etripamil (Cardamyst™)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO342

Description

Etripamil (Cardamyst) is a calcium channel blocker administered intranasally.

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
etripamil (Cardamyst)	Conversion of acute symptomatic episodes of paroxysmal supraventricular tachycardia (PSVT) to sinus rhythm in adults	Nasal spray devices	2 devices/28 days; 6 fills/year

Initial Evaluation

I. **Etripamil (Cardamyst)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a cardiologist or electrophysiologist; **AND**
   C. Diagnosis of **paroxysmal supraventricular tachycardia (PSVT)**; **AND**
      1. Documentation tachycardia is atrioventricular nodal dependent (e.g., atrioventricular nodal reentrant tachycardia, [AVNRT], atrioventricular reentrant tachycardia [AVRT]); **AND**
      2. Documented history of sustained episodes (≥20 minutes) of paroxysmal supraventricular tachycardia (PSVT); **AND**
      3. Documented history of ≥1 emergency department or provider visit for the treatment of an acute episode of paroxysmal supraventricular tachycardia (PSVT); **AND**
   D. Treatment with vagal maneuvers (e.g., Valsalva maneuver, carotid sinus massage) has been ineffective, contraindicated, or not tolerated; **AND**
   E. Treatment with diltiazem, verapamil, or beta-blockers (e.g., propranolol, metoprolol) has been ineffective, contraindicated, or not tolerated; **OR**
      1. Treatment with diltiazem, verapamil, or beta-blockers (e.g., propranolol, metoprolol) will be used concurrently with etripamil (Cardamyst)

II. **Etripamil (Cardamyst)** is considered investigational when used for all other conditions, including but not limited to:
   A. Arrhythmias outside of paroxysmal supraventricular tachycardias (PSVT)
   B. Members <18 years of age

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., conversion to sinus rhythm after an acute episode, improvement in symptoms [e.g., dizziness, headache, etc.], decreased emergency department visits)

Supporting Evidence

I. Paroxysmal supraventricular tachycardias (PSVT) are a subset of supraventricular tachycardias (SVTs) characterized by abrupt onset and termination episodes of rapid heart rate (>100 beats per minute). Paroxysmal supraventricular tachycardias (PSVT) and SVT naming conventions are used interchangeably. These arrhythmias originate from or conduct through the atria or atrioventricular (AV) node. Subtypes of PSVT include atrioventricular nodal reentrant tachycardia (AVNRT), atrioventricular reentrant tachycardia (AVRT), and less frequently atrial tachycardia (AT). When symptoms occur, they can be severe, and include palpitations, chest discomfort, dyspnea, light-headedness, syncope, and distress. The timing and severity of PSVT episodes are unpredictable and can vary significantly both within an individual and between different patients. Most patients experience several episodes each year. The goal of acute therapy is to terminate an arrhythmia episode and resolve symptoms. Ongoing management is intended to prevent the recurrence of PSVT.
II. Etripamil (Cardamyst) is FDA approved and has been studied in adults with PSVT only at this time. The safety and effectiveness in the pediatric population have not been established. The NODE-202 is a Phase 2 study evaluating etripamil (Cardamyst) in the treatment of PSVT in pediatric patients down to six years of age. Estimated study completion date is in 2027. Etripamil (Cardamyst) is structurally similar to another drug in the same pharmacologic class that has been associated with a high risk of potentially non-reversible electromechanical dissociation or cardiovascular collapse in pediatric patients less than one year of age, including neonates.
III. Members diagnosed with PSVT are typically evaluated by cardiology at the outset because confirming the diagnosis usually requires electrocardiogram (ECG) documentation or ambulatory monitoring. A cardiology assessment is also important for risk stratification and to guide treatment decisions. Specialist involvement is necessary to determine appropriate candidates for therapies such as antiarrhythmic medications, pill-in-the-pocket approaches, and newer agents like etripamil (Cardamyst).
IV. Paroxysmal supraventricular tachycardia (PSVT) is frequently identified in the emergency department, where it is a common cause of palpitations. The rhythm disturbance is confirmed with a 12-lead ECG, which allows clinicians to characterize the arrhythmia. Typical ECG features of PSVT include a narrow QRS complex measuring less than 120 milliseconds, a regular rhythm,

and visible atrial activity such as P waves. Because PSVT episodes can occur unpredictably and often resolve on their own, capturing an event on ECG can be challenging. For patients with infrequent symptoms or a normal baseline ECG, ambulatory monitoring tools—such as Holter monitors, event recorders, or implantable loop recorders—may be necessary to document an episode and establish the diagnosis.

