BRETYLIUM TOSYLATE- bretylium tosylate injection
ANI Pharmaceuticals, Inc.

Bretylium Tosylate Injection, USP

Rx only

AQUEOUS SOLUTION FOR THE ACUTE MANAGEMENT OF CARDIAC ARRHYTHMIAS

Glass Vial

FOR INTRAMUSCULAR OR INTRAVENOUS USE ONLY

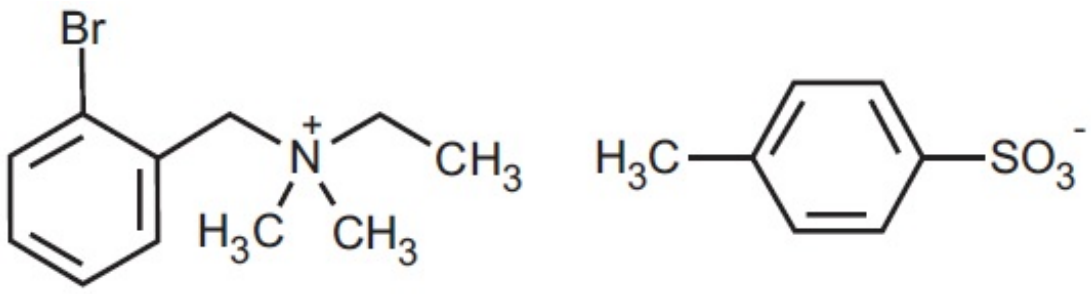
DESCRIPTION

Bretylium Tosylate Injection, USP is a sterile, nonpyrogenic solution for use in the management of ventricular arrhythmias.

Each milliliter contains 50 mg bretylium tosylate in water for injection. The osmolarity is 0.174 mOsm/mL (approx.). May contain sodium hydroxide and hydrochloric acid for pH adjustment. pH is approximately 5.2.

The solution contains no bacteriostatic, antimicrobial agent or added buffer (except for pH adjustment) and is intended only for use as a single-dose administration. When smaller doses are required, the unused portion should be discarded.

Bretylium tosylate, a bromobenzyl quaternary ammonium compound is chemically designated (o-Bromobenzyl) ethyldimethyl-ammonium p-toluenesulfonate, a white powder freely soluble in water. It has the following structural formula:



Therapeutic class: Bretylium tosylate is classified as an antiarrhythmic agent.

CLINICAL PHARMACOLOGY

Bretylium tosylate selectively accumulates in sympathetic ganglia and their postganglionic adrenergic neurons when administered slowly or incrementally where it inhibits norepinephrine release by depressing adrenergic nerve terminal excitability.

Bretylium tosylate also suppresses ventricular fibrillation and ventricular arrhythmias. The mechanisms of the antifibrillatory and antiarrhythmic actions of bretylium tosylate are not established.

In efforts to define these mechanisms, the following electrophysiologic actions of bretylium tosylate have been demonstrated in animal experiments:

1. Increase in ventricular fibrillation threshold.

2. Increase in action potential duration and effective refractory period without changes in heart rate.
3. Little effect on the rate of rise or amplitude of the cardiac action potential (Phase 0) or in resting membrane potential (Phase 4) in normal myocardium. However, when cell injury slows the rate of rise, decreases amplitude, and lowers resting membrane potential, bretylium tosylate transiently restores these parameters toward normal.
4. In canine hearts with infarcted areas bretylium tosylate decreases the disparity in action potential duration between normal and infarcted regions.
5. Increase in impulse formation and spontaneous firing rate of pacemaker tissue as well as increased ventricular conduction velocity.

The restoration of injured myocardial cell electrophysiology toward normal, as well as the increase of the action potential duration and effective refractory period without changing their ratio to each other, may be important factors in suppressing re-entry of aberrant impulses and decreasing induced dispersion of local excitable states.

