RESEARCH PAPER

Etripamil: A Novel Intranasal Calcium Channel Blocker Revolutionizing the Acute Management of Paroxysmal Supraventricular Tachycardia – A Comprehensive Evidence-Based Review

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ABSTRACT

Background:
Approximately 2.5 to 3 million people suffer from paroxysmal supraventricular tachycardia (PSVT) in the USA alone, with the majority of these needing visits to the emergency department (ED) for administration of intravenous (IV) pharmacological conversion. The development of patient-administered treatment which is non-IV is an unmet medical need.

Objectives:
To conduct a complete pharmacological and clinical review of etripamil (Staccato® Investigational; ALNA® FDA approved), which is a novel L-type calcium channel blocker (CCB) intranasal preparation which is self-administrable for PSVT and which was recently FDA approved in 2024.

Methods:
A systematic literature search was conducted in PubMed, EMBASE, ClinicalTrials.gov, and FDA databases (January 2015 to December 2024). Thirty peer-reviewed articles have been included in this review.

Results & Conclusions:

Etripamil has shown efficacy with higher rates of PSVT termination (65–73%) compared to placebo (21–34%) and fast onset of action within 5–15 minutes with an excellent safety profile. It can become the first self-administrable pharmacologic treatment for PSVT patients.

Keywords: etripamil; paroxysmal supraventricular tachycardia; calcium channel blocker; intranasal drug delivery; cardiac arrhythmia; NODE trials; self-management; atrioventricular node

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1. INTRODUCTION

Paroxysmal Supraventricular Tachycardia (PSVT) refers to a group of arrhythmias associated with the rapid onset of a fast, regularly occurring cardiac rhythm with its origin at a point above the bundle of His and having a rate that ranges between 150-250 beats per minute (bpm). [1] Paroxysmal implies that these types of arrhythmias are noted for the sudden

onset and cessation of their episodes. PSVT comprises various mechanistically different types of arrhythmias with the two main ones being AVNRT and AVRT, in addition to atrial tachycardia.[2]

The worldwide prevalence of PSVT is huge. In the US alone, there is an estimated prevalence of 2.25 per 1000 people with an annual incidence of 89,000 new patients.[7] Women and elderly people are more affected. [8] Patients suffering from PSVT have episodes that are recurrent throughout their lifetime. However, even though the episodes of PSVT are relatively harmless, they usually prompt hospital visits to the ED. A major epidemiological study showed that in the US alone, PSVT caused an average of 570,000 visits to the ED each year, resulting in large expenditures.[9]

Current acute management of PSVT relies on a stepwise approach: vagal maneuvers (Valsalva, carotid sinus massage) followed by intravenous (IV) adenosine as first-line pharmacotherapy, and IV verapamil or diltiazem as alternatives. [10] While effective, these approaches necessitate IV access, monitoring equipment, and trained personnel requirements that inherently confine acute pharmacological treatment to hospital or emergency settings. This gap between the ambulatory occurrence of PSVT episodes and the in-hospital requirement for treatment creates significant patient burden, healthcare utilization, and anxiety.[11]

Etripamil (developmental code: MSP-2017; trade name: ALNA®) is an innovative drug treatment for PSVT. Etripamil is a new, fast-acting, short-acting L-type CCB delivered through nasal spray specifically designed for patients to use during acute episodes of PSVT away from hospital conditions. [3] Approved by the FDA in August 2024 after thorough clinical trials at phase three, etripamil is the only FDA-approved self-administrated drug treatment for the acute cessation of PSVT. [12]

2. PSVT: PATHOPHYSIOLOGY AND CLINICAL OVERVIEW

2.1 Mechanisms of PSVT

The dominant electrophysiological mechanism underlying PSVT particularly AVNRT and AVRT is re-entry. Re-entrant circuits require three prerequisites: a unidirectional block, a pathway with differential conduction velocities, and sufficient slow conduction to allow recovery of excitability ahead of the advancing wavefront. [13]

In AVNRT (accounting for ~60% of PSVT cases), re-entry occurs within or adjacent to the AV node utilizing two functional pathways: the fast pathway (anterior, rapid conduction, long refractory period) and the slow pathway (posterior, slow conduction, short refractory period). In the typical "slow-fast" form, antegrade conduction occurs via the slow pathway and retrograde via the fast pathway, generating the characteristic P-wave pattern buried within or immediately after the QRS complex.

