ISOPROTERENOL HYDROCHLORIDE - isoproterenol hydrochloride injection, solution
Gland Pharma Limited

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ISOPROTERENOL HYDROCHLORIDE INJECTION safely and effectively. See full prescribing information for ISOPROTERENOL HYDROCHLORIDE INJECTION.
ISOPROTERENOL HYDROCHLORIDE injection, for Intravenous use
Initial U.S. Approval: 1956

INDICATIONS AND USAGE

Isoproterenol hydrochloride injection is a beta-adrenergic agonist indicated:
• To improve hemodynamic status in patients in distributive shock and shock due to reduced cardiac output (1)
• For treatment of bronchospasm occurring during anesthesia (1)

DOSAGE AND ADMINISTRATION

• Initiate isoproterenol hydrochloride injection at the lowest recommended dose and increase gradually based on patient response (2.2)
Recommended initial dosage:
• Shock: 0.5 mcg to 5 mcg per minute as an intravenous infusion (2.2)
• Bronchospasm: 10 mcg to 20 mcg intravenous injection (2 2)

DOSAGE FORMS AND STRENGTHS

Injection: 0.2 mg/mL and 1 mg/5 mL (0.2 mg/mL) Single-Dose Vial (3)

CONTRAINDICATIONS

Isoproterenol hydrochloride injection is contraindicated in patients with:
• Tachycardia (4)
• Ventricular arrhythmias (4)
• Angina pectoris (4)

WARNINGS AND PRECAUTIONS

• Cardiac arrhythmias and ischemia may be induced by isoproterenol hydrochloride injection (5.1)
• Sulfite: Isoproterenol hydrochloride injection contains metabisulfite, which may cause allergic reaction (5.2)

ADVERSE REACTIONS

Common adverse reactions with isoproterenol include tachycardia and palpitations (6)
To report SUSPECTED ADVERSE REACTIONS, contact Gland Pharma at (609)-250-7990 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

• Do not administer isoproterenol hydrochloride injection and epinephrine simultaneously due to combined effects may induce serious arrhythmias (7)
• Concomitant use of tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium and certain antihistamines; hemodynamic parameters may potentiate a clinical response of isoproterenol (7)
• Beta-adrenergic blocking drugs may reduce cardiostimulating and bronchodilating effects of isoproterenol (7)

Revised: 7/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Isoproterenol hydrochloride injection is indicated:
• To improve hemodynamic status in patients in distributive shock and shock due to reduced cardiac output
• For bronchospasm occurring during anesthesia

2 DOSAGE AND ADMINISTRATION

2.1. General Considerations

Inspect visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the injection is pinkish or darker than slightly

yellow or contains a precipitate. Discard any unused portion.

Diluted solution should be used immediately. Unused material should be discarded.

2.2. Recommended Dosage

Dosage should generally be started at the lowest recommended dose and increased gradually based on patient response.

Recommended dosage for adults with shock and hypoperfusion states:

Route of Administration	Preparation of Dilution*	Infusion Rate**
Intravenous infusion	Dilute 5 mL (1 mg) in 500 mL of 5% Dextrose Injection, USP	0.5 mcg to 5 mcg per minute (0.25 mL to 2.5 mL of diluted solution)
* Concentrations up to 10 times greater have been used when limitation of volume is essential.		
** Rates over 30 mcg per minute have been used in advanced stages of shock. Adjust the rate of infusion based on heart rate, central venous pressure, systemic blood pressure, and urine flow. If the heart rate exceeds 110 beats per minute, consider decreasing or temporarily discontinuing the infusion.		

Recommended dosage for adults with bronchospasm occurring during anesthesia:

Route of Administration	Preparation of Dilution	Initial Dose	Subsequent Dose
Bolus Intravenouos injection	Dilute 1 mL (0.2 mg) to 10 mL with Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP	10 mcg to 20 mcg (0.5 mL to 1 mL of diluted solution)	The initial dose may be repeated when necessary

There are no well-controlled studies in children to establish appropriate dosing; however, the American Heart Association recommends an initial infusion rate of 0.1 mcg/kg/min, with the usual range being 0.1 mcg/kg/min to 1 mcg/kg/min.

