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Medical Benefit		Effective Date: 10/01/09	Next Review Date: 11/17
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Preauthorization is not required.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With patent foramen ovale and cryptogenic stroke 	Interventions of interest are: <ul style="list-style-type: none"> Patent foramen ovale closure with a transcatheter device 	Comparators of interest are: <ul style="list-style-type: none"> Medical management 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Morbid events Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With patent foramen ovale and migraine 	Interventions of interest are: <ul style="list-style-type: none"> Patent foramen ovale closure with a transcatheter device 	Comparators of interest are: <ul style="list-style-type: none"> Medical management 	Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Quality of life Medication use Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With patent foramen ovale and conditions associated with PFO other than cryptogenic stroke or migraine 	Interventions of interest are: <ul style="list-style-type: none"> Patent foramen ovale closure with a transcatheter device 	Comparators of interest are: <ul style="list-style-type: none"> Usual care 	Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Change in disease status Morbid events Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With atrial septal defect and evidence of left-to-right shunt or right ventricular overload 	Interventions of interest are: <ul style="list-style-type: none"> Atrial septal defect closure with a transcatheter device 	Comparators of interest are: <ul style="list-style-type: none"> Surgical ASD repair 	Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Change in disease status Treatment-related mortality Treatment-related morbidity

Description

Patent foramen ovale (PFO) and atrial septal defects (ASDs) are relatively common congenital heart defects associated with a range of symptoms. Depending on their size, ASDs may lead to left-to-right shunting and signs and symptoms of pulmonary overload. Repair of ASDs is indicated for patients with a significant degree of left-to-right shunting. PFOs may be asymptomatic but have been associated with higher rates of cryptogenic stroke. PFOs have also been investigated for a variety of other conditions, such as migraine. Transcatheter "closure" devices are intended as less invasive, catheter-based approaches of repairing PFO or ASDs. These devices are

alternatives to open surgical repair for ASDs or treatment with antiplatelet and/or anticoagulant medications in patients with cryptogenic stroke and PFO.

Summary of Evidence

The evidence for PFO closure with a transcatheter device in individuals who have PFO and cryptogenic stroke includes three randomized controlled trials (RCTs) comparing device-based PFO closure with medical therapy, multiple nonrandomized comparative studies, and multiple systematic reviews and meta-analyses of these studies. Relevant outcomes include overall survival, morbid events, and treatment-related morbidity and mortality. None of the three trials reported statistically significant improvements on their main outcome using intention-to-treat analysis. In all three trials, low numbers of outcome events in both groups limited the power to detect differences between groups. One trial showed a significant benefit for the closure group on per protocol analysis and another showed significant benefit on secondary outcomes. Meta-analyses of these trials have also come to different conclusions, with some reporting a statistically significant reduction in recurrent events on pooled analysis and others reporting a trend for benefit that is not statistically significant. While these results suggest that a benefit might be present, the evidence is not definitive and the risk-benefit ratio of transcatheter PFO closure as an alternative to medical therapy is not well-defined. The evidence is insufficient to determine the effects of the technology on health outcomes.

Given the conflicting findings from multiple systematic reviews related to the use of PFO closure devices for stroke prevention, clinical input was obtained to address the use of PFO closure devices. Clinical input did not consistently support the use of PFO closure devices in patients with cryptogenic stroke or for other indications.

