

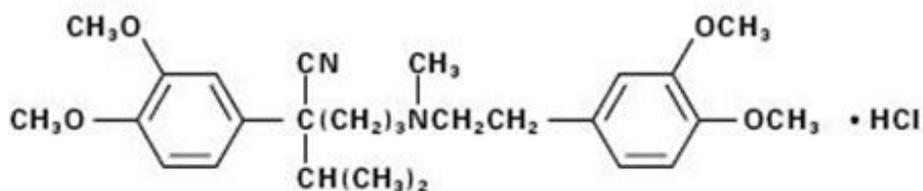
VERAPAMIL HYDROCHLORIDE- verapamil hydrochloride injection
EXELA PHARMA SCIENCES, LLC

Verapamil
Hydrochloride Injection, USP
For Intravenous Injection
Protect from light

DESCRIPTION

Verapamil hydrochloride is a calcium antagonist or slow-channel inhibitor available as a sterile solution for intravenous injection in 5-mg (2 ml) and 10-mg (4 ml) vials. Each form contains Verapamil HCl 2.5 mg/ml and sodium chloride 8.5 mg/ml in water for injection. Hydrochloric acid and/or sodium hydroxide is used for pH adjustment. The pH of the solution is between 4.1 and 6.0.

The structural formula of verapamil HCl is given below:



$C_{27}H_{38}N_2O_4 \cdot HCl$

M.W. = 491.08

Benzeneacetonitrile, α -[3-[[2-(3,4-dimethoxyphenyl)ethyl] methylamino]propyl]-3,4-dimethoxy- α -(1-methylethyl) hydrochloride

Verapamil hydrochloride is an almost white, crystalline powder, practically free of odor, with a bitter taste. It is soluble in water, chloroform, and methanol. Verapamil hydrochloride is not chemically related to other antiarrhythmic drugs.

CLINICAL PHARMACOLOGY

Mechanism of action: Verapamil inhibits the calcium ion (and possibly sodium ion) influx through slow channels into conductile and contractile myocardial cells and vascular smooth muscle cells. The antiarrhythmic effect of Verapamil appears to be due to its effect on the slow channel in cells of the cardiac conductile system.

Electrical activity through the SA and AV nodes depends, to a significant degree, upon calcium influx through the slow channel. By inhibiting this influx, Verapamil slows AV conduction and prolongs the effective refractory period within the AV node in a rate-related manner. This effect results in a reduction of the ventricular rate in patients with atrial flutter and/or atrial fibrillation and a rapid ventricular response. By interrupting reentry at the AV node, Verapamil can restore normal sinus rhythm in patients with

paroxysmal supraventricular tachycardias (PSVT), including Wolff-Parkinson-White (WPW) syndrome. Verapamil has no effect on conduction across accessory bypass tracts. Verapamil does not alter the normal atrial action potential or intraventricular conduction time but depresses amplitude, velocity of depolarization, and conduction in depressed atrial fibers.

In the isolated rabbit heart, concentrations of Verapamil that markedly affect SA nodal fibers or fibers in the upper and middle regions of the AV node have very little effect on fibers in the lower AV node (NH region) and no effect on atrial action potentials or His bundle fibers.

Verapamil does not induce peripheral arterial spasm.

Verapamil has a local anesthetic action that is 1.6 times that of procaine on an equimolar basis. It is not known whether this action is important at the doses used in man.

Verapamil does not alter total serum calcium levels.

Hemodynamics: Verapamil reduces afterload and myocardial contractility. In most patients, including those with organic cardiac disease, the negative inotropic action of Verapamil is countered by reduction of afterload, and cardiac index is usually not reduced, but in patients with moderately severe to severe cardiac dysfunction (pulmonary wedge pressure above 20 mm Hg, ejection fraction less than 30%), acute worsening of heart failure may be seen. Peak therapeutic effects occur within 3 to 5 minutes after a bolus injection. The commonly used intravenous doses of 5-10 mg Verapamil produce transient, usually asymptomatic, reduction in normal systemic arterial pressure, systemic vascular resistance and contractility; left ventricular filling pressure is slightly increased.

