

## BRETYLIUM TOSYLATE INJECTION, USP MONOGRAPH AND THERAPEUTIC REVIEW

	<b>Medication</b>
<b>Generic Name</b>	Bretylium Tosylate Injection, USP (aka Bretylium)
<b>Trade Name</b>	Not Applicable (previously marketed under other FDA approved applications as Bretylate, Bretylol and others)
<b>Therapeutic Class</b>	Class III antiarrhythmic (antifibrillatory and antiarrhythmic)
<b>FDA Approved Indication</b>	Prophylaxis and therapy of ventricular fibrillation (VF) and also the treatment of life-threatening ventricular arrhythmias, such as ventricular tachycardia (VT) that have failed to respond to adequate doses of a first-line antiarrhythmic agent, such as lidocaine.
<b>Dose<sup>1-3, 5-7</sup></b>	<p><b>Immediately Life-threatening Ventricular Arrhythmias (Ventricular Fibrillation or Hemodynamically Unstable Ventricular Tachycardia)</b></p> <ul style="list-style-type: none"> <li>• Bolus: 5 mg/kg of body weight undiluted by rapid intravenous (IV) injection; follow immediately with an electrical countershock. May increase to 10 mg/kg and repeat as necessary every 15 to 30-minute intervals up to 30 mg/kg of body weight if ventricular fibrillation persists.</li> <li>• Continuous suppression: Dilute 10 mL (500 mg) in 50 mL or more of 5 percent dextrose (D5W) or sodium chloride (NS) for injection, administer as a constant infusion of 1 to 2 mg/minute or 5 to 10 mg/kg body weight every 6 hours infused over eight minutes or more.</li> </ul> <p><b>Other Ventricular Arrhythmias</b></p> <ul style="list-style-type: none"> <li>• Intravenous (IV) Use: 5 to 10 mg/kg body weight diluted in 50 mL or more of 5 percent dextrose (D5W) or sodium chloride (NS) for injection every 6 hours, infused over eight minutes or more.</li> <li>• Intramuscular (IM) Use: 5 to 10 mg/kg of body weight undiluted; may be repeated at 1 to 2-hour intervals, rotating site, if the arrhythmia persists. After that, maintain the same dosage every 6 to 8 hours.</li> </ul> <p><b>Dosage Adjustment in Renal Impairment</b></p> <ul style="list-style-type: none"> <li>• Increase dosage interval in patients with renal impairment.</li> </ul> <p><b>Note</b></p> <ul style="list-style-type: none"> <li>• Limit the use to intensive care units, coronary care units, or other facilities with equipment and personnel for constant monitoring of cardiac rhythm and blood pressure.</li> <li>• The onset of antiarrhythmic action may be delayed by 20 minutes to 2 hours despite fast ventricular antifibrillatory response (within minutes).</li> </ul>