3 DOSAGE FORMS AND STRENGTHS

Injection solution: single dose, clear glass ampules containing isoproterenol in a clear, colorless to slightly yellow color solution;
- 1 mL containing 0.2 mg/1 mL (0.2 mg/mL)
- 5 mL containing 1 mg/5 mL (0.2 mg/mL)

4 CONTRAINDICATIONS

Isoproterenol hydrochloride injection is contraindicated in patients with:
• tachycardia
• ventricular arrhythmias
• angina pectoris

5 WARNINGS AND PRECAUTIONS

5.1. Cardiac Arrhythmias and Ischemia

Isoproterenol may induce cardiac arrhythmias and myocardial ischemia in patients, especially patients with coronary artery disease, or cardiomyopathy.

5.2 Allergic Reactions associated with Sulfite

Isoproterenol hydrochloride injection contains sodium metabisulfite, which may cause mild to severe allergic reactions including anaphylaxis or asthmatic episodes, particularly in patients with a history of allergies. However, the presence of metabisulfite in this product should not preclude its use for treatment in emergency situations, even if the patient is sulfite-sensitive, as the alternatives to using isoproterenol in a life threatening situation may not be satisfactory.

6 ADVERSE REACTIONS

The following adverse reactions have been associated with use of isoproterenol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Nervous system disorders: Nervousness, headache, dizziness, visual blurring
Cardiovascular: Tachycardia, tachyarrhythmias, palpitations, angina, ventricular arrhythmias, Adams-Stokes attacks, pulmonary edema
Respiratory: Dyspnea
Other: Flushing of the skin, sweating, mild tremors, pallor, nausea

7 DRUG INTERACTIONS

Table 1. Clinically Relevant Interactions with Isoproterenol

Epinephrine	
Clinical impact	Both drugs are direct cardiac stimulants, and their combined effects may induce serious arrhythmias upon simultaneous administration.
Intervention	Isoproterenol hydrochloride injection and epinephrine should not be administered simultaneously.

Drugs that may potentiate clinical response of Isoproterenol	
Clinical Impact	The effects of isoproterenol may be potentiated by tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines, notably chlorpheniramine, tripelennamine, and diphenhydramine.
Intervention	Monitor hemodynamic parameters in patients who concurrently are taking tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium and certain antihistamines. Adjust doses appropriately.
Drugs that may reduce clinical response of Isoproterenol	
Clinical Impact	The cardiostimulating and bronchodilating effects of isoproterenol are antagonized by beta-adrenergic blocking drugs, such as propranolol.
Intervention	Monitor for hemodynamic response and relief of bronchospasm and adjust dose appropriately.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged experience with isoproterenol use in pregnant women over several decades, based on published literature, do not identify a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. However, there are risks to the mother and fetus associated with isoproterenol use during labor or delivery (*see Clinical Considerations*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Hypotension associated with shock is a medical emergency in pregnancy which can be fatal if left untreated. Delaying treatment in pregnant women with hypotension associated with shock may increase the risk of maternal and fetal morbidity and mortality. Life-sustaining therapy for the pregnant woman should not be withheld due to potential concerns regarding the effects of isoproterenol on the fetus.

Labor and Delivery

Isoproterenol usually inhibits spontaneous or oxytocin induced contractions of the pregnant human uterus and may delay the second stage of labor. Avoid isoproterenol during the second stage of labor. Avoid isoproterenol in obstetrics when maternal blood pressure exceeds 130/80 mmHg.

Although isoproterenol may improve maternal hypotension associated with shock, it may result in uterine vasoconstriction, decreased uterine blood flow, uterine atony with hemorrhage, and fetal anoxia.

8.2. Lactation

Risk Summary

There is no information regarding the presence of isoproterenol in milk or the effects of isoproterenol on the breastfed infant or on milk production. However, due to its short half-life, isoproterenol exposure is expected to be very low in the breastfed infant.

8.4 Pediatric Use

Safety and efficacy of isoproterenol in pediatric patients have not been established.