Pharmacokinetics: Intravenously administered Verapamil has been shown to be rapidly metabolized. Following intravenous infusion in man, verapamil is eliminated bi-exponentially, with a rapid early distribution phase (half-life about 4 minutes) and a slower terminal elimination phase (half-life 2-5 hours). In healthy men, orally administered Verapamil undergoes extensive metabolism in the liver, with 12 metabolites having been identified, most in only trace amounts. The major metabolites have been identified as various N- and O-dealkylated products of Verapamil. Approximately 70% of an administered dose is excreted in the urine and 16% or more in the feces within 5 days. About 3% to 4% is excreted as unchanged drug.

INDICATIONS AND USAGE

Verapamil is indicated for the treatment of supraventricular tachyarrhythmias, including:

- Rapid conversion to sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory bypass tracts (Wolff-Parkinson-White [WPW] and Lown-Ganong-Levine [LGL] syndromes). When clinically advisable, appropriate vagal maneuvers (e.g., Valsalva maneuver) should be attempted prior to Verapamil administration.
- Temporary control of rapid ventricular rate in atrial flutter or atrial fibrillation, **except** when the atrial flutter and/or atrial fibrillation are associated with accessory bypass tracts (Wolff-Parkinson-White [WPW] and Lown-Ganong-Levine [LGL] syndromes).

In controlled studies in the U.S., about 60% of patients with supraventricular tachycardia converted to normal sinus rhythm within 10 minutes after intravenous Verapamil hydrochloride. Uncontrolled studies reported in the world literature describe a conversion rate of about 80%. About 70% of patients with atrial flutter and/or fibrillation with a fast ventricular rate respond with a decrease in heart rate of at least 20%. Conversion of atrial flutter or fibrillation to sinus rhythm is uncommon (about 10%) after Verapamil hydrochloride and may reflect the spontaneous conversion rate, since the conversion rate after placebo was similar. The effect of a single injection lasts for 30–60 minutes when conversion to sinus rhythm does not occur.

Because a small fraction (<1.0%) of patients treated with Verapamil hydrochloride respond with life-threatening adverse responses (rapid ventricular rate in atrial flutter/fibrillation with an accessory bypass tract, marked hypotension, or extreme bradycardia/asystole— see *Contraindications* and *Warnings*), the initial use of intravenous Verapamil hydrochloride should, if possible, be in a treatment setting with monitoring and resuscitation facilities, including DC-cardioversion capability (see *Suggested Treatment of Acute Cardiovascular Adverse Reactions*). As familiarity with the patient’s response is gained, an office setting may be acceptable.

Cardioversion has been used safely and effectively after intravenous Verapamil.

CONTRAINDICATIONS

Verapamil hydrochloride injection is contraindicated in:

1. Severe hypotension or cardiogenic shock
2. Second- or third-degree AV block (except in patients with a functioning artificial ventricular pacemaker)
3. Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker)
4. Severe congestive heart failure (unless secondary to a supraventricular tachycardia amenable to Verapamil therapy)
5. Patients receiving **intravenous** beta-adrenergic blocking drugs (e.g., propranolol). **Intravenous** Verapamil and **intravenous** beta-adrenergic blocking drugs should not be administered in close proximity to each other (within a few hours), since both may have a depressant effect on myocardial contractility and AV conduction.
6. Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g., Wolff-Parkinson-White, Lown-Ganong-Levine syndromes). These patients are at risk to develop ventricular tachyarrhythmia including ventricular fibrillation if Verapamil is administered.
7. Ventricular tachycardia. Administration of intravenous Verapamil to patients with wide-complex ventricular tachycardia ($QRS \geq 0.12$ sec) can result in marked hemodynamic deterioration and ventricular fibrillation. Proper pretherapy diagnosis and differentiation from wide-complex supraventricular tachycardia is imperative in the emergency room setting.
8. Known hypersensitivity to Verapamil hydrochloride

WARNINGS

VERAPAMIL SHOULD BE GIVEN AS A SLOW INTRAVENOUS INJECTION OVER AT LEAST A TWO-MINUTE PERIOD OF TIME. (See *Dosage and Administration*.)