<b>Adverse Reactions</b> <sup>1-3,5-8</sup>	<p>Transient hypertension followed by hypotension and postural hypotension are most common. Hypotension can persist in about 50% of patients while supine and may occur at doses lower than those needed to suppress arrhythmias. Patients 65 years or more are at higher risk for postural hypotension.</p> <p>Other side effects:</p> <ul style="list-style-type: none"> <li>• Nausea and vomiting occurred in about 3%, especially with rapidly IV infusion</li> <li>• Vertigo, dizziness, lightheadedness, and syncope, which may be associated with postural hypotension in about 0.7%</li> <li>• Dysrhythmias, including bradycardia, increased the frequency of premature ventricular contractions, transitory hypertension, the initial increase in arrhythmias, precipitation of anginal attacks, and sensation of substernal pressure in about 0.2%</li> <li>• Renal dysfunction, diarrhea, abdominal pain, hiccups, erythematous macular rash, flushing, hyperthermia, confusion, paranoid psychosis, emotional lability, lethargy, generalized tenderness, anxiety, shortness of breath, diaphoresis, nasal stuffiness, and mild conjunctivitis in about 0.1%</li> <li>• Hyperthermia, characterized by temperature excess of 106°F within an hour to days after administration</li> </ul>
<b>Warnings</b> <sup>1-3,6-7</sup>	<p>Administration regularly results in postural hypotension. Keep patients in the supine position until tolerance to the hypotensive effect of bretylium develops. Patients over 65 years may be at increased risk of developing orthostatic hypotension, especially when the recommended rate of intravenous infusion is exceeded. Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. Hypotension can be corrected with volume where appropriate.</p> <p>Transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients, especially after too vigorous a dosing.</p> <p>Can precipitate digitalis toxicity in patients receiving digitalis glycosides (digoxin, digitoxin), avoid concurrent use if possible. Do not use in patients with arrhythmias due to digitalis toxicity.</p> <p>Avoid in patients with fixed cardiac output (i.e., severe aortic stenosis or severe pulmonary hypertension).</p> <p>If hyperthermia is suspected or diagnosed, discontinue bretylium and institute appropriate therapy.</p>
<b>Drug Interactions</b> <sup>1-3,5-7</sup>	<ul style="list-style-type: none"> <li>• Digitalis toxicity may be aggravated by Bretylium, avoid simultaneous initiation of therapy with digoxin or digitalis glycosides.</li> <li>• Bretylium can enhance the pressor effects of catecholamines such as dopamine or norepinephrine (use a diluted solution and monitor blood pressure closely).</li> <li>• Monoamine oxidase inhibitors will potentiate catecholamines release from nerve endings produced by bretylium tosylate.</li> </ul>
<b>Contraindications</b> <sup>1-3,5-7</sup>	<p>There are no contraindications to use bretylium tosylate in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias, except in the case of digitalis induced arrhythmias. If the arrhythmia is thought to be due to digitalis, bretylium tosylate should not be used.</p>
<b>Monitoring</b> <sup>2,5</sup>	<p>ECG and blood pressure during and after bretylium administration.</p>
<b>REMS Requirements</b>	<p>Not applicable</p>
<b>Cost</b>	<p>WAC = \$249.00 per vial</p>

### **IMPACT ON PRESCRIBING/PREPARATION/ADMINISTRATION/MONITORING**

Bretylium Tosylate Injection, USP is supplied as 50 mg/mL in 10 mL single-dose glass vials (contains no preservative) for IM or IV administration. It should be stored at controlled room temperature 20° to 25°C (68° to 77°F). The intramuscular dose should be administered undiluted and at different sites each time. Each IV dose should be diluted with 50 mL or higher of D5W or NS for intermittent dosing and higher volume for continuous infusion and given one day (24 hours) expiration.

During ACLS, administer an electrical countershock immediately after bolus dose of bretylium. If the arrhythmia persists, bretylium can be repeated every 15 to 30 minutes, up to a total dose of 30 mg/kg for a patient in VF or hemodynamically unstable ventricular tachycardia. If the arrhythmia is abolished, a maintenance dose, the same as the initial dose, can be given every 6 to 8 hours or by continuous infusion at 1 to 2 mg/min in adults. For hemodynamically stable, recurring VT, a bolus can be repeated every 1 to 2 hours up to a total dose of 30 mg/kg body weight.

### **ADVERSE REACTIONS**

Transient hypertension followed by hypotension and postural hypotension are most common. Hypotension can persist in about 50% of patients while supine and may occur at doses lower than those needed to suppress arrhythmias. Patients 65 years or more are at higher risk for postural hypotension. Patients on bretylium can have enhanced response to dopamine, norepinephrine, and epinephrine because of the impaired uptake of these drugs. Nausea and vomiting are common with rapid infusion of bretylium.

### **ADMINISTRATION**

Bretylium is to be administered in a setting with cardiac monitoring (intensive care units, coronary care units, or other facilities with equipment and personnel for constant monitoring of cardiac rhythm and blood pressure). The patient should be supine during administration, and other usual CPR procedures, including electrical cardioversion, should be employed before and following the injection of bretylium. If ventricular fibrillation persists, the dosage may be increased to 10 mg/kg and repeated as necessary (see below).