V. Paroxysmal supraventricular tachycardia (PSVT) encompasses several mechanisms, most commonly atrioventricular nodal reentrant tachycardia (AVNRT) and atrioventricular reentrant tachycardia (AVRT), with atrial tachycardia (AT) occurring less frequently. Atrioventricular nodal reentrant tachycardia and AVRT both rely on the AV node for maintenance of the tachycardia, whereas AT does not. Because etripamil (Cardamyst) has demonstrated efficacy only in AV-node–dependent circuits—based on the inclusion criteria of clinical trials such as NODE-301, RAPID, NODE-302, and NODE-303—it may not successfully terminate AT, as its mechanism targets AV nodal conduction. Distinguishing these subtypes can be challenging due to similarities in rate, onset, and regularity, and often requires ECG analysis or electrophysiology study. On ECG, AVNRT typically presents with a short RP interval, while AVRT is more often associated with a long RP interval.

VI. A documented history of sustained PSVT episodes lasting at least 20 minutes is required because this criterion was used across the clinical trials that established the safety and effectiveness of etripamil (Cardamyst). The 20-minute threshold helps ensure that the arrhythmia is truly sustained rather than a brief, self-terminating episode, as many PSVT events resolve on their own within seconds to a few minutes and do not require treatment. Shorter episodes may also terminate before etripamil (Cardamyst) can exert its therapeutic effect—its onset of action is approximately seven minutes, with a half-life of 20–30 minutes—making treatment unnecessary for episodes lasting less than 20 minutes.

VII. Documentation of one or more emergency department (ED) visits or provider visits for an acute episode of paroxysmal supraventricular tachycardia (PSVT) is required to confirm that the member's symptoms are clinically significant, consistent with PSVT requiring medical intervention, and aligned with the disease burden observed in clinical trials of etripamil (Cardamyst). In the NODE clinical program, participants reported a mean of approximately five lifetime ED visits for PSVT, underscoring that the target population commonly seeks medical care for episodes.

VIII. Vagal maneuvers—such as the Valsalva maneuver and carotid sinus massage—are required first-line therapy for acute PSVT unless they have been previously ineffective, not tolerated, or are contraindicated. These maneuvers are strongly recommended by the 2015 ACC/AHA/HRS guidelines for AVNRT and AVRT because they increase vagal tone and can interrupt AV-node–dependent reentrant circuits. The Valsalva maneuver generally involves having the patient bear down to temporarily increase intrathoracic pressure, while carotid sinus massage involves applying gentle pressure to one carotid sinus after confirming no bruit is present. Other vagal techniques, such as cold-stimulus application to the face (diving-reflex–based methods), may also be used to slow AV-node conduction and potentially terminate the arrhythmia. The NODE clinical program required patients to first attempt to terminate a PSVT episode using vagal maneuvers, and only if symptoms persisted were they instructed to administer etripamil

(Cardamyst). Therefore, the safety and efficacy of etripamil (Cardamyst) is established in those failing first line therapy with vagal maneuvers.

IX. Documentation of prior treatment with oral diltiazem, verapamil, or beta-blockers (e.g., propranolol, metoprolol) is required unless these agents were previously ineffective, contraindicated, or not tolerated. Both pill-in-the-pocket use and maintenance/prophylactic therapy are acceptable, provided adequate therapeutic trials have been attempted. The 2015 ACC/AHA/HRS supraventricular tachycardia guidelines give a Class IIb (weak) recommendation for as-needed oral diltiazem, verapamil, or beta-blockers for acute treatment of hemodynamically stable AVNRT, acknowledging limited direct evidence for oral beta-blocker monotherapy. Two clinical studies demonstrated that a single oral combination of diltiazem plus propranolol can successfully terminate AVNRT or AVRT. Oral beta-blockers and calcium channel blockers are inexpensive, widely available, and generally safe options that may be used alongside vagal maneuvers when appropriate. Guidelines also provide a Class I recommendation for oral beta-blockers or non-dihydropyridine calcium channel blockers for ongoing management in patients with AVNRT who are not candidates for, or prefer not to undergo, catheter ablation. Diltiazem and verapamil are effective alternatives for chronic symptom control but must be used cautiously in patients at risk for bradyarrhythmias, hypotension, or systolic heart failure. Beta-blockers are contraindicated in individuals with severe bradycardia, cardiogenic shock, or decompensated heart failure. In general, oral CCBs or beta-blockers may be inappropriate for patients whose PSVT episodes have been associated with syncope, marked bradycardia, hypotension, or high-grade AV block.