Hypotension: Intravenous Verapamil often produces a decrease in blood pressure below baseline levels that is usually transient and asymptomatic but may result in dizziness. Systolic pressure less than 90 mm Hg and/or diastolic pressure less than 60 mm Hg was seen in 5%-10% of patients in controlled U.S. trials in supraventricular tachycardia and in about 10% of the patients with atrial flutter/fibrillation. The incidence of symptomatic hypotension observed in studies conducted in the U.S. was approximately 1.5%. Three of the five symptomatic patients required pharmacologic treatment (norepinephrine bitartrate IV, metaraminol bitartrate IV, or 10% calcium gluconate IV). All recovered without sequelae.

Extreme bradycardia/asystole: Verapamil affects the AV and SA nodes and rarely may produce second- or third-degree AV block, bradycardia, and, in extreme cases, asystole. This is more likely to occur in patients with a sick sinus syndrome (SA nodal disease), which is more common in older patients. Bradycardia associated with sick sinus syndrome was reported in 0.3% of the patients treated in controlled double-blind trials in the U.S. The total incidence of bradycardia (ventricular rate less than 60 beats/min) was 1.2% in these studies. Asystole in patients other than those with sick sinus syndrome is usually of short duration (few seconds or less), with spontaneous return to AV nodal or normal sinus rhythm. If this does not occur promptly, appropriate treatment should be initiated immediately. (See *Adverse Reactions* including suggested treatment of adverse reactions.)

Heart failure: When heart failure is not severe or rate related, it should be controlled with digitalis glycosides and diuretics, as appropriate, before Verapamil is used.

In patients with moderately severe to severe cardiac dysfunction (pulmonary wedge pressure above 20 mm Hg, ejection fraction less than 30%), acute worsening of heart failure may be seen.

Concomitant antiarrhythmic therapy:

Digitalis: Intravenous Verapamil has been used concomitantly with digitalis preparations without the occurrence of serious adverse effects. However, since both drugs slow AV conduction, patients should be monitored for AV block or excessive bradycardia.

Procainamide: Intravenous Verapamil has been administered to a small number of patients receiving oral procainamide without the occurrence of serious adverse effects.

Quinidine: Intravenous Verapamil has been administered to a small number of patients receiving oral quinidine without the occurrence of serious adverse effects. However a few cases of hypotension have been reported in patients taking oral quinidine who received intravenous Verapamil. Caution should therefore be used when employing this combination of drugs.

Beta-adrenergic blocking drugs: Intravenous Verapamil has been administered to patients receiving oral beta blockers without the development of serious adverse effects. However, since both drugs may depress myocardial contractility or AV conduction, the possibility of detrimental interactions should be considered. The concomitant administration of intravenous beta blockers and intravenous Verapamil has resulted in serious adverse reactions (see *Contraindications*), especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Disopyramide: Until data on possible interactions between Verapamil and disopyramide are obtained, disopyramide should not be administered within 48 hours before or 24 hours after Verapamil administration.

Heart block: Verapamil prolongs AV conduction time. While high-degree AV block has not been observed in controlled clinical trials in the U.S., a low percentage (less than 0.5%) has been reported in the world literature. Development of second- or third-degree AV block or unifascicular, bifascicular, or trifascicular bundle branch block requires reduction in subsequent doses or discontinuation of Verapamil and institution of appropriate therapy, if needed. (See Adverse Reactions and Concomitant antiarrhythmic therapy.)

