Diltiazem Hydrochloride Injection is a calcium ion (Ca2+) ion exchange resin. It is an ion-exchange resin that is used to exchange calcium ions for sodium ions during membrane depolarization of cardiac and vascular smooth muscle. The therapeutic effects of diltiazem in supraventricular arrhythmias are related to its ability to slow AV nodal conduction time and prolong AV nodal refractoriness.

Mechanisms of Action
Diltiazem inhibits the influx of calcium (Ca2+) ions through membrane depolarization of cardiac and vascular smooth muscle. The therapeutic effects of diltiazem in supraventricular arrhythmias are related to its ability to slow AV nodal conduction time and prolong AV nodal refractoriness. Diltiazem exhibits frequency dependent effects as AV nodal conduction such that it may selectively reduce the heart rate during tachycardias involving the AV node with little or no effect on normal AV nodal conduction at normal heart rates.

In patients with atrial fibrillation or atrial flutter, the prolongation of the ventricular rate in patients with a rapid ventricular response during atrial fibrillation or atrial flutter. Diltiazem converts paroxysmal supraventricular tachycardia (PST) to normal sinus rhythm by interrupting the reentry circuit in AV nodal reentrant tachycardia and reciprocating tachycardia, e.g., Wolff-Parkinson-White syndrome (WPW).

Diltiazem prolongs the sinus cycle. It has no effect on the sinus node recovery time or the slow conducted atrial response time in patients without AV nodal dysfunction. There has been no significant pharmacodynamic effect on tissues in the heart that fast and slow sodium channel dependent, e.g., His-Purkinje tissue, atrial and ventricular myocardium, and peripheral extracellular smooth muscle.

Like other calcium channel antagonists, because of its effect on vascular smooth muscle, diltiazem decreases total peripheral resistance resulting in a decrease in both systemic and diastolic blood pressure.

Hemodynamics
Patients with cardiovascular disease, diltiazem hydrochloride administered intravenously in single bolus, followed by a continuous infusion, reduced blood pressure, systemic vascular resistance, the rate-pressure product, and coronary blood flow. Patients with normal ventricular function and in patients with normal ventricular function and in patients with normal ejection fraction do not have a significant increase in heart rate when cardiac output is increased. However, sinus nodal dysfunction and sinus bradycardia was observed in patients with preexisting impaired ventricular function.

Changes in heart rate, systolic blood pressure, and diastolic blood pressure were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in normal Wistar rats and in rats with bilirubinemia were associated with hepatic necrosis.

Drug Interactions
Diltiazem prolongs the AV conduction and refractoriness that may rarely result in complete heart block. Diltiazem may affect other antiarrhythmic agents that suppress atrioventricular conduction. Adverse effects include bradycardia, AV block, and increased toxicity of buspirone may be possible during concomitant administration with diltiazem. Subsequent administration of diltiazem with propafenone in patients with normal sinus rhythm resulted in increased propafenone plasma concentrations.

The prolongation of PR interval correlated significantly with plasma diltiazem concentration in normal volunteers with the Sigmoidal E_max model. However, changes in heart rate did not correlate with plasma diltiazem concentrations in normal volunteers. Reduction in mean atrial pressure correlated linearly with diltiazem plasma concentrations over the range from 1.7 to 33 mg, systemic clearance averaged 36 L/h.

In patients with atrial fibrillation and atrial flutter, a significant correlation was observed between the percent reduction in heart rate and plasma diltiazem concentrations using the Sigmoidal E_max model. Based on this relationship, the mean plasma concentration of diltiazem at 30% reduction in heart rate was determined to be 80 mg/L. Mean plasma diltiazem concentrations of 130 mg/L and 300 mg/L, were determined to produce reductions in heart rate of 50% and 40%.

Pharmacokinetics and Metabolism
Following a single intravenous injection in healthy male volunteers, diltiazem hydrochloride appears to obey linear pharmacokinetics over a dose range of 10.5 to 21 mg. The plasma elimination half-life is approximately 3.4 hours. The apparent volume of distribution of diltiazem is approximately 0.36 to 0.54 L/kg in the liver with a systemic clearance of approximately 65 L/h.

Following intravenous constant rate infusion to healthy male volunteers, diltiazem exhibits linear pharmacokinetics over an infusion rate of 4.8 to 13.2 mg/h for 24 hours. Over this infusion range, as the dose is increased, systemic clearance decreases from 64 to 48 L/h while the plasma elimination half-life increases from 4.1 to 4.9 hours. The apparent volume of distribution remains unchanged (360 ± 391). In patients with atrial fibrillation or atrial flutter, diltiazem systemic clearance has been found to be decreased compared to healthy volunteers. In patients administered doses ranging from 0.25 to 2 mg/kg, systemic clearance averaged 66 L/h. In patients administered continuous infusions at 10 mg/h or 15 mg/h for 24 hours, diltiazem systemic clearance averaged 42 L/h and 31 L/h, respectively.

Diltiazem provides a significant, sustained effect on tissues in the heart that fast sodium channel dependent, e.g., His-Purkinje tissue, atrial and ventricular myocardium, and peripheral extracellular smooth muscle. The therapeutic benefits of diltiazem in supraventricular tachycardias are related to its ability to effect tissues in the heart that are fast sodium channel dependent, e.g., His-Purkinje tissue, atrial and ventricular myocardium, and peripheral extracellular smooth muscle. Diltiazem provides a significant, sustained effect on tissues in the heart that fast sodium channel dependent, e.g., His-Purkinje tissue, atrial and ventricular myocardium, and peripheral extracellular smooth muscle. Diltiazem can be used to control rapid ventricular rate when used in conjunction with other drugs that slow AV nodal conduction such as digoxin.

Diltiazem hydrochloride injection is for direct intravenous bolus injection and continuous infusion. Each mL contains 5 mg of diltiazem hydrochloride, 0.75 mg citric acid (hydrated), 0.65 mg sodium citrate dihydrate, 71.4 mg sorbitol solution USP, and water for injection USP. Sodium hydroxide or hydrochloric acid is used for pH adjustment.

CLINICAL PHARMACOLOGY
The use of diltiazem hydrochloride injection should be undertaken with caution when the patient is receiving other calcium channel blockers. Diltiazem enhances the depressant effect on tissues in the heart that fast sodium channel dependent, e.g., His-Purkinje tissue, atrial and ventricular myocardium, and peripheral extracellular smooth muscle. Diltiazem increases the depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation effect on tissues in the heart that fast sodium channel dependent, e.g., His-Purkinje tissue, atrial and ventricular myocardium, and peripheral extracellular smooth muscle.

- **Contraindications**: Patients who have demonstrated hypersensitivity to the drug.
- **Warnings**: Cardiovascular disease. Studies showed the increased incidence of AV nodal reentrant tachycardia and reciprocating tachycardia associated with an extranodal accessory pathway such as the WPW syndrome or PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of diltiazem hydrochloride injection.