Bretylium tosylate induces a chemical sympathectomy-like state which resembles a surgical sympathectomy. Catecholamine stores are not depleted by bretylium tosylate but catecholamine effects on the myocardium and on peripheral vascular resistance are often seen shortly after administration because bretylium tosylate causes an early release of norepinephrine from the adrenergic postganglionic nerve terminals. Subsequently bretylium tosylate blocks the release of norepinephrine in response to neuron stimulation. Peripheral adrenergic blockade regularly causes orthostatic hypotension but has less effect on supine blood pressure. The relationship of adrenergic blockade to the antifibrillatory and antiarrhythmic actions of bretylium tosylate is not clear. In a study in patients with frequent ventricular premature beats, peak plasma concentration of bretylium tosylate and peak hypotensive effects were seen within one hour of intramuscular administration, presumably reflecting adrenergic neuronal blockade. However, suppression of premature ventricular beats was not maximal until 6 to 9 hours after dosing, when mean plasma concentration had declined to less than one-half of peak level. This suggests a slower mechanism, other than neuronal blockade, was involved in suppression of the arrhythmia. On the other hand, antifibrillatory effects can be seen within minutes of an intravenous injection, suggesting that the effect on the myocardium may occur quite rapidly.

Bretylium tosylate has a positive inotropic effect on the myocardium but it is not yet certain whether this effect is direct or is mediated by catecholamine release.

Bretylium tosylate is eliminated intact by the kidneys. Seventy to 80% of a bretylium dose is excreted unchanged in the urine within 24 hours, and an additional 10% during the next three days. The half-life for elimination is 6 to 10 hours; a longer half-life is to be expected in patients with renal insufficiency. Bretylium tosylate is able to be removed from the body by hemodialysis.

Effect on Heart Rate: There is sometimes an initial small increase in heart rate when bretylium tosylate is administered. This is usually an inconsistent and transient occurrence but can be severe with rapid large doses.

Hemodynamic Effects: Following intravenous administration of 5 mg/kg of bretylium tosylate to patients with acute myocardial infarction, there was a mild increase in arterial pressure, followed by a modest decrease, remaining within normal limits throughout. Pulmonary artery pressures, pulmonary capillary wedge pressure, right atrial pressure, cardiac index, stroke volume index and stroke work index were not significantly changed. These hemodynamic effects were not correlated with antiarrhythmic activity.

Onset of Action: Suppression of ventricular fibrillation is rapid, usually occurring within minutes following intravenous administration. Suppression of ventricular tachycardia and other ventricular arrhythmias develops more slowly, usually 20 minutes to 2 hours after parenteral administration.

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.

CONTRAINDICATIONS

There are no contraindications to use 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

1. Hypotension

Administration of bretylium tosylate regularly results in postural hypotension, subjectively recognized by dizziness, lightheadedness, vertigo or faintness. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses lower than those needed to suppress arrhythmias.

Patients should be kept in the supine position until tolerance to the hypotensive effect of bretylium tosylate develops. Tolerance occurs unpredictably but may be present after several days.

Patients over 65 years may be at increased risk of developing orthostatic hypotension, especially when the recommended rate of intravenous infusion is exceeded. See **DOSAGE AND ADMINISTRATION**.

Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of dopamine or norepinephrine may be used to raise blood pressure. When catecholamines are administered, a dilute solution should be employed and blood pressure monitored closely because the pressor effects of the catecholamines are enhanced by bretylium tosylate. Volume expansion with blood or plasma and correction of dehydration should be carried out where appropriate.

2. Transient Hypertension and Increased Frequency of Arrhythmias

Due to the initial release of norepinephrine from adrenergic postganglionic nerve terminals by bretylium tosylate, transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients, especially after too vigorous a dosing.

3. Caution During Use With Digitalis Glycosides

The initial release of norepinephrine caused by bretylium tosylate may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia occurs in a digitalized patient, 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. Simultaneous initiation of therapy with digitalis glycosides and bretylium tosylate should be avoided.