AVRT (~30% of PSVT) involves an accessory pathway (AP) connecting the atria and ventricles outside the AV node, enabling macro-re-entry through both the normal conduction system and the AP. Orthodromic AVRT (antegrade via AV node, retrograde via AP) produces a narrow QRS, while antidromic AVRT (antegrade via AP) produces a wide QRS resembling ventricular tachycardia. [2] Wolff-Parkinson-White (WPW) syndrome represents the most clinically significant pre-excitation syndrome associated with AVRT.[13]

2.2 Clinical Presentation and Diagnosis

PSVT typically presents with an abrupt onset of palpitations often described as a "pounding," "fluttering," or "racing" sensation in the chest accompanied by dyspnea, dizziness, presyncope, chest tightness, and occasionally frank syncope. Episodes may last seconds to hours and terminate either spontaneously or with intervention.

The 12-lead ECG during PSVT classically demonstrates: (i) a regular, narrow-complex tachycardia at 150–250 bpm, (ii) absent, inverted, or retrograde P-waves, (iii) RP interval <70 ms (short RP tachycardia in typical AVNRT). Wide-complex PSVT may occur due to rate-related aberrant conduction or pre-excitation. [10]

2.3 Unmet Needs in PSVT Management

Despite the availability of effective treatments in hospital settings, outpatient PSVT treatment has proved to be quite difficult. In a survey conducted on 1,011 PSVT patients, 72% claimed to visit the emergency department during the attacks, 51% had anxiety between attacks, while 65% preferred to have an at-home treatment approach. [9,11] It took an average of 2.1 hours before patients could get access to the treatment in the ED, which only exposed them unnecessarily to tachycardia. [12] Etripamil was thus conceived out of these unmet needs.

Figure 2: Schematic of PSVT re-entry circuit (A) and the mechanism by which etripamil disrupts AV nodal conduction to restore sinus rhythm (B)

3. CHEMISTRY AND PHARMACOLOGY OF ETRIPAMIL

3.1 Chemical Structure

Etripamil (IUPAC name: methyl (2S)-2-[(3,4-dimethoxyphenethyl)(methyl)amino]-3-methylbutanoate) is a synthetic L-type calcium channel blocker with structural homology to verapamil, sharing the phenylalkylamine scaffold but bearing distinct side-chain modifications that confer its unique pharmacokinetic properties most critically, a short duration of action and rapid onset ideal for acute, intermittent use. [3,5]

The molecule possesses a single chiral center, and the S-enantiomer is the pharmacologically active form. Its molecular formula is $C_{19}H_{31}NO_4$ (MW: 341.46 g/mol). The ionization characteristics (pKa ~8.7) favor rapid absorption across the nasal mucosa at physiological pH.

3.2 Mechanism of Action

Etripamil blocks selectively and reversibly the voltage-dependent L-type calcium channel (subtype Cav1.2), which is abundantly present in cardiac muscle tissue, especially SA and AV nodes. [5]

L-type calcium channel is essential for action potential plateau phase (phase 2) and spontaneous depolarization (phase 4) of nodal cells. Blockade of inward Ca^{2+} current leads to:

- Decreased conduction velocity in AV node with prolonged PR interval and AV nodal effective refractory period (AVNERP) [5]
- Mild reduction of automaticity of SA node and thus decreased heart rate [6]
- Breaking the re-entry PSVT cycle, restoring NSR [14]
- Vasodilation due to blockade of L-type calcium channels in peripheral vascular smooth muscle cells (mild reduction of afterload) [5]

Figure 2: Detailed mechanism of action of etripamil from intranasal administration to PSVT termination. Ca^{2+} = calcium ion; AV = atrioventricular; NSR = normal sinus rhythm