### **DOSAGE AND ADMINISTRATION**

- **Ventricular fibrillation (VF) / hemodynamically unstable ventricular tachycardia**
  - 5-10 mg/kg of bodyweight rapid IV bolus undiluted. Follow immediately with countershock, may repeat at a dose of 10 mg/kg every 15 to 30 minutes to a maximum dose of 30 mg/kg of body weight if ventricular fibrillation persists.
- **Refractory or recurrent stable ventricular tachycardia**
  - 5-10 mg/kg body weight in to 50-100 mL, IV over 8 minutes or more. May be repeated in 1 to 2 hour intervals if needed to a max of 30 mg/kg.
- **The maintenance dose (same dose used above)**
  - 5-10 mg/kg in 50-100 mL over 8 minutes or more every q 6-8 hours thereafter.  
It can be administered as an IV infusion at a rate of 1 to 2 mg/min
- **Intramuscular injection (IM)**
  - Use undiluted solution.
  - 5-10 mg/kg IM; may repeat dose at 1 to 2 hour intervals if arrhythmia persists.
  - Rotate injection site with each subsequent dose and do not inject near a major nerve.
  - Maintain: 5-10 mg/kg IM q 6-8 hours.

Antifibrillatory occurs within minutes, while the onset of antiarrhythmic action may occur between 20 minutes and 2 hours. The delay in effect appears to be longer after IM than after IV injection.

### **MONITORING**

Monitor ECG and BP during and after bretylium administration, monitor for hypersensitivity reactions. Monitor temperature (hyperthermia, characterized by temperature excess of 106°F within an hour to days after administration).

### **PLACE IN THERAPY**

Cardiac arrest or sudden cardiac death (SCD) results from ventricular fibrillation, and pulseless ventricular tachycardia is associated with high mortality. Out-of-hospital cardiac arrests (OHCAs) have a reported incidence of 395,000 events in the US with 5.5% surviving to hospital discharge, while in-hospital cardiac arrests (IHCA) are estimated at 200,000 with 24.4% surviving to discharge. Pharmacologic therapy, including antiarrhythmics, is employed as a resuscitative measure to break the dysrhythmia and restore adequate circulation to vital organs. Antiarrhythmics are used in shock-refractory ventricular fibrillation (VF) and pulseless ventricular tachycardia (pVT) in an effort to restore perfusing rhythm and maintain spontaneous circulation.

Bretylium Tosylate Injection, USP is a class III antiarrhythmic medication approved for short-term prophylaxis and therapy of ventricular fibrillation and for the treatment of life-threatening ventricular arrhythmia unresponsive to first-line antiarrhythmic agents such as lidocaine. Experimental and clinical data established electrophysiologic restoration of the injured myocardial cells toward normal, increased action potential duration and effective refractory period without changing their ratio to each other as a possible mechanism in suppressing re-entry of aberrant impulses and decreasing induced dispersion of excitable local states. Several small studies reported successful conversion of VF to a stable rhythm with bretylium after the failure of standard electrical and pharmacologic therapy. A few studies suggest that early use of bretylium may be associated with improved outcomes.

Administration of IV and IM bretylium is associated with significant hypotension (postural/orthostatic); thus, patients should remain supine during administration and until tolerance to hypotensive effect develops. Monitor ECG and BP during and after administration. Nausea and vomiting may occur with rapid intravenous administration. Bretylium is eliminated mostly unchanged by the kidney; thus, increase dosage interval in patients with impaired renal function.

The 2018 American Heart Association (AHA) ACLS guidelines update recommendations include consideration of either amiodarone or lidocaine for shock-refractory VF/pulseless VT (pVT), although a recent systematic review and meta-analysis, based on current literature and data, indicated that there has been no conclusive evidence that any antiarrhythmic agents improve the rates of return of spontaneous circulation (ROSC), survival to admission, survival to discharge or neurological outcomes. However, potential benefits in short-term outcomes such as ROSC or survival to hospital admission are reasons for the recommendations.

