# Milestone Pharmaceuticals Receives Refusal to File Letter from U.S. FDA for New Drug Application for Etripamil in the Treatment of PSVT

December 26, 2023

MONTREAL and CHARLOTTE, N.C., Dec. 26, 2023 (GLOBE NEWSWIRE) -- Milestone® Pharmaceuticals Inc. (Nasdaq: MIST) announced today that the Company received a Refusal to File (RTF) letter from the U.S. Food and Drug Administration (FDA) for the New Drug Application (NDA) for self-administered etripamil nasal spray for the treatment of paroxysmal supraventricular tachycardia (PSVT).

Upon preliminary review, the FDA determined that the NDA, submitted in October 2023, was not sufficiently complete to permit substantive review. The FDA requested clarification about the time of data recorded for adverse events in Phase 3 clinical trials; FDA did not express concerns about the nature or severity of adverse events. Milestone will seek clarification and is in the process of planning a meeting with the FDA.

"We intend to work with the FDA to better understand the open issues and to agree on a path forward," said Joseph Oliveto, President, and Chief Executive Officer of Milestone Pharmaceuticals. "We are committed to advancing etripamil nasal spray as a first-of-its kind portable and fast acting solution that would allow patients with episodic cardiovascular conditions to actively self-manage their condition outside of the healthcare setting."

**About Pivotal RAPID Phase 3 Trial**
Recently published in *The Lancet*, RAPID is a global, randomized, double-blind Phase 3 clinical trial of etripamil versus placebo in patients with PSVT. The trial was designed to evaluate the safety and efficacy of self-administered etripamil for treating PSVT. RAPID achieved its primary endpoint with 64% of patients who self-administered etripamil converting from supraventricular tachycardia (SVT) to sinus rhythm within 30 minutes compared to 31% on placebo (HR = 2.62, p<0.001). At one hour, the benefit was demonstrated in 73% of patients. In addition, significant reductions in time to conversion in patients who took etripamil were evident early and durable, with a median time to conversion of 17 minutes (95% CI: 13.4, 26.5) for patients treated with etripamil versus 54 minutes (95% CI: 38.7, 87.3) for patients treated with placebo. Data demonstrated statistically significant improvement in multiple defined symptoms of PSVT in patients receiving etripamil compared to placebo, using a patient-reported outcome (PRO) questionnaire. The safety and tolerability profile of etripamil is supportive of the NDA submission.

**About Paroxysmal Supraventricular Tachycardia (PSVT)**
An estimated two million people in the United States are currently diagnosed with PSVT which is a type of arrhythmia or abnormal heart rhythm. PSVT is characterized by episodes of rapid heartbeats often exceeding 150 to 200 beats per minute. Key features of PSVT include the sudden occurrence of episodes and very rapid heart rate. The heart rate can spike unpredictably and rapidly during an episode. The rapid heart rate often causes severe palpitations, shortness of breath, chest discomfort, dizziness, or lightheadedness, and distress, forcing patients to limit their daily activities. The uncertainty of when an episode of PSVT will strike or how long it will persist can provoke anxiety in patients and negatively impact their day-to-day life between episodes. The impact and morbidity from an attack can be especially detrimental in patients with underlying cardiovascular or medical conditions, such as heart failure, obstructive coronary disease, or dehydration. Many health care providers are dissatisfied with the lack of effective treatment options in addition to a prolonged, burdensome, and costly trip to the emergency department or, for some patients, an invasive ablation procedure.

**About Etripamil**
Etripamil is Milestone's lead investigational product. It is a novel calcium channel blocker nasal spray under clinical development for frequent and often highly symptomatic and episodic attacks associated with PSVT and atrial fibrillation with rapid ventricular rate (AFib-RVR). It is designed to be a rapid-response therapy that is self-administered by the patient, without the need for direct medical oversight. If approved, etripamil is intended to provide health care providers with a new treatment option to enable on-demand care and patient self-management. If approved, the portable, self-administered treatment may provide patients with active management and a greater sense of control over their condition. CARDAMYST™, the conditionally approved brand name for etripamil nasal spray, is well studied with a robust clinical trial program that includes a completed Phase 3 clinical-stage program for the treatment of PSVT and Phase 2 trial for the treatment of patients with AFib-RVR.