Hepatic and renal failure: Significant hepatic and renal failure should not increase the effects of a single intravenous dose of Verapamil but may prolong its duration. Repeated injections of intravenous Verapamil in such patients may lead to accumulation and an excessive pharmacologic effect of the drug. There is no experience to guide use of multiple doses in such patients, and this generally should be avoided. If repeated injections are essential, blood pressure and PR interval should be closely monitored and smaller repeat doses should be utilized. Data on the clearance of Verapamil by dialysis are not yet available.

Premature ventricular contractions: During conversion to normal sinus rhythm or marked reduction in ventricular rate, a few benign complexes of unusual appearance (sometimes resembling premature ventricular contractions) may be seen after treatment with Verapamil. Similar complexes are seen during spontaneous conversion of supraventricular tachycardia and after DC-cardioversion or other pharmacologic therapy. These complexes appear to have no clinical significance.

Duchenne's muscular dystrophy: Intravenous Verapamil can precipitate respiratory muscle failure in these patients and should, therefore, be used with caution.

Increased intracranial pressure: Intravenous Verapamil has been seen to increase intracranial pressure in patients with supratentorial tumors at the time of anesthesia induction. Caution should be taken and appropriate monitoring performed.

PRECAUTIONS

Drug interactions: (See *Warnings: Concomitant antiarrhythmic therapy.*) Intravenous Verapamil has been used concomitantly with other cardioactive drugs (e.g., digitalis) without evidence of serious negative drug interactions. In rare instances, including when patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction were given **intravenous** beta-adrenergic blocking agents or disopyramide concomitantly with intravenous Verapamil, serious adverse effects have occurred. Concomitant use of Verapamil with agents that decrease adrenergic function may result in an exaggerated hypotensive response. Animal studies suggest concomitant use of intravenous Verapamil and intravenous dantrolene sodium may result in cardiovascular collapse. The clinical relevance of these findings is unknown.

Cimetidine has no effect on intravenous Verapamil kinetics. As Verapamil is highly bound to plasma proteins, it should be administered with caution to patients receiving other highly protein-bound drugs.

Animal experiments have shown that inhalation anesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anesthetics and calcium antagonists, such as Verapamil, should each be titrated carefully to avoid excessive cardiovascular depression.

Clinical data and animal studies suggest that Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of Verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

Telithromycin: Hypotension and bradyarrhythmias have been observed in patients receiving concurrent telithromycin, an antibiotic in the ketolide class.

Clonidine: Sinus bradycardia resulting in hospitalization and pacemaker insertion has been reported in association with the use of clonidine concurrently with Verapamil. Monitor heart rate in patients receiving concomitant Verapamil and clonidine.

HMG-CoA reductase inhibitors: The use of HMG-CoA reductase inhibitors that are CYP3A4 substrates in combination with Verapamil has been associated with reports of myopathy/rhabdomyolysis.

Co-administration of multiple doses of 10 mg of Verapamil with 80 mg simvastatin resulted in exposure to simvastatin 2.5-fold that following simvastatin alone. Limit the dose of simvastatin in patients on Verapamil to 10 mg daily. Limit the daily dose of lovastatin to 40 mg. Lower starting and maintenance doses of other CYP3A4 substrates (e.g., atorvastatin) may be required as Verapamil may increase the plasma concentration of these drugs.

Ivabradine: Concurrent use of verapamil increases exposure to Ivabradine and may exacerbate bradycardia and conduction disturbances. Avoid concomitant use of Ivabradine and verapamil.

Pregnancy: Pregnancy Category C. Reproduction studies have been performed in rabbits and rats at oral Verapamil doses up to 1.5 (15 mg/kg/day) and 6 (60 mg/kg/day) times the human oral daily dose, respectively, and have revealed no evidence of teratogenicity. In the rat, however, this multiple of the human dose was embryocidal and retarded fetal growth and development, probably because of adverse maternal effects reflected in reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and delivery: There have been few controlled studies to determine whether the use of Verapamil during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetric intervention. Such adverse experiences have not been reported in the literature, despite a long history of use of intravenous Verapamil in Europe in the treatment of cardiac side effects of beta-adrenergic agonist agents used to treat premature labor.