### **SUMMARY**

Bretylium Tosylate Injection, USP would be a promising addition to the few medications for the acute/short-term management of shock-refractory VF/hemodynamically unstable VT during ACLS, especially in patients with witnessed arrest. It is an alternative for short-term management of VT in patients with allergy to amiodarone and lidocaine and those at high risk for amiodarone toxicity.

### **ESTIMATED BUDGET IMPACT**

Cost per patient: The minimum vial usage for one patient is (1) vial and a max of (4) vials per day. The average patient will use (2) vials in a day.

Vials (WAC): 1 (\$249), 2 (\$498), 4 (\$996)

Estimated number of patients per year is based on the size of the hospital or population covered by emergency response service.

**EVIDENCE TABLE**

**Article**

Antiarrhythmics in Cardiac Arrest: A Systematic Review and Meta-Analysis

Journal: *Heart, Lung, and Circulation*. 2018;27:280-90.

Authors: Chowdhury et al.

<p>Study Design and Methods</p>	<p>Systematic Review and Meta-Analysis</p> <p><b>Methods</b> Systematic search of bibliographic databases including CINAHL, SCOPUS, PubMed, Web of Science, Medline (Ovid), and the Cochrane Clinical Trials Registry.</p> <p>N = 31 studies, involving 39,914 patients</p> <ul style="list-style-type: none"> <li>• Compared an antiarrhythmic to either a control group, placebo or another antiarrhythmic in adult cardiac arrests</li> <li>• Eight antiarrhythmic (AA) including amiodarone, bretylium, esmolol, lidocaine, nifekalant, and others were identified (most common being amiodarone and lidocaine).</li> </ul> <p>Patient Population</p> <ul style="list-style-type: none"> <li>• Adults over 18 years of age with cardiac arrest</li> <li>• Out of hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA)</li> </ul>
<p>Purpose</p>	<p>Perform a thorough, in-depth review and analysis of current literature to assess the efficacy of antiarrhythmics in advanced life support. Level of evidence, heterogeneity, sensitivity, and presence of bias were determined for each article.</p>
<p>Efficacy and Other Outcomes</p>	<p><b>Efficacy</b> Effect of antiarrhythmics on ROSC; short-term survival: survival to hospital admission for OHCA patients, survival to hospital discharge; and neurologic outcomes at discharge</p> <ul style="list-style-type: none"> <li>• 30 studies met the inclusion criteria</li> <li>• Eight intervention medications and 39,914 evaluated</li> </ul> <p><b>Overall</b></p> <ul style="list-style-type: none"> <li>• No one AA delivered during resuscitation has been shown to improve patient outcomes</li> <li>• No conclusive evidence that any AA improves rates of ROSC, survival to admission, survival to discharge or neurological outcomes</li> </ul> <p><b>Bretylium</b></p> <ul style="list-style-type: none"> <li>• Two studies examined the effect of bretylium compared to placebo (n=108)</li> <li>• Bretylium significantly improved survival to admission (OR = 4.04; 95%CI = 1.22–13.43; I<sup>2</sup> = 0%; p = 0.02)</li> <li>• There was no significant improvement in survival to discharge (OR = 4.44; 95%CI = 0.51–39.03; p = 0.18)</li> </ul> <p><b>Lidocaine vs. Bretylium</b></p> <ul style="list-style-type: none"> <li>• Three studies investigated lidocaine versus bretylium (n = 486)</li> <li>• There was no difference in ROSC (OR = 1.78; 95%CI = 0.95–3.34; I<sup>2</sup> = 43%; p = 0.07), survival to admission (OR = 0.98; 95%CI = 0.37–2.60; p = 0.97) or survival to discharge (OR = 1.14; 95%CI = 0.46–2.82; I<sup>2</sup> = 28%; p = 0.78)</li> </ul>