The evidence for PFO closure with a transcatheter device in individuals who have PFO and migraines includes one randomized, sham-controlled trial of PFO closure, along with multiple observational studies reporting on the association between PFO and migraine. Relevant outcomes are symptoms, quality of life, medication use, and treatment-related morbidity and mortality. The available sham-controlled RCT did not demonstrate significant improvements in migraine symptoms after PFO closure. Nonrandomized studies have shown highly variable rates of migraine improvement after PFO closure. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for PFO closure with a transcatheter device in individuals who have PFO and conditions associated with PFO other than cryptogenic stroke or migraine (e.g., platypnea-orthodeoxia syndrome, myocardial infarction with normal coronary arteries, decompression illness, high altitude pulmonary edema, obstructive sleep apnea) includes small case series and case reports. Relevant outcomes are symptoms, change in disease status, morbid events, and treatment-related morbidity and mortality. The body of evidence consists only of small case series and case reports. Comparative studies are needed to evaluate outcomes in similar patient groups treated with and without PFO closure. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for ASD closure with a transcatheter device in individuals who have ASD and evidence of left-to-right shunt or right ventricular overload includes nonrandomized comparative studies and single-arm studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity and mortality. The available nonrandomized comparative studies and single-arm case series have shown rates of closure using transcatheter-based devices approaching the high success rates of surgery, which are supported by meta-analyses of these studies. The percutaneous approach has a low complication rate and avoids the morbidity and complications of open surgery. If the percutaneous approach is unsuccessful, ASD closure can be achieved using surgery. Because of the benefits of percutaneous closure over open surgery, it can be determined that transcatheter ASD closure improves outcomes in patients with an indication for ASD closure. The evidence is

sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Policy

Closure of patent foramen ovale using a transcatheter approach is considered **investigational**. (There are currently no transcatheter devices with the U.S. Food and Drug Administration [FDA] approval or clearance for this indication.)

Transcatheter closure of secundum atrial septal defects may be considered **medically necessary** when using a device that has been FDA approved for that purpose and used according to the labeled indications.

Policy Guidelines

At present, no PFO closure devices are approved by the FDA for patients with cryptogenic stroke. All uses of these PFO closure devices are currently off-label.

There are two FDA-approved devices for ASD closure: the AMPLATZER™ Septal Occluder, and the GORE HELEX™ Septal Occluder.

The labeled indications for these devices are similar and include:

- Those with echocardiographic evidence of ostium secundum atrial septal defect; AND
- Clinical evidence of right ventricular volume overload (i.e., 1.5:1 degree of left to right shunt or right ventricular enlargement).

Generally recognized indications for closure include a pulmonary-to-systemic flow ratio of greater than 1.5, right atrial and right ventricular enlargement, and paradoxical embolism.

Background

Patent Foramen Ovale

The foramen ovale, a component of fetal cardiovascular circulation, consists of a communication between the right and left atrium that functions as a vascular bypass of the uninflated lungs. The ductus arteriosus is another feature of the fetal cardiovascular circulation, consisting of a connection between the pulmonary artery and the distal aorta. Before birth, the foramen ovale is held open by the large flow of blood into the left atrium from the inferior vena cava. Over a course of months after birth, an increase in left atrial pressure and a decrease in right atrial pressure result in permanent closure of the foramen ovale in most individuals. However, a PFO is a common finding in 25% of normal adults.¹ In some epidemiologic studies, PFO has been associated with cryptogenic stroke, defined as an ischemic stroke occurring in the absence of potential cardiac, pulmonary, vascular, or neurologic sources. Studies have also shown an association between PFO and migraine headache. There has been interest in either open surgery or transcatheter approaches to close the PFO in patients with a history of cryptogenic stroke to prevent recurrent stroke.

Atrial Septal Defects

Unlike PFO, which represents the postnatal persistence of normal fetal cardiovascular physiology, ASDs represent an abnormality in the development of the heart that results in free communication between the atria. ASDs are categorized by their anatomy. Ostium secundum describes defects located midseptally and are typically near the fossa ovalis. Ostium primum defects lie immediately adjacent to the atrioventricular valves and are within the spectrum of atrioventricular septal defects. Primum defects occur commonly in patients with

Down syndrome. Sinus venous defects occur high in the atrial septum and are frequently associated with anomalies of the pulmonary veins.