4. Patients with Fixed Cardiac Output

In patients with fixed cardiac output (i.e., severe aortic stenosis or severe pulmonary hypertension) bretylium tosylate should be avoided since severe hypotension may result from a fall in peripheral resistance without a compensatory increase in cardiac output. If survival is threatened by the arrhythmia, bretylium tosylate may be used but vasoconstrictive catecholamines should be given promptly if severe hypotension occurs.

5. Hyperthermia

In a small number of patients, hyperthermia, characterized by temperature excess of 106°F, has been reported in association with bretylium tosylate administration. Temperature rise can begin within one hour or later after administration of drug, and reach a peak within 1-3 days. If hyperthermia is suspected or diagnosed, bretylium tosylate should be discontinued and appropriate treatment instituted immediately.

PRECAUTIONS

General

1. Dilution for Intravenous Use

Bretylium Tosylate Injection, USP should be diluted (one part bretylium tosylate with four parts of Dextrose Injection, USP or Sodium Chloride Injection, USP) prior to intravenous use. Rapid intravenous administration may cause severe nausea and vomiting and even provoke a hypertensive crisis. Therefore, the diluted solution should be infused over a period greater than 8 minutes. In treating existing ventricular fibrillation, bretylium tosylate should be given as rapidly as possible and may be given without dilution.

2. Use Various Sites for Intramuscular Injection

When injected intramuscularly, not more than 5 mL should be given in a site, and injection sites should be varied, since repeated intramuscular injection into the same site may cause atrophy and necrosis of muscle tissue, fibrosis, vascular degeneration and inflammatory changes.

3. Reduce Dosage in Impaired Renal Function

Since bretylium tosylate is excreted principally via the kidney, the dosage intervals should be increased in patients with impaired renal function. See **CLINICAL PHARMACOLOGY** section for information on the effect of reduced renal function on half-life.

Drug Interactions

Digitalis Glycosides:
See **WARNINGS** and **CONTRAINDICATIONS**.

Catecholamines: See **WARNINGS**.

Monoamine Oxidase Inhibitors: The effects of the release of catecholamines from nerve endings produced by bretylium tosylate (see **CLINICAL PHARMACOLOGY**) will be potentiated by monoamine oxidase inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Bretylium tosylate has not been evaluated for carcinogenic or mutagenic potential. There are no available data on potential for impairment of fertility.

Pregnancy Category C. Animal reproduction studies have not been conducted with dextrose or bretylium tosylate. It is also not known whether dextrose or bretylium tosylate can cause fetal harm when

administered to a pregnant woman or can affect reproduction capacity. Bretylium tosylate should be given to a pregnant woman only if clearly needed.

Pediatric Use:

The safety and effectiveness of Bretylium Tosylate Injection, USP have not been established. Its limited use in pediatric patients has been inadequate to fully define proper dosage and limitations for use.

Geriatric Use:

Clinical studies of bretylium tosylate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or drug therapy.

Intravenous infusion, especially if administered at a rate beyond that recommended in the **DOSAGE AND ADMINISTRATION** section, may produce an increased risk of orthostatic hypotension in the elderly. See **WARNINGS**.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. See **CLINICAL PHARMACOLOGY**.

ADVERSE REACTIONS

Hypotension and postural hypotension have been the most frequently reported adverse reactions (see **WARNINGS**). Nausea and vomiting occurred in about three percent of patients, primarily when bretylium tosylate was administered rapidly by the intravenous route. Vertigo, dizziness, lightheadedness and syncope, which sometimes accompanied postural hypotension, have been reported with an incidence of about 0.7%.

Bradycardia, increased frequency of premature ventricular contractions, transitory hypertension, initial increase in arrhythmias (see **WARNINGS**), precipitation of anginal attacks and sensation of substernal pressure have also been reported in a small number of patients with an incidence of about 0.2%.

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 have been reported with an incidence of about 0.1%. The relationship of bretylium tosylate administration to these reactions has not been clearly established. Hyperthermia has also been reported (see **WARNINGS**).

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.