<b>Article</b> Efficacy of Bretylium Tosylate for Ventricular Tachycardia Journal: <i>The American Journal of Cardiology</i> . 1999 Jan;83:115-7 Authors: Chandrasekaran S, Steinberg JS.	
Study Design and Methods	<p>Single Center Prospective Study</p> <p><b>Methods</b></p> <p>N= Twenty patients (14 men and 6 women) with inducible, sustained (&gt;30 seconds), monomorphic VT selected from consecutive patients referred for electrophysiologic testing for cardiac arrest, VT, and syncope were enrolled</p> <ul style="list-style-type: none"> <li>• Bretylium 10 mg/kg over 30 min followed by 2 mg/min maintenance infusion</li> <li>• The electrophysiologic study was completed at baseline and repeated 20 minutes after loading during the maintenance infusion</li> </ul> <p>Patient Population</p> <ul style="list-style-type: none"> <li>• 14 males, 6 females with reproducibly inducible, sustained, monomorphic VT at baseline</li> <li>• Most (75%) had coronary artery disease</li> </ul>
Purpose	<p>Evaluate the efficacy and safety of bretylium to prevent inducibility of VT in the electrophysiology laboratory.</p> <p>Control electrophysiologic study was performed using programmed electrical stimulation of the right ventricular apex and outflow tract with 6Fr quadripolar catheters with up to 3 extra stimuli.</p>
Efficacy and Other Outcomes	<p><b>Efficacy</b></p> <p>Eighteen patients completed the electrophysiologic testing; two did not due to severe hypotension.</p> <ul style="list-style-type: none"> <li>• Mean systolic pressure in sinus rhythm was <math>88 \pm 6</math> mm Hg vs. <math>110 \pm 8</math> mm Hg at baseline (<math>p &lt; 0.00001</math>)</li> <li>• Mean atrial effective refractory period was <math>232 \pm 26</math> ms vs. <math>228 \pm 27</math> ms at baseline (NS)</li> <li>• Mean atrioventricular nodal effective refractory period was <math>246 \pm 40</math> ms vs. <math>269 \pm 79</math> ms at baseline (NS)</li> <li>• Mean ventricular effective refractory period was <math>234 \pm 28</math> ms vs. <math>234 \pm 21</math> ms at baseline (NS)</li> <li>• Mean VT cycle length was <math>280 \pm 43</math> ms vs. <math>270 \pm 41</math> ms at baseline (NS)</li> <li>• Mean number of extrastimuli needed to induce VT was <math>1.8 \pm 0.8</math> vs. <math>2.3 \pm 0.6</math> at baseline (<math>p = 0.03</math>)</li> </ul> <p>There was no significant difference in refractory periods between baseline and after bretylium loading. All 18 patients were persistently inducible after bretylium indicating a lack of efficacy in the acute prevention of sustained VT.</p> <p><b>Safety</b></p> <p>Significant hypotension was documented with bretylium therapy, and two patients could not complete the post-therapy electrophysiologic study due to severe hypotension.</p>

**Article**  
 Randomized, Double-Blind Comparison of Intravenous Amiodarone and Bretylium in the Treatment of Patients with Recurrent, Hemodynamically Destabilizing Ventricular Tachycardia or Fibrillation  
 Journal: *Circulation* 1995;92:3255-3263  
 Authors: Kowey et al.