X. The quantity limit of six fills per year aligns with the expected frequency of use for etripamil (Cardamyst). Although episode frequency varies among patients, this limit is supported by the NODE-303 trial, which evaluated safety across multiple PSVT episodes (up to four), and NODE-302, which assessed treatment of up to 11 episodes. Additionally, a Milestone Pharmaceuticals representative stated on December 15, 2025, that the average patient is projected to refill Cardamyst four to six times annually. Patients may also require replacement devices due to use or product expiration; according to the FDA approval letter, etripamil (Cardamyst) has a 36-month shelf life when stored at 20–25 °C (68–77 °F). Exceptions to the six-fill limit may be clinically appropriate when documentation shows that a member experiences more frequent PSVT episodes requiring treatment.

XI. Etripamil (Cardamyst) was studied in several Phase 3 studies with the RAPID trial serving as the pivotal trial for FDA approval. RAPID was a double-blind, placebo-controlled, Phase 3 study in 255 patients with a history of symptomatic PSVT. Patients with an episode of perceived PSVT were to self-administer the study drug intranasally in a medically unsupervised setting and self-administer a second dose of the study drug if symptoms persisted at 10 minutes after the first dose. The median age was 54 years, 71% were female, 93% White, 63% were taking concomitant BB or CCB. The mean number of PSVT episodes in the past year was six and the mean number of reported emergency department visits for PSVT in patients' lifetime was five. The primary endpoint was time-to-conversion of confirmed PSVT to sinus rhythm for at least 30 seconds within the 30 minutes of the first dose. The primary endpoint was statistically significant in favor of etripamil (Cardamyst) with 63 (64%) of patients converting to sinus rhythm

compared to 26 (31%) in the placebo arm. Secondary endpoints were evaluated hierarchically and included time to conversion at time points before and after 30 minutes, the percentage of patients requiring additional medical intervention in emergency departments, and patient-reported outcomes. Secondary endpoints are considered exploratory as the first secondary endpoint in the hierarchy, conversion by 10 minutes post dose, did not meet statistical significance.

XII. Most treatment-related adverse reactions have been related to, at, or near the nasal administration site, including the nose, throat, and eyes. The most common adverse reactions (incidence >5%) were nasal discomfort, nasal congestion, rhinorrhea, throat irritation, and epistaxis. There were no serious adverse events (SAEs) in the etripamil (Cardamyst)-treated subjects during the double-blind, randomized treatment period. In the open label extension studies (OLE), there were five SAEs including acute coronary syndrome, acute myocardial infarction, atrial fibrillation, stress cardiomyopathy, and appendicitis. Adverse events leading to permanent discontinuation were reported in four subjects in the etripamil (Cardamyst) group compared to zero in the placebo group during the double-blind randomized period, and in 18 subjects in the OLE period with two syncope related events. Contraindications to therapy include hypersensitivity, heart failure NYHA Class II to IV, Wolff-Parkinson-White (WPW), Lown-Ganong-Levine (LGL) syndromes, or manifest pre-excitation (delta wave) on a 12-lead ECG, sick sinus syndrome (except in patients with a permanent pacemaker), second degree atrioventricular (AV) Mobitz 2 block or higher degree of AV block. Warnings and precautions include syncope and for administration to be in the sitting position.

Investigational or Not Medically Necessary Uses

I. Etripamil (Cardamyst) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
    A. Arrhythmias outside of paroxysmal supraventricular tachycardias (PSVT)
    B. Members <18 years of age
        i. The safety and effectiveness in the pediatric population have not been established. The NODE-202 is a Phase 2 study evaluating etripamil (Cardamyst) in the treatment of PSVT in pediatric patients down to six years of age. Estimated study completion date is in 2027. Etripamil (Cardamyst) is structurally similar to another drug in the same pharmacologic class that has been associated with a high risk of potentially non-reversible electromechanical dissociation or cardiovascular collapse in pediatric patients less than one year of age, including neonates.

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Related Policies

Currently there are no related policies

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2026