Nursing mothers: Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery. Also, verapamil is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Verapamil, nursing should be discontinued while Verapamil is administered.

Pediatric use: Controlled studies with Verapamil have not been conducted in pediatric patients, but uncontrolled experience with intravenous administration in more than 250 patients, about half under 12 months of age and about 25% newborn, indicates that results of treatment are similar to those in adults. However, in rare instances, severe hemodynamic side effects have occurred following the intravenous administration of verapamil in neonates and infants. Caution should therefore be used when administering Verapamil to this group of pediatric patients. The most commonly used single doses in patients up to 12 months of age have ranged from 0.1 to 0.2 mg/kg of body weight, while in patients aged 1 to 15 years, the most commonly used single doses ranged from 0.1 to 0.3 mg/kg of body weight. Most of the patients received the lower dose of 0.1 mg/kg once, but in some cases, the dose was repeated once or twice every 10 to 30 minutes.

ADVERSE REACTIONS

The following reactions were reported with intravenous Verapamil use in controlled U.S. clinical trials involving 324 patients:

Cardiovascular: Symptomatic hypotension (1.5%); bradycardia (1.2%); severe tachycardia (1.0%). The worldwide experience in open clinical trials in more than 7,900 patients was similar.

Central nervous system effects: Dizziness (1.2%); headache (1.2%). Although rare, cases of seizures during verapamil injection has been reported.

Gastrointestinal: Nausea (0.9%); abdominal discomfort (0.6%).

In rare cases of hypersensitivity, broncho/laryngeal spasm accompanied by itch and urticaria has been reported.

The following reactions were reported in a few patients: emotional depression, rotary nystagmus, sleepiness, vertigo, muscle fatigue, or diaphoresis.

Suggested Treatment of Acute Cardiovascular Adverse Reactions*

The frequency of these adverse reactions was quite low, and experience with their treatment has been limited.

Adverse Reaction	Proven Effective Treatment	Supportive Treatment
1. Symptomatic hypotension requiring treatment	Dopamine HCl IV Calcium chloride IV Norepinephrine bitartrate IV Metaraminol bitartrate IV Isoproterenol HCl IV	Intravenous fluids Trendelenburg position
2. Bradycardia, AV block, Asystole	Isoproterenol HCl IV Calcium chloride IV Norepinephrine bitartrate IV Atropine sulfate IV Cardiac pacing	Intravenous fluids (slow drip)
3. Rapid ventricular rate (due to antegrade con-	DC-cardioversion (high energy may be required)	Intravenous fluids (slow drip)

duction in
flutter/fibrilla-
tion with
WPW or LGL
syndromes)

Procainamide IV
Lidocaine HCl IV

*Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

OVERDOSAGE

Treatment of overdose should be supportive and individualized. Beta-adrenergic stimulation and/or parenteral administration of calcium solutions (calcium chloride) have been effectively used in treatment of deliberate overdose with oral Verapamil. Clinically significant hypotensive reactions or high-degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Asystole should be handled by the usual measures including isoproterenol hydrochloride, other vasopressor agents, or cardiopulmonary resuscitation (see *Suggested Treatment of Acute Cardiovascular Adverse Reactions*).

DOSAGE AND ADMINISTRATION

For intravenous use only. VERAPAMIL SHOULD BE GIVEN AS A SLOW INTRAVENOUS INJECTION OVER AT LEAST A TWO-MINUTE PERIOD OF TIME UNDER CONTINUOUS ECG AND BLOOD PRESSURE MONITORING. The recommended intravenous doses of Verapamil are as follows:

Adult:

Initial dose—5-10 mg (0.075-0.15 mg/kg body weight) given as an intravenous bolus. *Repeat dose*—10 mg (0.15 mg/kg body weight) 30 minutes after the first dose if the initial response is not adequate.

Older patients—The dose should be administered over at least 3 minutes to minimize the risk of untoward drug effects.