<p>Study Design and Methods</p>	<p>Multicenter, Randomize, Double-Blind, Parallel, Controlled Study</p> <p><b>Methods</b></p> <p>Three hundred two patients with recurring VT, VF, or at least 2 (mean, 4.93) episodes of hemodynamically destabilizing VT or VF in the 24 hours before enrollment and arrhythmia not drug-induced. No amiodarone or bretylium within five half-lives of study entry.</p> <p>Three study groups</p> <ul style="list-style-type: none"> <li>• Amiodarone - Low dose (N = 94): 200 mg administered as 18.75 mg over 10 min followed by 0.125 mg/min for 6 h, then 0.065 mg/min for remainder of 48 h</li> <li>• Amiodarone - high dose (N = 105): 1800 mg administered as 150 mg over 10 min followed by 1 mg/min for 6 h, then 0.52 mg/min for remainder of 48 h</li> <li>• Bretylium (N = 103): 4700 mg administered as 350 mg over 10 min followed by 1.5 mg/min for 6 h, then 1.5 mg/min for remainder of 48 h</li> </ul> <p>Patient Population:</p> <ul style="list-style-type: none"> <li>• Mean age: low dose amiodarone (66 ± 12), high dose amiodarone (63 ± 12) and bretylium (66 ± 12)</li> <li>• Gender: Mostly male, over 70% in each group</li> </ul> <p>Assessment</p> <ul style="list-style-type: none"> <li>• Assessments completed at predetermined point intervals – 6 h, 12 h, 18 h, etc.</li> </ul>
<p>Purpose</p>	<p>To compare the safety and efficacy of a high and a low dose of intravenous amiodarone with bretylium to prevent recurrent ventricular arrhythmias.</p> <p>Hemodynamic instability defined as a loss of consciousness or systolic blood pressure of &lt; 80 mm Hg with signs or symptoms of shock.</p> <p>Continuous ECG telemetry monitoring while on therapy.</p>
<p>Efficacy and Other Outcomes</p>	<p><b>Efficacy</b></p> <p>The ability of the study drug to prevent recurrent ventricular arrhythmias as assessed by clinical evaluation.</p> <ul style="list-style-type: none"> <li>• 75% of patients in each group completed study and data evaluated based on intention to treat (p = 0.237)</li> <li>• Most events occurred in the first 12 hours and a higher event rate in the low dose amiodarone group</li> <li>• Significant difference in event occurrence amongst the group in the first six-hour point (p = 0.049)</li> <li>• No difference overall in the primary endpoint of hemodynamically destabilizing VT/VF event per hour by the 48-hour</li> <li>• There was insufficient power to detect significant difference in recurrent VT despite attempted cardioversion</li> </ul> <p><b>Safety</b></p> <p>A total of 259 patients (86%) had at least one adverse event</p> <ul style="list-style-type: none"> <li>• Significant adverse events (hypotension, congestive failure, and diarrhea) were frequent in the bretylium group</li> <li>• Ninety-seven patients (32%) died during the 30-day study</li> <li>• Gender: Mostly male, over 70% in each group</li> </ul> <p>High-dose IV amiodarone (1800 mg/48 h) was effective in suppressing highly malignant ventricular arrhythmias in patients with severe underlying heart disease and is at least as effective as bretylium.</p>

**Article**  
 The Use of Bretylium in Prehospital Ventricular Fibrillation  
 Journal: *The American Journal of Emergency Medicine*. 1983;1:1-6.  
 Authors: Harrison EE, Amey BD

<p>Study Design and Methods</p>	<p>Single Center Prospective Study</p> <p><b>Methods</b></p> <ul style="list-style-type: none"> <li>• 15 paramedic units performed basic and advanced CPR as directed by a physician via radio contact or written protocol</li> <li>• An encounter form was developed and recorded time of medication administration, rhythm, presence of a pulse prior and after bretylium, and other responses</li> <li>• Electrocardiographic sequential strips of observed rhythm and blood gas from ED were attached to the document</li> <li>• The protocol employed             <ol style="list-style-type: none"> <li>1. 400 wattsec countershock</li> <li>2. Intubation</li> <li>3. 88 mEq sodium bicarbonate</li> <li>4. If VF persisted, 400 wattsec countershock</li> <li>5. If persistent VF, epinephrine 1 mg IVIC or bretylium 500 mg IV or lidocaine 100 mg IV after each succeeding countershock</li> </ol> </li> <li>• Ninety-six patients received bretylium over 24 months (98% male)</li> </ul> <p>Patient population: ACLS patients with prehospital ventricular fibrillation</p>
<p>Purpose</p>	<p>Assess the clinical and rhythm responses of patients in cardiac arrest to bretylium administration in patients with refractory ventricular fibrillation.</p> <p>Positive response defined as the presence of a palpable pulse following bretylium and countershock.</p>
<p>Efficacy and Other Outcomes</p>	<p><b>Efficacy</b></p> <p>Ninety-six patients who received bretylium were divided into three groups based on clinical and rhythm response.</p> <p>No statistical difference amongst the three groups in the average age, sex, witnessed or unwitnessed cardiac arrest, or resuscitation protocol.</p> <p>Eighty-five percent of patients received epinephrine before bretylium, and 50% received lidocaine before bretylium.</p> <p>Bretylium administered after a mean of 3 or 4 countershock:</p> <ul style="list-style-type: none"> <li>• Group 1 (62/96, 64%): No response (no viable rhythm or pulse following bretylium and subsequent resuscitative efforts)</li> <li>• Group 2 (20/96, 21%): Temporary response (temporary rhythm sustaining a pulse and reverted to an unstable rhythm without a pulse)</li> <li>• Group 3 (14/96, 15%): Survivors (had a viable rhythm and a sustained pulse; delivered to the emergency department in and admitted to the hospital). This group received bretylium earlier than the other two groups</li> </ul> <p><b>Safety</b></p> <ul style="list-style-type: none"> <li>• Downtime (time between arrest and initiation of CPR) could not be accurately assessed</li> <li>• Mean paramedic response time did not differ amongst the three groups</li> </ul>



