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Health Technology Briefing
February 2025

Etripamil for treating paroxysmal supraventricular tachycardia

Company/Developer	Milestone Pharmaceuticals Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 10768	NICE ID: N/A	UKPS ID: N/A

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Etripamil is a new drug in development for the treatment of paroxysmal supraventricular tachycardia (PSVT), a condition whereby the heart occasionally beats too fast. Supraventricular tachycardia (SVT) occurs when the heart's electrical system malfunctions, causing a sudden increase in heart rate above 100 bpm, even at rest. Episodes, often paroxysmal (PSVT), can last minutes to months and vary in frequency. Symptoms include palpitations, fatigue, chest discomfort, breathlessness, increased urination, and fainting. Many patients experience anxiety and frustration due to the unpredictability of episodes, with 27% avoiding driving out of fear of fainting. Etripamil nasal spray addresses an unmet medical need since there are currently no fast-acting products available for patient self-administered treatment of episodes of PSVT.

Etripamil is designed to be self-administered up the nose where it is absorbed into the bloodstream in less than 10 minutes. Etripamil reduces electrical activity in a section of the heart by blocking calcium channels, which reduces the heartrate. A self-administered product for PSVT would give patients the option to safely terminate acute episodes of PSVT without the need for a hospital visit and potential admission. If licenced, etripamil would offer an additional treatment option for those with PSVT.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Proposed Indication

Treatment of paroxysmal supraventricular tachycardia (PSVT).[1]

Technology

Description

Etripamil (MSP-2017) is a new chemical entity, L-type, calcium channel blocker designed to act rapidly upon the desired organ.[1-3] This technology is designed to be self-administered intranasally where it is absorbed into the bloodstream through the nasal mucosa of the nose in less than 10 minutes.[2,3] Etripamil reduces electrical activity in the slow pathway region of the high-density voltage map, temporarily impairing its ability to conduct signals and disrupting the abnormal electrical circuits responsible for PSVT.[4]

Etripamil is currently in clinical development for the treatment of PVST. In the phase III trial (NCT04952610), participants self-administered 70mg of etripamil nasal spray during acute episodes of PSVT. Participants were provided with a maximum of 4 pre-filled devices at a time. If the symptoms of PSVT persist 10 minutes after the first dose of etripamil nasal spray 70mg, a second dose of etripamil nasal spray 70mg can be self-administered by the patient. A second dose of etripamil nasal spray 70mg should be taken not earlier than 10, and not later than 15 minutes after the first dose.[1]

Key Innovation

Etripamil nasal spray addresses an unmet medical need since there are currently no fast-acting products available for patient self-administered treatment of episodes of PSVT. The only currently available acute pharmacological therapies are administered in a hospital or medically supervised environment.[1] A self-administered product for PSVT would give patients the option to safely terminate acute episodes of PSVT without the need for a hospital visit and potential admission. An episodic treatment option may also allow selected patients to discontinue chronic prophylactic therapy with Class I, II (e.g., beta-blockers), III, and/or IV (e.g., calcium channel blockers) antiarrhythmic agents, thus avoiding the side effects and quality of life implications associated with these medications. Furthermore, patients weighing the risks of bridging therapy and an invasive catheter ablation procedure to address their PSVT would have the opportunity to consider episodic management with etripamil nasal spray as a viable alternative treatment option.[1]

If licensed, etripamil will offer an additional treatment option for patients with PSVT, wherever their episodes may occur. This would be the only treatment option that can be administered outside of a medically supervised environment.[1,2]

Regulatory & Development Status

Etripamil does not currently have marketing authorisation in the EU/UK for any indication.