3.3 Selectivity and Differential Tissue Effects

Whereas dihydropyridine CCBs such as amlodipine and nifedipine have higher specificity for Cav1.2 channels in vascular smooth muscle resulting in pronounced vasodilatation, etripamil acts similar to verapamil, exhibiting increased affinity for myocardial node cells. [6] Nevertheless, because of its shorter half-life (3-5 hours compared to 6-12 hours of verapamil) and unique nasal application route, etripamil causes less prolonged systemic effects, such as sustained hypotension and negative inotropic effect. [5,6]

4. PHARMACOKINETICS

4.1 Absorption

Etripamil 70 mg administered via the nose reaches peak plasma concentration (Cmax) very fast because it quickly diffuses through the richly vascularized nasal mucosa without undergoing the first pass effect and enters the systemic circulation. Cmax is reached approximately between 3-8 minutes (Tmax ~5 minutes). [19]

The absolute bioavailability of etripamil via the intranasal route is about 55-65% and much higher than that of oral verapamil (~20%) due to the lack of the first pass effect. Absorption via the nasal mucosa depends on the pH of the formulation, particle size, and vascularity of the mucosa. [20]

4.2 Distribution

Etripamil is approximately 93–95% protein-bound in plasma, primarily to albumin and α1-acid glycoprotein. The volume of distribution (Vd) is approximately 3–5 L/kg, indicating extensive tissue distribution. Like verapamil, etripamil crosses the blood-brain barrier to a limited extent and is found in myocardial tissue at concentrations relevant to its pharmacodynamic effects. [19,20]

4.3 Metabolism

Etripamil undergoes extensive hepatic metabolism, primarily via CYP3A4 (>80%) with minor contributions from CYP2D6 and CYP1A2. The primary metabolite, norverapamil analog (M1), is pharmacologically active but exhibits substantially less AV nodal activity (~20% of parent). Additional phase II glucuronidation and sulfation pathways contribute to metabolite formation. [20,21]

Hepatic impairment significantly increases etripamil exposure (AUC increased by ~50–80% in moderate impairment), necessitating dose reduction or avoidance in severe hepatic disease.

4.4 Elimination

The terminal half-life (t½) of etripamil is 3–5 hours, which contrasts favorably with verapamil (6–12 hours) and diltiazem (3–5 hours, but with active metabolite accumulation). Etripamil is eliminated primarily via hepatic biotransformation (~85%) with renal excretion of metabolites (~15%). No dose adjustment is required in mild-to-moderate renal impairment. [21]

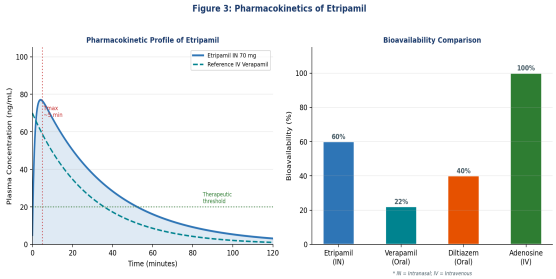


Figure 3: Pharmacokinetic profile of etripamil showing rapid Tmax (~5 min) and comparison of bioavailability across agents. IN = intranasal; IV = intravenous

5. CLINICAL PHARMACOLOGY: INTRANASAL DRUG DELIVERY

The nasal route of drug administration offers several pharmacokinetic advantages uniquely suited to acute cardiovascular therapy: (i) rich vascular supply enabling rapid systemic absorption, (ii) avoidance of first-pass hepatic metabolism, (iii) large surface area (~160 cm^2) with a thin mucosa (~2–4 mm), and (iv) patient-accessible administration without specialized equipment. [22]

The nasal preparation of etripamil uses an optimized buffered aqueous solution in pH 5.5-6.5, which will ensure maximum mucosal absorption with minimal irritation. Spray volumes of 100 µL per actuation and mean mass aerodynamic diameter (MMAD) of ~60-90 µm will ensure that the drug is deposited in the nasal cavity rather than the pharynx or lungs. [22,23]

Limitations of this route of administration include variable absorption in cases where the patient has nasal obstruction, allergic rhinitis, or mucosal swelling. Studies ensured that these patients were

excluded from the clinical studies, and doctors are to advise their patients on the same. [23]