**About Milestone Pharmaceuticals**
Milestone Pharmaceuticals Inc. (Nasdaq: MIST) is a biopharmaceutical company developing and commercializing innovative cardiovascular solutions to improve the lives of people living with complex and life-altering heart conditions. The Company's focus on understanding unmet patient needs and improving the patient experience has led us to develop new treatment approaches that provide patients with an active role in self-managing their care. Milestone's lead investigational product is etripamil, a novel calcium channel blocker nasal spray that is being studied for patients to self-administer without medical supervision to treat highly symptomatic episodic attacks associated with PSVT and AFib-RVR.

**Forward-Looking Statements**
This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Words such as "believe," "continue," "could," "demonstrate," "designed," "develop," "estimate," "expect," "may," "pending," "plan," "potential," "progress," "will", "intend" and similar expressions (as well as other words or expressions referencing future events, conditions, or circumstances) are intended to identify forward-looking statements. These forward-looking statements are based on Milestone's expectations and assumptions as of the date of this press release. Each of these forward-looking statements involves risks and uncertainties. Actual results may differ materially from these forward-looking statements. Forward-looking statements contained in this press release include statements regarding the potential of etripamil to help patients living with these serious heart arrythmias; the continued ability of etripamil to achieve statistically superior ventricular rate reduction and improved symptom-relief when compared to placebo; the timing and outcomes of future interactions with U.S. and foreign regulatory bodies, including the FDA, including the timing of the FDA's potential review of the NDA; the timing of the launch of etripamil; the clinical benefit of etripamil for self-treating recurrent episodes of PSVT without medical supervision; and the timing of a Phase 3 registrational program for etripamil. Important factors that could cause actual results to differ materially from those in the forward-looking statements include, but are not limited to, whether a Type A meeting will be granted and whether our future interactions with the FDA will have satisfactory outcomes; whether and when, if at all, our NDA for etripamil will be

approved by the FDA; whether the FDA will require additional trials or data which may significantly delay and put at risk our efforts to obtain approval and may not be successful, the risks inherent in biopharmaceutical product development and clinical trials, including the lengthy and uncertain regulatory approval process; uncertainties related to the timing of initiation, enrollment, completion, evaluation and results of our clinical trials; risks and uncertainty related to the complexity inherent in cleaning, verifying and analyzing trial data; and whether the clinical trials will validate the safety and efficacy of etripamil for PSVT or other indications, among others, general economic, political, and market conditions, including deteriorating market conditions due to investor concerns regarding inflation, Russian hostilities in Ukraine and ongoing disputes in Israel and Gaza and overall fluctuations in the financial markets in the United States and abroad, risks related to pandemics and public health emergencies, and risks related the sufficiency of Milestone's capital resources and its ability to raise additional capital in the current economic climate. These and other risks are set forth in Milestone's filings with the U.S. Securities and Exchange Commission, including in its annual report on Form 10-K for the year ended December 31, 2022, under the caption "Risk Factors," as such discussion may be updated from time to time by subsequent filings Milestone may make with the U.S. Securities & Exchange Commission. Except as required by law, Milestone assumes no obligation to update any forward-looking statements contained herein to reflect any change in expectations, even as new information becomes available.

**Contact:**
Kim Fox, Vice President, Communications
kfox@milestonepharma.com
704-803-9295

Investor Inquiries:
Chris Calabrese, Managing Director
ccalabrese@lifesciadvisors.com
Kevin Gardner, Managing Director
kgardner@lifesciadvisors.com

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