Etripamil is currently in phase II/III development for atrial fibrillation.[5]

Patient Group

Disease Area and Clinical Need

Supraventricular tachycardia (SVT) occurs when the electrical system that controls the heart rhythm is not working properly typically due to abnormalities in impulse conduction or disorders in impulse initiation.[6,7] This causes the heart to suddenly beat much faster than often slow down abruptly. A normal resting heart

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rate is 60 to 100 beats per minute (bpm). But with SVT your heart rate suddenly goes above 100bpm. This can happen during resting or exercise.[6] SVT is usually paroxysmal (PSVT) and episodes may occur regularly or very infrequently (sometimes years apart). Episodes may only last for a few minutes or may last for up to several months. Symptoms commonly include, palpitations, fatigue, chest discomfort, dyspnoea, polyuria, and syncope.[7] Episodes can be triggered by caffeine, alcohol, drugs, stress and anxiety but often there is no obvious trigger.[6,8] They can start at any age, but often start for the first time in children and young adults, between 25 and 40 years old. [6] It has also been reported that 27% of patients living with PSVT stopped driving for fear of temporary loss of consciousness. Furthermore, patients often feel anxious in anticipation of future PSVT episodes and frustrated by their lack of a sense of control over their disease.[9]

The prevalence of SVT in the general population has been estimated to be 2.25/1,000 persons and the incidence is 35/100,000 person-years. Women have a two times greater risk of developing SVT than men and individuals aged over 65 years have more than five times the risk of developing SVT than younger individuals.[7] In England in 2023-2024, there were 17,931 finished consultant episodes (FCE) for SVT (ICD-10 code: I47.1), with 13,451 hospital admissions resulting in 23,650 FCE bed days and 4,368 day cases.[10]

Recommended Treatment Options

There are no specific National Institute for Health and care Excellence (NICE) guidelines for treatment of PSVT.

The standard treatment as stated by the NICE British National Formulary involves the following pharmaceutical therapies for the treatment of PSVT:[11]

- Diltiazem hydrochloride
- Verapamil hydrochloride
- Beta-blockers including sotalol hydrochloride
- Flecainide acetate
- Propafenone hydrochloride.

Clinical Trial Information

Trial	**NODE-303**, NCT04072835; The NODE-303 study: multi-Centre, multi-national, open label, safety study of etripamil nasal spray for patients with paroxysmal supraventricular tachycardia. **Phase III:** Completed **Locations:** USA, Canada and other countries **Study completion date:** January 2023	NCT04952610; An open label extension study of etripamil nasal spray in patients with paroxysmal supraventricular tachycardia **Phase III:** Enrolling by invitation **Locations:** USA and Canada **Study completion date:** April 2025
Trial Design	Non-randomised, open label, single group assignment	Open label, single group assignment
Population	N=1,116 (actual); subjects diagnosed with PSVT and reported having at least one previous episode of PSVT; adults aged 18 years and older	N=130 (estimated); subjects with PSVT who have previously participated in a Milestone Pharmaceuticals clinical trial of etripamil nasal spray for PSVT; adults aged 18 years and older

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Intervention(s)	Etripamil nasal spray	Etripamil nasal spray
Comparator(s)	No comparator	No comparator
Outcome(s)	Primary outcome: Number of participants with adverse events for self-administered etripamil nasal spray outside of the clinical setting. See trial record for full list of all outcomes.	Primary outcome: The safety of self-administered etripamil Nasal Spray (NS) for treatment of episodes of PSVT outside of the clinical setting as assessed by patient-reported adverse events.
Results (efficacy)	For all PSVT episodes, the rate of conversion was 69.9% (386/552) by 60 minutes post drug, and the median time-to-conversion was 17.0 minutes (95% CI: 13.9, 22.3). For the first, second, third, and fourth PSVT episodes, rates of conversion by 60 minutes ranged from 57.7%-77.8%, and median times-to-conversion were 14.0-19.1 minutes. Efficacy of etripamil for PSVT conversion in NODE-303 was similar to that demonstrated in single episodes in the double-blinded RAPID study.[12]	-
Results (safety)	NODE-303 evaluated self-administered etripamil in a real-world, outpatient setting, without prior test-dosing and over multiple episodes of PSVT, demonstrating symptom-prompted treatment with etripamil to be rapidly efficacious at restoring sinus rhythm and well-tolerated. Conversion-efficacy was similar among multiple PSVT episodes, and treatment emergent adverse events frequency apparently decreased with successive episodes. Adverse events were predominantly localised to the drug's administration site. NODE-303 results support the potential benefit of etripamil in treating PSVT in a medically unsupervised setting.[12]	-