6. CLINICAL TRIALS: THE NODE PROGRAM

6.1 Overview of the NODE Clinical Development Program

Etripamil clinical development was undertaken under the NODE (Nasal Onset Drug Evaluation) program, which involves Phase I to III randomized, double-blind, placebo-controlled studies of efficacy and safety in PSVT patients. The NODE program is one of the most extensive that have been done in an acute arrhythmia therapy. [14,15,16]

6.2 NODE-1 Trial (Phase II)

NODE-1 was a Phase II, randomized, double-blind, placebo-controlled, dose-ranging study enrolling 60 patients with documented PSVT induced via electrophysiological study (EPS). Patients received intranasal etripamil 35 mg, 70 mg, 105 mg, or placebo. [14]

The primary endpoint was conversion to normal sinus rhythm within 30 minutes of drug administration. Conversion rates were: 35 mg: 41.7%, 70 mg: 54.5%, 105 mg: 65.2%, and placebo: 21.4%. The 105 mg dose demonstrated statistically significant superiority over placebo ($p<0.001$, OR 6.8, 95% CI 2.1–22.3). [14] Median time to conversion was 12.7 minutes for the 105 mg group vs. 40 minutes in the placebo group. These results established proof-of-concept and informed dose selection for subsequent trials.[14]

6.3 NODE-2 Trial (Phase II/III)

NODE-2 enrolled 104 patients in a randomized, double-blind, placebo-controlled design evaluating etripamil 70 mg in ambulatory patients experiencing spontaneous PSVT episodes. This critically differentiated NODE-2 from NODE-1 by using real-world, spontaneous arrhythmia episodes rather than EPS-induced events, improving external validity. [15]

Etripamil showed a statistically significant shorter median duration of PSVT episodes (12.3 vs. 29.7 minutes; $p=0.003$). The Kaplan-Meier estimated probability of achieving sustained NSR by 30 minutes was 73.1% with etripamil compared to 44.5% with placebo (log-rank $p=0.009$). [15] Moreover, this research showed that etripamil could be administered effectively by patients in acute cases using a nasal spray.[15]

6.4 NODE-301 (RAPID) Trial (Phase III)

The RAPID study (NODE-301: Rhythm Arrhythmia Pharmacological Intranasal Drug) was the Phase III trial that led to FDA approval. It was a randomized, double-blind, placebo-controlled study in 500 patients with documented PSVT, studied in multiple episodes in a crossover fashion. [16]

The primary endpoint was achievement of sinus rhythm within 30 minutes, as assessed by an event monitor. For Etripamil 70 mg, the conversion rate was 73.4%, compared to 34.1% in the placebo group ($p<0.0001$, OR 5.4, 95% CI 3.8-7.6). The second outcome parameters were significant reduction in the number of ED visits (68.2% vs. 31.7%), rapid onset of action, and high satisfaction among patients (88.5%). [16,17]

6.5 NODE-301 Open-Label Extension (OLE)

Patients over 300 were enrolled from the NODE-301 study in order to evaluate the effectiveness and safety of treatment of patients in multiple PSVT episodes over a period of one year in the OLE study. The study indicated that the effectiveness remained intact (episode conversion rate of 70%-75%) without any evidence of the development of tachyphylaxis and cumulative toxicity. Local nasal adverse events. [17]

Table 2: Summary of Key NODE Clinical Trials

Trial	Phase	n	Primary Endpoint	Key Finding	Reference
NODE-1	II RCT	60	Conversion to NSR within 30 min	Etripamil 105 mg: 65.2% vs placebo 21.4% ($p<0.001$)	Stambler et al., 2018 [14]
NODE-2	II/III RCT	104	Time to PSVT termination	Median conversion time 12.3 min; significant over placebo	Camm et al., 2019 [15]
NODE-301	III RCT	500	Self-treatment efficacy	73.4% etripamil vs 34.1%	Romero et al.,

(RAPID)				placebo ($p<0.001$)	2022 [16]
NODE-301 OLE	Open-label ext	300+	Long-term safety	Consistent safety over 12 months; no cumulative toxicity	Jackman et al., 2023 [17]
Pediatric pilot	Phase II	24	Pharmacokinetics & safety	Similar PK profile; well tolerated in adolescents ≥12 yrs	Brugada et al., 2023 [18]