Pediatric:

Initial dose

0-1 year: 0.1-0.2 mg/kg body weight (usual single dose range: 0.75-2 mg) should be administered as an intravenous bolus.

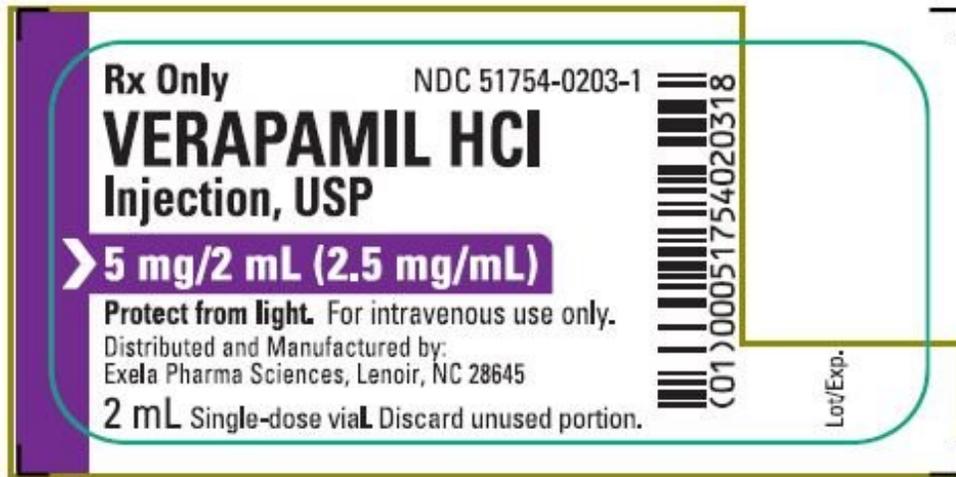
1-15 years: 0.1-0.3 mg/kg body weight (usual single dose range: 2-5 mg) should be administered as an intravenous bolus. *Do not exceed 5 mg.*

Repeat dose

0-1 year: 0.1-0.2 mg/kg body weight (usual single dose range: 0.75-2 mg) 30 minutes after the first dose if the initial response is not adequate.

Exela Pharma Sciences, Lenoir, NC 28645

2 mL Single-dose vial. Discard unused portion.



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL-2 mL Carton

Rx Only NDC 51754-0203-2

VERAPAMIL HCl Injection, USP

5 mg/2 mL (2.5 mg/mL)

Protect from Light. For intravenous use only.

Five-2 mL Single-dose vial. Discard unused portion.