Trial	**NODE-1,** NCT02296190; Multi-centre, Placebo-Controlled, Dose-Ranging Phase 2 Electrophysiological Study of Intranasal Administration of MSP-2017 for the

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	Conversion of Induced Paroxysmal Supraventricular Tachycardia (PSVT) to Sinus Rhythm **Phase II** - Completed **Locations:** USA and Canada **Study completion date:** December 2016
Trial Design	Randomised, parallel assignment, double blind
Population	N=199 (actual); subjects with subjects with PSVT; adults aged 18 years and older
Intervention(s)	Etripamil nasal spray
Comparator(s)	Placebo
Outcome(s)	Primary outcome: The percentage of subjects successfully converted from PSVT to sinus rhythm within 15 minutes of study drug administration.
Results (efficacy)	A statistically significant difference in the rate of conversion to sinus rhythm was detected for the top three doses of etripamil when compared against placebo, with evidence of plateauing beyond 70 mg according to a maximal efficacy dose-response model (R2 = 0.915). The median time to cardioversion in each of the top three dosing groups was <3 minutes.[13]
Results (safety)	No major adverse events were seen that led to study termination. The most common adverse events were often attributable to local irritation, oropharyngeal pain, cough, rhinorrhoea, nasal congestion, dysgeusia, lacrimation, and headache. One patient (from the 35 mg group) experienced severe facial flushing, dyspnoea and chest discomfort; one patient (in the 105 mg group) had nausea and vomiting; and one (in the 105 mg group) experienced severe cough.[1,13]

Trial	**NODE-301 and RAPID, NCT03464019;** Multi-Centre, Randomised, Double-Blind, Placebo-Controlled, Efficacy, and Safety Study of Etripamil Nasal Spray for the Termination of Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia **Phase III** - Completed **Locations:** USA and Canada **Study completion date:** January 2023
Trial Design	Three-part, multi-centre, randomised, double-blind, placebo-controlled study. NODE-301 Part 1 included participants that received the randomised study drug to treat an episode of PSVT until the 150th positively adjudicated PSVT episode. Part 2 (also referred as the RAPID study) included participants that did not receive the randomised study drug in Part 1 and newly enrolled participants until the 180th positively adjudicated PSVT episode in Part 2. The study continued for approximately 6 months after the 180th positively adjudicated PSVT episode in Part 2 and this extension is referred to as Part 3 (also referred to as RAPID Extension).