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## **Indications and Usage**

Bretylium Tosylate Injection, USP is indicated in the prophylaxis and therapy of ventricular fibrillation.

Bretylium Tosylate Injection, USP is also indicated in the treatment of life-threatening ventricular arrhythmias, such as ventricular tachycardia that have failed to respond to adequate doses of a first-line antiarrhythmic agent, such as lidocaine.

Use of Bretylium Tosylate Injection, USP should be limited to intensive care units, coronary care units or other facilities where equipment and personnel for constant monitoring of cardiac arrhythmias and blood pressure are available.

Following injection of Bretylium Tosylate there may be a delay of 20 minutes to 2 hours in the onset of antiarrhythmic action, although it appears to act within minutes in ventricular fibrillation. The delay in effect appears to be longer after intramuscular than after intravenous injection.

## **Bretylium Tosylate Injection, USP Important Safety Information**

### **Contraindications**

There are no contraindications to use bretylium tosylate in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias, except in the case of digitalis induced arrhythmias. If the arrhythmia is thought to be due to digitalis, bretylium tosylate should not be used.

### **Warnings and Precautions**

- **Hypotension:** Postural hypotension, subjectively recognized by dizziness, lightheadedness, vertigo or faintness may occur. Some degree of hypotension is present in about 50% of patients while they are supine; patients over 65 years may be at greater risk. Keep patients supine until tolerance to the hypotensive effect of bretylium tosylate develops.
- **Transient Hypertension and Increased Frequency of Arrhythmias:** Transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients, especially after too vigorous a dosing.
- **Caution During Use with Digitalis Glycosides:** Bretylium tosylate may aggravate digitalis toxicity. In digitalized patients, bretylium tosylate should be used only if the etiology of the arrhythmia does not appear to be digitalis toxicity and other antiarrhythmic drugs are not effective. Avoid simultaneous initiation of therapy with digitalis glycosides and bretylium tosylate.
- **Patients with Fixed Cardiac Output:** Bretylium tosylate should be avoided in patients with fixed cardiac output since severe hypotension may result.
- **Hyperthermia:** Hyperthermia, characterized by temperature excess of 106°F, has been reported.
- **General Precautions:**
  - Bretylium Tosylate Injection, USP should be diluted prior to intravenous use, but may be given undiluted for immediately life-threatening ventricular arrhythmias.
  - When injected intramuscularly, not more than 5 mL should be given in a site, and injection sites should be varied.
  - Dosage intervals should be increased in patients with impaired renal function.

### **Adverse Reactions**

Hypotension and postural hypotension are the most frequently reported adverse reactions. Nausea and vomiting occurred in about three percent of patients. This is not a complete list of side effects and others may occur. Please see the full Prescribing Information for a complete list of adverse reactions.

To report SUSPECTED ADVERSE REACTIONS, contact ANI Pharmaceuticals, Inc. at 1-800-308-6755 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**This Important Safety Information does not include all the information needed to use Bretylium Tosylate Injection, USP safely and effectively. See full Prescribing Information for Bretylium Tosylate Injection, USP.**