DOSAGE AND ADMINISTRATION

Bretylium Tosylate Injection, USP is to be used clinically only for treatment of life-threatening ventricular arrhythmias under constant electrocardiographic monitoring. The clinical use of bretylium tosylate is for short-term use only. Patients should either be kept supine during the course of bretylium tosylate therapy or be closely observed for postural hypotension. The optimal dose schedule for parenteral administration of bretylium tosylate has not been determined. There is comparatively little experience with dosages greater than 40 mg/kg/day, although such doses have been used without apparent adverse effects. The following schedule is suggested.

A. For Immediately Life-threatening Ventricular Arrhythmias such as Ventricular Fibrillation or

Hemodynamically Unstable Ventricular Tachycardia:

Administer undiluted Bretylium Tosylate Injection, USP at a dosage of 5 mg/kg of body weight by rapid intravenous injection. Other usual cardiopulmonary resuscitative procedures, including electrical cardioversion, should be employed prior to and following the injection in accordance with good medical practice. If ventricular fibrillation persists, the dosage may be increased to 10 mg/kg and repeated as necessary.

For continuous suppression, dilute contents of one Bretylium Tosylate Injection, USP 10 mL container (500 mg) to a minimum of 50 mL with 5% Dextrose Injection, USP or Sodium Chloride Injection, USP and administer the diluted solution as a constant infusion of 1 to 2 mg bretylium tosylate per minute. An alternative maintenance schedule is to infuse the diluted solution at a dosage of 5 to 10 mg bretylium tosylate per kg body weight, over a period greater than 8 minutes, every 6 hours. More rapid infusion may cause nausea and vomiting, and in patients older than 65 years, may increase the risk of developing orthostatic hypotension.

B. Other Ventricular Arrhythmias:

1. Intravenous Use:

Bretylium Tosylate Injection,USP must be diluted as described above before intravenous use.

Administer the diluted solution at a dosage of 5 to 10 mg bretylium tosylate per kg of body weight by intravenous infusion over a period greater than 8 minutes. More rapid infusion may cause nausea and vomiting, and in patients older than 65 years, may increase the risk of developing orthostatic hypotension. Subsequent doses may be given at 1 to 2 hour intervals if the arrhythmia persists.

For maintenance therapy, the same dosage may be administered every 6 hours, or a constant infusion of 1 to 2 mg bretylium tosylate per minute may be given.

2. For intramuscular injection:

Do not dilute Bretylium Tosylate Injection, USP prior to intramuscular injection. Inject 5 to 10 mg bretylium tosylate per kg of body weight. Subsequent doses may be given at 1 to 2 hour intervals if the arrhythmia persists. Thereafter maintain the same dosage every 6 to 8 hours.

Intramuscular injection should not be made directly into or near a major nerve, and the site of injection should be varied on repeated injection. No more than 5 mL should be injected intramuscularly in one site.

As soon as possible, and when indicated, patients should be changed to an oral antiarrhythmic agent for maintenance therapy.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Slight discoloration does not alter potency.

Do not administer unless solution is clear and container is undamaged. Discard unused portion.

HOW SUPPLIED

Bretylium Tosylate Injection, USP is supplied in 10 mL single-dose glass vials (NDC 62559-870-11).

Store at 20° to 25°C (68° to 77°F); [see USP Controlled Room Temperature].