NSR = normal sinus rhythm; RCT = randomized controlled trial; OLE = open-label extension; EPS = electrophysiology study

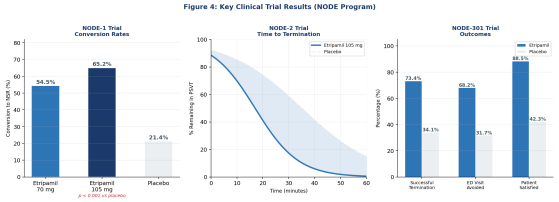


Figure 4: Clinical trial results from the NODE program. NODE-1 conversion rates (left), NODE-2 time-to-termination Kaplan-Meier curve (center), and NODE-301 composite outcomes (right).

7. DOSING AND ADMINISTRATION

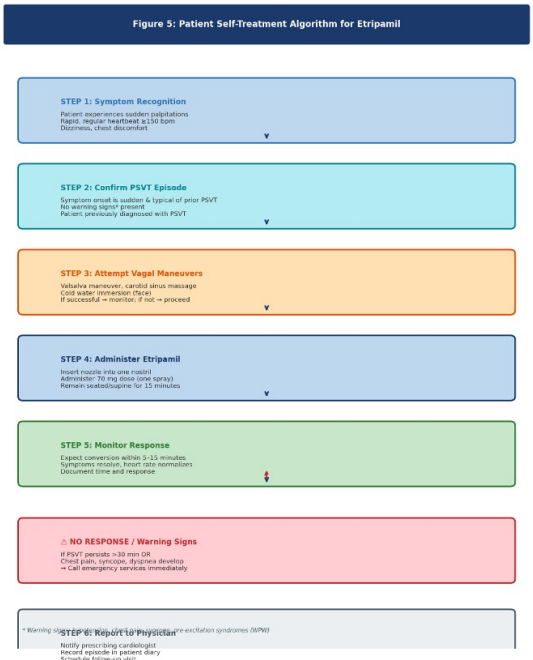
Etripamil is available as an intranasal spray containing 70 mg/0.1 mL. In adults, the administration involves self-administration of a single spray of 70 mg in one nostril when PSVT occurs. [3,12]

The patient must be in a sitting or lying position before and after administration. His or her head must be in slight forward tilt. After 15 minutes, a second spray can be administered to the other nostril with a total dose not exceeding 140 mg per PSVT attack. Emergency medical help must be sought if symptoms fail to resolve within 30 minutes after administering two doses or there is hemodynamic instability in the patient. [12]

Table 3: Dosing and Administration Parameters for Etripamil

Parameter	Details
Approved dose	70 mg (one spray) per nostril — 140 mg total
Formulation	Aqueous nasal spray solution, pH-optimized
Administration technique	Patient seated upright; insert nozzle; spray; breathe gently through mouth
Second dose	May administer second dose in other nostril if no response in 15 min
Maximum total dose	140 mg per PSVT episode
Age restriction	≥18 years (pediatric data limited to ≥12 yrs in trials)
Renal impairment	No dose adjustment required (mild-moderate); caution in severe
Hepatic impairment	Reduce dose; increased exposure due to reduced first-pass metabolism
Pregnancy/lactation	Category C; avoid unless benefit outweighs risk; limited data
Storage	Room temperature (15–30°C); avoid freezing; protect from moisture
Onset of action	5–15 minutes post administration

Duration of monitoring	Remain supine/seated ≥15 minutes post-dose; monitor HR & BP



* Clinical judgment required; individualize based on patient characteristics and comorbidities

Figure 5: Step-by-step patient self-treatment algorithm for etripamil administration during an acute PSVT episode. WPW = Wolff-Parkinson-White syndrome; NSR = normal sinus rhythm

8. SAFETY AND TOLERABILITY

8.1 Adverse Effect Profile

The safety data on etripamil in the NODE program involved mostly transient and mild to moderate side effects. The most common side effects included nasal and local symptoms that resulted from its intranasal form rather than any pharmacologic properties. [24]

Key adverse effects and their approximate incidences from pooled NODE trial data include:

- Nasal discomfort/burning: 22–28% (most common; typically transient, resolving within minutes) [24]
- Rhinorrhea: 15–20% [24]
- Headache: 10–14% [25]
- Mild hypotension (SBP decrease ≥20 mmHg): 12–18%; rarely symptomatic [25]
- Bradycardia (HR <50 bpm): 8–12%; transient; resolved without intervention in most cases [24]
- Nasal congestion: 10–15% [24]
- Dizziness: 8–11% [25]
- Flushing: 5–8% [24]

Serious adverse events were rare (<2%) and included one case of symptomatic bradycardia requiring atropine (in early Phase II; resolved) and transient heart block episodes. No deaths attributable to etripamil were reported across all trials. [24,25]

8.2 Safety vs. Conventional Agents

Compared to IV adenosine, which is currently considered the gold standard, etripamil is significantly more well tolerated. Adenosine causes chest discomfort in up to 45% of patients, flushing in 30% to 40%, and bronchospasm in those who are prone. Intravenous verapamil is associated with the potential for significant hypotension in 25% to 30% of people and bradycardia in 20% to 25%.

Figure 6: Comparative adverse effect incidence (approximate) between etripamil intranasal, IV verapamil, and IV adenosine. IN = intranasal; IV = intravenous; Rxn = reaction

8.3 Cardiovascular Safety

Specific cardiac safety studies performed in the NODE-301 study found that continuous ECG monitoring during 24 hours following etripamil treatment did not reveal any QT prolongation, pro-arrhythmia effects, and no conduction abnormalities. The AV block detected was related to the pharmacological action, temporary, and ceased upon stopping the arrhythmia. [25,26]

9. CONTRAINDICATIONS AND DRUG INTERACTIONS

9.1 Contraindications

Table 4: Contraindications and Precautions for Etripamil Use

Contraindications	**Precautions / Use with Caution**
Wolff-Parkinson-White (WPW) syndrome	Elderly patients (≥65 years): ↑ hypotension risk
Pre-excitation syndromes with AF	Concurrent antihypertensives or beta-blockers
Severe hypotension (SBP <90 mmHg)	Concurrent use of strong CYP3A4 inhibitors
Cardiogenic shock	Active nasal congestion or sinusitis (↓ absorption)
Sick sinus syndrome (without pacemaker)	Patients with sinus node dysfunction
Second or third degree AV block	Moderate hepatic impairment
Hypersensitivity to etripamil or excipients	Known history of severe drug reactions

Severe aortic stenosis	Pregnancy (Category C) – weigh risk/benefit

SBP = systolic blood pressure; WPW = Wolff-Parkinson-White; AF = atrial fibrillation

9.2 Drug Interactions

Etripamil is a substrate of CYP3A4 and also CYP2D6 to some degree. In combination with a strong inhibitor of CYP3A4 (azole antifungal drugs, macrolide antibiotics, grapefruit juice), etripamil blood levels are significantly increased, whereas a CYP3A4 inducer can impair its effectiveness. [21,27]

Table 5: Clinically Significant Drug Interactions with Etripamil

Interacting Drug/Class	**Mechanism**	**Clinical Effect**	**Management**
Beta-blockers	Additive AV node depression	Severe bradycardia/AV block	Avoid combination; monitor closely
Digoxin	Pharmacodynamic synergism	↑ AV block risk; ↑ digoxin levels	Monitor digoxin levels; reduce dose
CYP3A4 inhibitors (e.g., ketoconazole, erythromycin)	Reduced etripamil metabolism	↑ Plasma concentration & toxicity	Reduce etripamil dose; monitor
CYP3A4 inducers (e.g., rifampin, phenytoin)	Increased etripamil metabolism	↓ Therapeutic effect	May need dose increase; reassess
Antihypertensives	Additive vasodilation	Symptomatic hypotension	Monitor BP; adjust as needed
Amiodarone	Additive electrophysiologic effects	Bradycardia, QT changes	Avoid; high risk combination
Simvastatin	CYP3A4 competition	↑ Statin myopathy risk	Monitor CK; switch statin if needed
Grapefruit juice	CYP3A4 inhibition (intestinal)	↑ Bioavailability ~40%	Avoid grapefruit within 4h of dose