Ostium secundum ASDs are the third most common form of congenital heart disorder and one of the most common congenital cardiac malformations in adults, accounting for 30% to 40% of these patients older than age 40 years. The ASD often goes unnoticed for decades because the physical signs are subtle and the clinical sequelae are mild. However, virtually all patients who survive into their sixth decade are symptomatic; fewer than 50% of patients survive beyond age 40 to 50 years due to heart failure or pulmonary hypertension related to the left-to-right shunt. Symptoms related to ASD depend on the size of the defect and the relative diastolic filling properties of the left and right ventricles. Reduced left ventricular compliance and mitral stenosis will increase left-to-right shunting across the defect. Conditions that reduce right ventricular compliance and tricuspid stenosis will reduce left-to-right shunting or cause a right-to-left shunt. Symptoms of an ASD include exercise intolerance and dyspnea, atrial fibrillation, and, less commonly, signs of right heart failure. Patients with ASDs are also at risk for paradoxical emboli.

Repair of ASDs is recommended for those with a pulmonary to systemic flow ratio ($Q_p:Q_s$) exceeding 1.5:1.0. Despite the success of operative repair, there has been interest in developing a transcatheter-based approach to ASD repair to avoid the risks and morbidity of open heart surgery. A variety of devices have been researched. Technical challenges include minimizing the size of device so that smaller catheters can be used, developing techniques to properly center the device across the ASD, and ensuring that the device can be easily retrieved or repositioned, if necessary.

Several devices have been developed to treat PFO via a transcatheter approach, including the CardioSEAL® STARFlex™ Septal Occlusion System (NMT Medical), the Amplatzer® PFO Occluder (Amplatzer Inc., now St. Jude Medical, St. Paul, MN), the Figulla® ASD Occluder (Occlutech GmbH, Jena, Germany), and the CeraFlex™ ASD Occluder (Lifetech Scientific, Shenzhen, China). The STARFlex system is no longer manufactured. Transcatheter PFO occluders consist of a single or paired wire mesh discs that are covered or filled with polyester or polymer fabric that are placed over the septal defect. Over time, the occlusion system is epithelialized.

ASD occluder devices consist of flexible mesh discs that are delivered via catheter to cover the ASD.

Regulatory Status

Patent Foramen Ovale Closure Devices

In 2002, two transcatheter devices were cleared for marketing through a humanitarian device exemption (HDE) by the FDA as a treatment for patients with cryptogenic stroke and PFO: the CardioSEAL® Septal Occlusion System (no longer commercially available) and the Amplatzer® PFO Occluder. HDE approval is applicable to devices designed to treat a patient population of fewer than 4000 patients per year. This approval process requires the manufacturer to submit data on the safety and the probable clinical benefit. Clinical trials validating the device effectiveness are not required. The labeled indications of both limited the use of these devices to closure of PFO in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a PFO and who have failed conventional drug therapy.

Following this limited FDA approval, use of PFO closure devices increased by more than 50-fold, well in excess of the 4000 per year threshold intended under the HDE.² As a result, in 2006, FDA withdrew the HDE approval for these devices. At this time, FDA also reiterated the importance of randomized controlled trials (RCTs) of PFO closure devices versus medical therapy but noted that ongoing trials were hampered by slow enrollment. Withdrawal of the HDE approval was, in part, intended to spur greater enrollment in ongoing RCTs of these devices.² Currently, all uses of closure devices to treat PFO are off-label uses.

Atrial Septal Defect Closure Devices

At present, two devices have been approved by FDA through the premarket approval process for ASD closure: the Amplatzer™ Septal Occluder (St. Jude Medical, Minneapolis, MN) and the GORE HELEX™ Septal Occluder (W.L. Gore & Associates, Newark, DE). In 2002, the Amplatzer Septal Occluder was approved for the occlusion of ASDs in the secundum position or in patients who have undergone a fenestrated Fontan procedure who required closure of the fenestration. Patients indicated for ASD closure have echocardiographic evidence of ostium secundum ASD and clinical evidence of right ventricular volume overload.

In August 2006, the GORE HELEX Septal Occluder was approved through the premarket approval process for the percutaneous, transcatheter closure of ostium secundum ASDs.

FDA product code: MLV.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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