrophy and left atrial size in heart failure patients without reduced left ventricular ejection fraction: a cohort study. *BMJ Open* 2012; 2(6). *Eur Heart J* 2008; 29(9):1147-59.
8. Doi T, Nakata T, Hashimoto A, et al. Synergistic prognostic values of cardiac sympathetic innervation with left ventricular hypertrophy and left atrial size in heart failure patients without reduced left ventricular ejection fraction: a cohort study. *BMJ Open*. 2012; 2(6).
9. Flotats A, Carrio I, Agostini D et al. Proposal for standardization of ¹²³I-metaiodobenzylguanidine (MIBG) cardiac sympathetic imaging by the EANM Cardiovascular Committee and the European Council of Nuclear Cardiology. *Eur J Nucl Med Mol Imaging* 2010; 37(9):1802-12.
10. Food and Drug Administration (FDA). Approval letter: NDA 22-290. AdreView®, (Iobenguane I 123) 2mCi/mL Injection. 2008; www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022290s000toc.cfm. Accessed August 9, 2018.
11. Food and Drug Administration (FDA). AdreView: Highlights of Prescribing Information. Available online at: www.accessdata.fda.gov/drugsatfda_docs/label/2013/022290s001lbl.pdf.
12. Food and Drug Administration (FDA). Supplemental Approval letter: NDA 22-290/S-001. AdreView (Iobenguane I 123) Injection. 2013; www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/022290orig1s001ltr.pdf. Accessed August 9, 2018.
13. Jacobson AF, Senior R, Cerqueira MD et al. Myocardial iodine-¹²³ meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. *J Am Coll Cardiol* 2010; 55(20):2212-21.
14. Jain KK, Hauptman PJ, Spertus JA, et al. Incremental utility of iodine-123 meta-iodobenzylguanidine imaging beyond established heart failure risk models. *J Card Fail*. Aug 2014; 20(8):577-583.
15. Katoh S, Shishido T, Kutsuzawa D et al. Iodine-¹²³-metaiodobenzylguanidine imaging can predict future cardiac events in heart failure patients with preserved ejection fraction. *Ann Nucl Med* 2010; 24(9):679-86.
16. Ketchum ES, Jacobson AF, Caldwell JH et al. Selective improvement in Seattle Heart Failure Model risk stratification using iodine-¹²³ meta-iodobenzylguanidine imaging. *J Nucl Cardiol* 2012; 19(5):1007-16.
17. Klein T, Abdulghani M, Smith M, et al. Three-Dimensional ¹²³I-Meta-Iodobenzylguanidine Cardiac Innervation maps to assess substrate and successful

- ablation sites for ventricular tachycardia: a feasibility study for a novel paradigm of innervation imaging. *Circ Arrhythm Electrophysiol*. Feb 23 2015.
18. Minamisawa M, Izawa A, Motoki H, et al. Prognostic significance of neuroadrenergic dysfunction for cardiovascular events in patients with acute myocardial infarction. *Circ J*. 2015; 79(10):2238-2245.
 19. Nakata T, Nakajima K, Yamashina S et al. A pooled analysis of multicenter cohort studies of (123) I-MIBG imaging of sympathetic innervation for assessment of long-term prognosis in heart failure. *JACC Cardiovasc Imaging* 2013; 6(7):772-84.
 20. Narula J, Gerson M, Thomas GS, et al. (1) (2) (3) I-MIBG Imaging for Prediction of Mortality and Potentially Fatal Events in Heart Failure: The ADMIRE-HFX Study. *J Nucl Med*. Jul 2015; 56(7):1011-1018.
 21. Scala O, Paolillo S, Formisano R, et al. Sleep-disordered breathing, impaired cardiac adrenergic innervation and prognosis in heart failure. *Heart*. Jun 23 2016.
 22. Sood N, Al Badarin F, Parker M et al. Resting perfusion MPI-SPECT combined with cardiac 123I-MIBG sympathetic innervation imaging improves prediction of arrhythmic events in non-ischemic cardiomyopathy patients: sub-study from the ADMIRE-HF trial. *J Nucl Cardiol* 2013; 20(5):813-20.
 23. Treglia G, Stefanelli A, Bruno I et al. Clinical usefulness of myocardial innervation imaging using Iodine-¹²³-meta-iodobenzylguanidine scintigraphy in evaluating the effectiveness of pharmacological treatments in patients with heart failure: an overview. *Eur Rev Med Pharmacol Sci* 2013; 17(1):56-68.
 24. Verberne HJ, Brewster LM, Somsen GA et al. Prognostic value of myocardial ¹²³I-metaiodobenzylguanidine (MIBG) parameters in patients with heart failure: a systematic review.
 25. Verschure DO, Veltman CE, Manrique A, et al. For what endpoint does myocardial 123I-MIBG scintigraphy have the greatest prognostic value in patients with chronic heart failure? Results of a pooled individual patient data meta-analysis. *Eur Heart J Cardiovasc Imaging*. Sep 2014; 15(9):996-1003.
 26. Yancy CW, Jessup M, Bozkurt B et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; 128(16):1810-52.
 27. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. Apr 28 2017; 136(6):e137-e161.

POLICY HISTORY:

Adopted for Blue Advantage, July 2013

Available for comment August 22 through October 5, 2013

Medical Policy Group, June 2014

Medical Policy Group, June 2015

Medical Policy Group, September 2016

Medical Policy Group, September 2017

Medical Policy Group, February 2018

Medical Policy Group, September 2020: Reinstated policy effective March 24, 2020. For dates of service before March 24, 2020, and on or after February 26, 2018, refer to LCD L34555.

L34555 (Non-Covered Category III CPT Codes) retired effective March 23, 2020.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.