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Population	N=1,179 (actual) (Test dose: Part 1 N=431; Part 2 N=706; Part 3 N=42; randomised study drug: Part 1 N=198; Part 2 N=255; Part 3 N=48); subjects with subjects with PSVT; adults aged 18 years and older
Intervention(s)	Etripamil nasal spray
Comparator(s)	Placebo
Outcome(s)	Primary outcome: Part 1: Time to an adjudicated termination of a confirmed episode of PSVT and conversion to SR for at least 30 seconds within 5 hours of start of study drug; Parts 2 and 3: Time to an adjudicated termination of a confirmed episode of PSVT and conversion to SR for at least 30 seconds within 30 minutes of start of study drug
Results (efficacy)	Part 1: At the end of the 5-hour observation period, there was no statistically significant difference between the etripamil 70mg and placebo group, with a hazard ratio of 1.086 in favour of etripamil 70mg (p=0.1212, Peto-Peto test). However, results of the study indicate a clear treatment effect at earlier timepoints. Patients in the etripamil 70mg group converted more rapidly, with a median time to conversion of 25.0 minutes compared to 49.9 minutes in the placebo group. Part 2: Primary endpoint was met: significant superiority of the etripamil treatment regimen (compared to placebo) in the time to conversion of PSVT to SR over 30 minutes following study drug administration (hazard ratio=2.62; p<0.001). There was a larger proportion of patients converting in the etripamil-regimen arm vs. placebo by 30 minutes (Kaplan-Meier estimates; 64.3% vs. 31.2%). There was a shorter median time to conversion of 17.2 minutes for the etripamil group compared to 53.5 minutes for the placebo group.[16] Parts 2 and 3 (the design of Parts 2 and 3 were the same and therefore their results are combined): Primary endpoint was met: significant superiority of the etripamil treatment regimen (compared to placebo) in the time to conversion of PSVT to SR over 30 minutes following study drug administration (hazard ratio=2.86; p<0.001). There was a larger proportion of patients converting in the etripamil-regimen arm vs. placebo (Kaplan-Meier estimates; 66.4% vs. 30.5%). There was a shorter median time to conversion of 17.0 minutes for the etripamil group compared to 51.6 minutes for the placebo group.
Results (safety)	Part 1: Overall, the safety and tolerability profile of study drug was favourable. The maximum severity of the majority of adverse events was mild, and adverse events were predominantly local reactions to the nasal spray, including nasal discomfort and congestion; most occurred within 24 hours after study drug administration. Parts 2 and 3: The most common adverse events within 24 hours after study drug administration were nasal discomfort, nasal congestion, rhinorrhoea, and epistaxis. Rates of adverse events were similar whether a patient took a single 70 mg dose or a second 70mg dose 10 minutes later. Etripamil was well tolerated when administered in a non-healthcare setting during PSVT or as a test dose during a clinic visit in sinus rhythm.[3]

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Trial	**NODE-302**, NCT03635996; Multi-Centre, Open-Label, Safety Study of Etripamil Nasal Spray in Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia **Phase III** - Terminated **Locations:** USA and Canada **Study completion date:** October 2020
Trial Design	Non-randomised, open label, single group assignment
Population	N=169 (actual); subjects with subjects with PSVT; adults aged 18 years and older
Intervention(s)	Etripamil nasal spray
Comparator(s)	No comparator
Outcome(s)	Primary outcome: The safety of etripamil nasal spray (NS) 70mg when self-administered by patients with an episode of PSVT in an outpatient setting (i.e., without medical supervision).
Results (efficacy)	Among 169 patients enrolled, 105 self-administered etripamil ≥1 time for perceived PSVT (median [range], 232 [8–584] days' follow-up). Probability of conversion within 30 minutes of etripamil was 60.2% (median time to conversion, 15.5 minutes) among 188 PSVT episodes (92 patients) positively adjudicated as atrioventricular nodal dependent by independent electrocardiogram (ECG) analysis. Among 40 patients who self-treated 2 episodes, 75% had a significantly consistent response by 30 minutes; 9 did not convert on either episode, and 21 converted on both episodes (χ^2=8.09; *P*=0.0045).[14]
Results (safety)	Forty-five of 105 patients (42.9%) had ≥1 treatment-emergent adverse event, generally transient and mild-to-moderate, including nasal congestion (14.3%), nasal discomfort (14.3%), or rhinorrhea (12.4%). No serious cardiac safety events were observed within 24 hours of etripamil.[14]

Estimated Cost

The cost of etripamil nasal spray is not yet known.

Relevant Guidance

NICE Guidance

No relevant guidance currently available.

NHS England (Policy/Commissioning) Guidance

No relevant guidance currently available.

Other Guidance

- European Society of Cardiology (ESC). 2019 Guidelines on Supraventricular Tachycardia (for the management of patients with). 2019.[15]

Additional Information

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Milestone Pharmaceuticals Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

1 ClinicalTrials.gov. *An Open Label Extension Study of Etripamil Nasal Spray in Patients With Paroxysmal Supraventricular Tachycardia*. *Trial ID: NCT04952610*. Status: Enrolling by invitation. Available from: https://clinicaltrials.gov/study/NCT04952610 [Accessed 22 November 2024].