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL- 2 mL Carton of 25

Rx Only

NDC 51754-0203-4

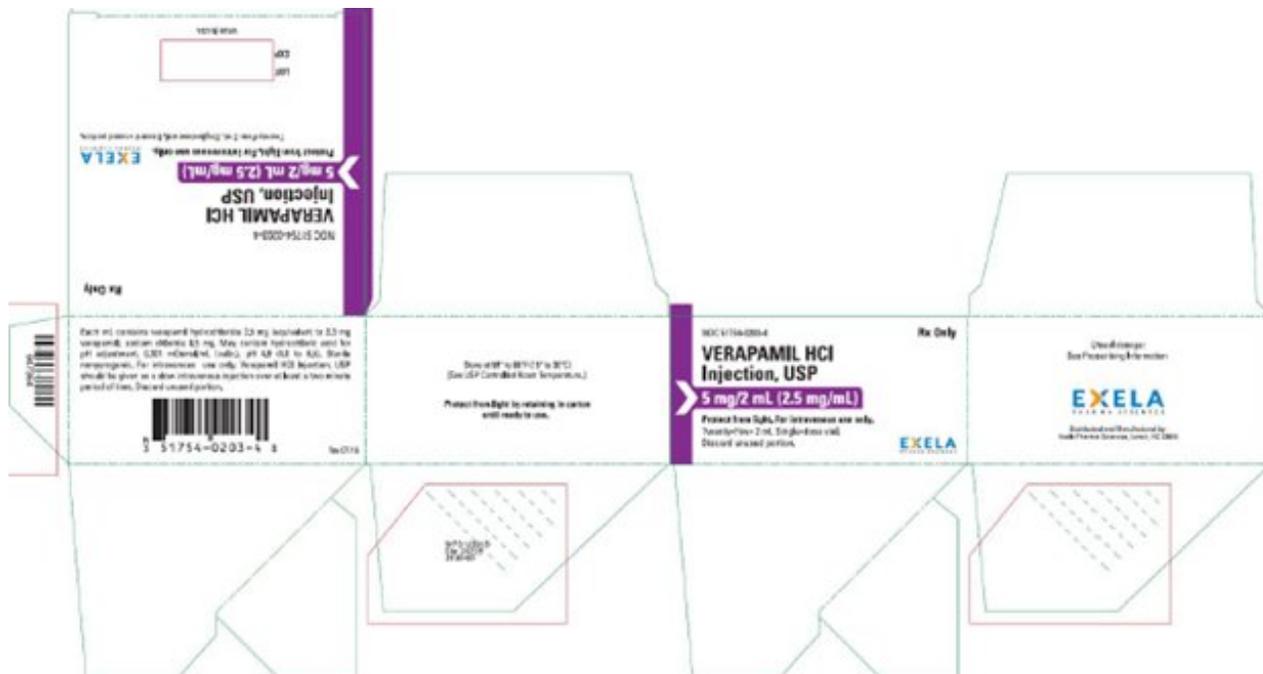
VERAPAMIL HCl Injection, USP

5 mg/2 mL (2.5 mg/mL)

Protect from Light. For intravenous use only.

Twenty-Five-2 mL Single-dose vial.

Discard unused portion.



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL-4 mL Vial Label

Rx Only

NDC 51754-0205-1

VERAPAMIL HCl Injection, USP

10 mg/4 mL (2.5 mg/mL)

Protect from Light. For intravenous use only.

4 mL Single-dose vial. Discard unused portion.



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL-4 mL Carton

Rx Only NDC 51754-0205-2

VERAPAMIL HCl Injection, USP

10 mg/4 mL (2.5 mg/mL)

Protect from Light. For intravenous use only.

Five-4 mL Single-dose vials.

Discard unused portion.



VERAPAMIL HYDROCHLORIDE			
verapamil hydrochloride injection			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:51754-0203
Route of Administration	INTRAVENOUS		
Active Ingredient/Active Moiety			
Ingredient Name		Basis of Strength	Strength
VERAPAMIL HYDROCHLORIDE (UNII: V3888OEY5R) (VERAPAMIL - UNII:CJ0037KU29)		VERAPAMIL HYDROCHLORIDE	2.5 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	8.5 mg in 1 mL
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51754-0203-2	5 in 1 CARTON	04/22/2016	
1		2 mL in 1 VIAL; Type 0: Not a Combination Product		
2	NDC:51754-0203-4	25 in 1 CARTON	12/09/2016	
2		2 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA018925	04/22/2016	

VERAPAMIL HYDROCHLORIDE

verapamil hydrochloride injection

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:51754-0205
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
VERAPAMIL HYDROCHLORIDE (UNII: V3888OEY5R) (VERAPAMIL - UNII:CJ0037KU29)	VERAPAMIL HYDROCHLORIDE	2.5 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	8.5 mg in 1 mL
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51754-0205-2	5 in 1 CARTON	06/11/2018	
1		4 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA018925	06/11/2018	

Labeler - EXELA PHARMA SCIENCES, LLC (831274399)

Registrant - EXELA PHARMA SCIENCES, LLC (831274399)

Establishment

Name	Address	ID/FEI	Business Operations
EXELA PHARMA SCIENCES, LLC		831274399	MANUFACTURE(51754-0203, 51754-0205)

Revised: 2/2017

EXELA PHARMA SCIENCES, LLC