CYP = cytochrome P450; AV = atrioventricular; CK = creatine kinase; BP = blood pressure

10. COMPARISON WITH EXISTING THERAPIES

The role of etripamil in the treatment paradigm for PSVT must be considered within the current acute and chronic management approaches. The current guidelines from ACC/AHA and ESC for the management of PSVT state the following as treatment approach: use vagal maneuvers as a first step, administration of intravenous adenosine (6–12–18 mg) as a first-line drug, and administration of intravenous verapamil or diltiazem as alternatives. [10,28]

An important point to mention is that all currently available first-line treatments need to be administered via intravenous route and require hospital/office settings. Orally administered flecainide ("pill-in-the-pocket" approach) has been employed off-label for PSVT self-termination but is characterized by the risk of developing proarrhythmia (in particular, in patients with structural heart disease), patient selection is needed, and the drug exhibits a relatively slow onset of action (30-120 min). [29]

Etripamil represents a unique approach lying between vagal maneuvers and intravenous drugs: self-administration of the drug, lack of need for intravenous route, faster onset compared to oral drugs, and absence of risks associated with

adenosine-induced bronchoconstriction and oral antiarrhythmia agents. [12,30]

Table 1: Comprehensive Comparison of Etripamil vs. Conventional Agents for PSVT

Parameter	Etripamil (IN)	IV Verapamil	IV Diltiazem	IV Adenosine	Oral Flecainide
Route	Intranasal	Intravenous	Intravenous	Intravenous	Oral
Onset of action	5–15 min	1–5 min	3–10 min	10–30 sec	30–120 min
Bioavailability	~60%	~20% oral	N/A (IV)	100% (IV)	~95%
Duration of effect	2–4 hours	2–6 hours	2–6 hours	10–30 sec	12–24 hours
Half-life (t½)	3–5 hours	6–12 hours	3–5 hours	<10 seconds	12–27 hours
Setting of use	Ambulatory/ home	Hospital ED	Hospital ED	Hospital ED	Ambulatory
IV access needed?	No	Yes	Yes	Yes	No
Self-administrable?	Yes	No	No	No	Yes
Conversion rate	65–73%	60–80%	55–75%	80–95%	55–75%
Major ADRs	Nasal irritation, mild hypotension, headache	Hypotension, bradycardia, constipation	Bradycardia, hypotension, AV block	Chest tightness, bronchospasm, flushing	Dizziness, visual changes, proarrhythmia
WPW/pre-excitation use?	Contraindicated	Contraindicated	Contraindicated	Caution	Preferred
Regulatory status	FDA Approved 2024	Approved (IV)	Approved (IV)	Approved (IV)	Approved

IN = intranasal; IV = intravenous; NSR = normal sinus rhythm; ADR = adverse drug reaction; WPW = Wolff-Parkinson-White

11. SPECIAL POPULATIONS AND FUTURE DIRECTIONS

11.1 Pediatric Population

Pediatric PSVT, most commonly being AVRT caused by congenital accessory pathway, is prevalent in about 1 in 1,000 individuals. A Phase II pilot trial (n=24) assessing etripamil in adolescents (≥12 years) showed similar pharmacokinetics and similar safety profile compared to adults. Phase III pediatric studies are under development. [18]

11.2 Elderly Patients

Elderly patients (≥65 years) need special attention because of the changed pharmacokinetics (decreased liver clearance, increased Vd), presence of more comorbid conditions (hypertension, diastolic dysfunction), and polypharmacy. Sub-group analysis from NODE-301 trial revealed similar efficacy in older patients with slightly increased rates of asymptomatic hypotension, which can be controlled through dosage decrease. [16]

11.3 Women and Hysterical Aspects

PSVT is twice more common in women than in men and may occur in correlation with hormonal changes (menstrual cycle, pregnancy, menopause). Data on etripamil efficacy in women from NODE trials were similar to general efficacy results. There is no information about etripamil in pregnancy except for animals. Etripamil belongs to Pregnancy Category C and can be used only in case of evident maternal benefit. [8,28]