2 Milestone Pharmaceuticals. *Etripamil Investigational Therapeutic for Episodic Cardiovascular Conditions*. Pharmaceuticals M. Available from: https://milestonepharma.com/research-development/etripamil/ [Accessed 22 November 2024].

3 Stambler BS, Camm AJ, Alings M, Dorian P, Heidbuchel H, Houtgraaf J, et al. Self-administered intranasal etripamil using a symptom-prompted, repeat-dose regimen for atrioventricular-nodal-dependent supraventricular tachycardia (RAPID): a multicentre, randomised trial. *The Lancet*. 2023;402(10396):118-28. Available from: https://doi.org/10.1016/S0140-6736(23)00776-6.

4 Choe WC, Sundaram S, Boorman C, Mullins N, Shamszad P, Plat F. High-density mapping of the slow pathway in a patient with atrioventricular nodal reentry given intranasal Etripamil during the NODE-1 study. *HeartRhythm Case Rep*. 2017;3(10):479-82. Available from: https://doi.org/10.1016/j.hrcr.2017.07.011.

5 ClinicalTrials.gov. *Showing results for: Etripamil | Not yet recruiting, Recruiting, Active, not recruiting studies*. Available from: https://clinicaltrials.gov/search?intr=Etripamil%20&aggFilters=status:not%20rec%20act [Accessed 25/11/2024].

6 National Health Service (NHS). *Supraventricular tachycardia (SVT)*. NHS. Available from: https://www.nhs.uk/conditions/supraventricular-tachycardia-svt/ [Accessed 25 November 2024].

7 Patient.info. *Supraventricular tachycardia in adults*. Patient.info. Available from: https://patient.info/doctor/supraventricular-tachycardia-in-adults.

8 National Health Service (NHS) Inform. *Supraventricular tachycardia*. Inform N. Available from: https://www.nhsinform.scot/illnesses-and-conditions/cardiovascular-disease/heart-disease/supraventricular-tachycardia/.

9 Milestone Pharmaceuticals. Pharmaceuticals M. Available from: https://milestonepharma.com/areas-of-focus/paroxysmal-supraventricular-tachycardia-psvt/ [Accessed 26 November 2024].

10 National Health Service (NHS) England. *Hospital Admitted Patient Care Activity, 2023-24: Diagnosis*. 2024. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2023-24#.

11 British National Formulary (BNF). *Arrhythmias*. (BNF) BNF. Available from: https://bnf.nice.org.uk/treatment-summaries/arrhythmias/#paroxysmal-supraventricular-tachycardia [Accessed 26 November 2024].

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12 Ip James E, Coutu B, Noseworthy Peter A, Parody Maria L, Rafii F, Sears Samuel F, et al. Etripamil Nasal Spray for Recurrent Paroxysmal Supraventricular Tachycardia Conversion. *Journal of the American College of Cardiology*. 2024;83(20):2032-4. Available from: https://doi.org/10.1016/j.jacc.2024.03.384.

13 Chu GS, Gupta D. Update on Etripamil Nasal Spray for the At-home Treatment of Acute Paroxysmal Supraventricular Tachycardia. *Heart Int*. 2021;15(1):2-6. Available from: https://doi.org/10.17925/hi.2021.15.1.2.

14 Ip JE, Coutu B, Bennett MT, Pandey AS, Stambler BS, Sager P, et al. Etripamil Nasal Spray for Conversion of Repeated Spontaneous Episodes of Paroxysmal Supraventricular Tachycardia During Long-Term Follow-Up: Results From the NODE-302 Study. *J Am Heart Assoc*. 2023;12(19):e028227. Available from: https://doi.org/10.1161/jaha.122.028227.

15 European Society of Cardiology (ESC). *2019 Guidelines on Supraventricular Tachycardia (for the management of patients with)*. Available from: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Supraventricular-Tachycardia [Accessed 02 December 2024].

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