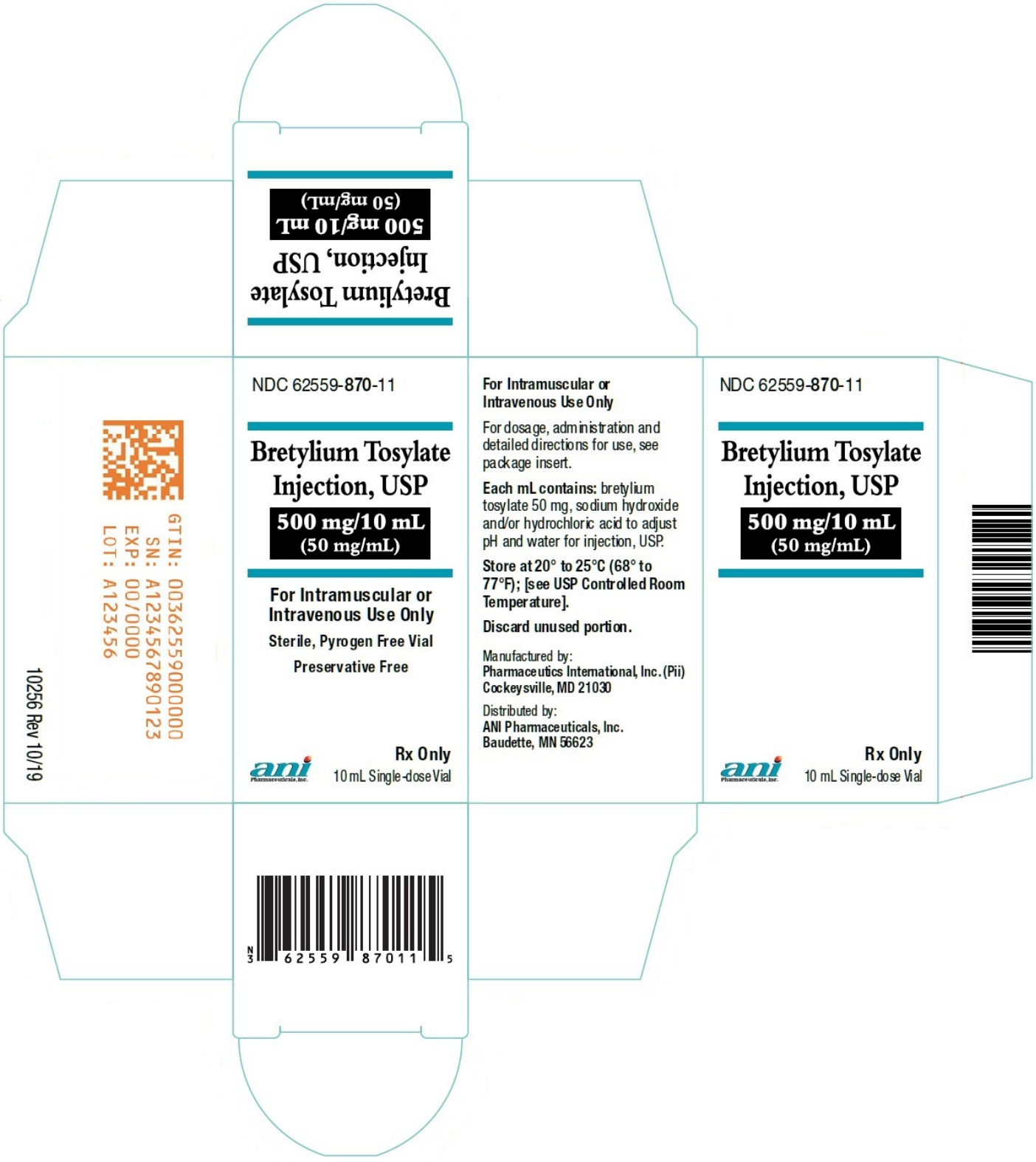
Manufactured by:
Pharmaceutics International, Inc. (Pii)
Cockeysville, MD 21030

Distributed by:
ANI Pharmaceuticals, Inc.
Baudette, MN 56623

10257 Rev 10/19

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

NDC 62559-870-11
Bretylium Tosylate Injection, USP
500 mg/10 mL
(50 mg/mL)
For Intramuscular or Intravenous Use Only
Sterile, Pyrogen Free Vial
Preservative Free
Rx Only
10 mL Single-dose Vial



BRETYLIUM TOSYLATE

bretylium tosylate injection

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:62559-870
Route of Administration	INTRAMUSCULAR, INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
BRETYLIUM TOSYLATE (UNII: 78ZP3YR353) (BRETYLIUM - UNII:RZR75EQ2KJ)	BRETYLIUM	50 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:62559-870-11	10 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product	12/11/2019	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204386	12/11/2019	

Labeler - ANI Pharmaceuticals, Inc. (145588013)

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