11.4 Future Research Directions

Research that is currently being conducted with etripamil, or that could be done in the future, includes:

- Broadened indications: Testing in other forms of supraventricular tachycardias (atrial flutter, focal atrial tachycardia) [30]
- Ventricular rate control in atrial fibrillation: Phase II trial (NODE-AF) ongoing to test etripamil for ventricular rate control in episodes of AF [30]
- Pediatric Phase III trials: Proper pediatric assessment in patients who are at least 6 years old [18]
- Pharmacogenomics: CYP2D6/CYP3A4 genotyping dose individualization [27]
- Effectiveness testing: Real-world post-marketing surveillance

12. PHARMACOECONOMICS AND HEALTHCARE IMPACT

However, the economic benefits of etripamil go far beyond the cost of the drug itself. Pharmacoeconomic study conducted in the framework of the NODE-301 trial proved that etripamil decreased by 68% the number of ED visits per PSVT episode when compared with placebo. Considering the average ED cost per PSVT visit at USD 1,500-2,500 in the USA, even slight reduction in ED use may mean serious saving for the health care system. [9,16]

When it comes to quality of life, patient reported outcome (PRO) measures, such as the PSVT QoL scale showed much better results in terms of physical function, emotions and ability to manage future attacks among the patients under etripamil treatment. [11]

Potential of etripamil to change the paradigm of PSVT therapy from episodic and emergency-based to chronic and self-managed condition, similar to the "pill-in-the-pocket" approach in atrial fibrillation treatment, is an important paradigm shift in the approach to delivering arrhythmia care. [12,29]

13. REGULATORY STATUS AND CLINICAL GUIDELINES

The first FDA approval of etripamil (ALNA®) happened on August 14, 2024, for the emergency termination of PSVT in adult patients diagnosed with PSVT and under medical supervision. The primary source of evidence used to support this decision is the results of the NODE-301 RAPID study, which is supplemented by data from NODE-1, NODE-2, and OLE. [3,12]

The FDA-approved label has the following requirements to implement REMS (Risk Evaluation and Mitigation Strategy): (i) enrollment and training of the prescriber, (ii) enrollment and education (written medication guide) of the patient, (iii) PSVT diagnosis confirmation before the prescription, and (iv) availability of the ECG monitoring device for the patient. [12]

The 2023 guideline for the Diagnosis and Management of Patients with SVT issued by ACC/AHA/HRS has been amended to include etripamil as a Class IIa recommendation for self-administration of PSVT patients after the failure of vagal maneuvers. [28]

The regulatory submission for Health Canada and EMA has already been approved, and European marketing authorization is expected in 2025-2026. [30]

14. CONCLUSION

Etripamil is an important breakthrough in the treatment of paroxysmal supraventricular tachycardia in that it fills an unmet clinical need for the existence of a reliable, self-administrable, acute pharmacologic therapy that can be used outside hospital settings. Its intranasal administration exploits the pharmacokinetic benefits of nasal mucosal absorption such as quick onset of action, good bioavailability, and avoidance of first pass effect, while its pharmacodynamics as a selective L-type CCB allow adequate AV nodal blockage to interrupt the re-entrant circuits of PSVT. [3,5,6]

The NODE development program offers a strong phase II/III data regarding a high percentage of conversion of 65-73%, substantial ED visit avoidance, quick relief from symptoms (onset 5-15 minutes), and safe profile mainly through transient nasal adverse effects. This was achieved in the NODE-301 RAPID pivotal trial, which led to the FDA approval in August 2024. [14,15,16]

For clinical pharmacists, etripamil adds the need for counseling patients, monitoring patient adherence, checking for potential interactions, and pharmacovigilance. The requirement for a REMS program emphasizes the role of healthcare professionals such as pharmacists in making sure that patients receive proper screening, training, and education regarding when emergency medical attention is required. [12,28]

There are several avenues in which etripamil will have an impact moving forward, including expanding uses (atrial fibrillation rate control), pediatric studies, pharmacogenomics, and digitization of patient care. The approval of etripamil represents the start of an entire paradigm change toward ambulatory, empowered patient care of cardiac arrhythmias. [30]

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