Intravenous infusions of isoproterenol in refractory asthmatic children at rates of 0.05-2.7 µg/kg/min have caused clinical deterioration, myocardial necrosis, congestive heart failure and death. The risks of cardiac toxicity appear to be increased by some factors [acidosis, hypoxemia, coadministration of corticosteroids, coadministration of methylxanthines (theophylline, theobromine) or aminophylline] that are especially likely to be present in these patients. If I.V. isoproterenol is used in children with refractory asthma, patient monitoring must include continuous assessment of vital signs, frequent electrocardiography, and daily measurements of cardiac enzymes, including CPK-MB.

8.5 Geriatric Use

Clinical studies of isoproterenol hydrochloride injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects in clinical circumstances. There are, however, some data that suggest that elderly healthy or hypertensive patients are less responsive to beta-adrenergic stimulation than are younger subjects. In general, dose selection for elderly patients 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 diseases or other drug therapy.

10 OVERDOSAGE

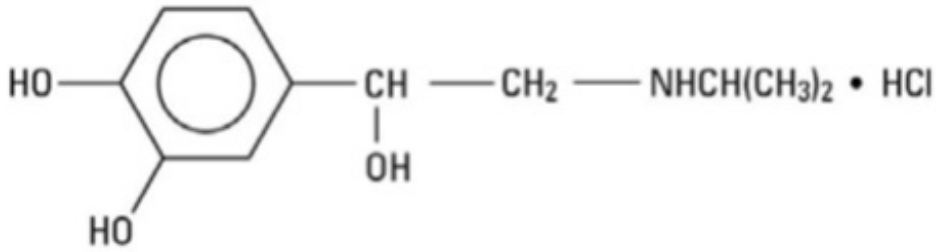
Overdosage of isoproterenol can cause tachycardia or other arrhythmias, palpitations, angina, hypotension, or hypertension. In case of overdosage, reduce the rate of administration or discontinue isoproterenol hydrochloride injection until patient’s condition stabilizes. Monitor blood pressure, pulse, respiration, and EKG.

It is not known whether isoproterenol hydrochloride is dialyzable.

11 DESCRIPTION

Isoproterenol hydrochloride is 3,4-Dihydroxy-α-[(isopropylamino)methyl] benzyl alcohol hydrochloride, a synthetic sympathomimetic amine that is structurally related to epinephrine but acts almost exclusively on beta receptors. The molecular formula is

$C_{11}H_{17}NO_3$ • HCl. It has a molecular weight of 247.72 and the following structural formula:



Isoproterenol hydrochloride is a racemic compound.

Each milliliter of the sterile solution contains:

Isoproterenol hydrochloride	0.2 mg
Edetate Disodium Dihydrate (EDTA)	0.22 mg
Sodium Citrate, Dihydrate	2.07 mg
Citric Acid, Anhydrous	2.5 mg
Sodium Chloride	7 mg
Water for Injection	qs to 1 mL

The pH is adjusted between 3.5 and 4.5 with hydrochloric acid or sodium hydroxide.

The sterile solution is nonpyrogenic and can be administered by the intravenous route.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Isoproterenol is a potent nonselective beta-adrenergic agonist with very low affinity for alpha-adrenergic receptors.

12.2 Pharmacodynamics

Intravenous infusion of isoproterenol in man lowers peripheral vascular resistance, primarily in skeletal muscle but also in renal and mesenteric vascular beds. Diastolic

pressure falls. Renal blood flow is decreased in normotensive subjects but is increased markedly in shock. Systolic blood pressure may remain unchanged or rise, although mean arterial pressure typically falls. Cardiac output is increased because of the positive inotropic and chronotropic effects of the drug in the face of diminished peripheral vascular resistance.

Isoproterenol relaxes almost all varieties of smooth muscle when the tone is high, but this action is most pronounced on bronchial and gastrointestinal smooth muscle. It prevents or relieves bronchoconstriction, but tolerance to this effect develops with overuse of the drug.

In man, isoproterenol causes less hyperglycemia than does epinephrine. Isoproterenol and epinephrine are equally effective in stimulating the release of free fatty acids and energy production.

12.3 Pharmacokinetics

Absorption
Isoproterenol is readily absorbed when given parenterally or as an aerosol.

Elimination

Isoproterenol is metabolized primarily in the liver and other tissues by COMT. Isoproterenol is a relatively poor substrate for MAO and is not taken up by sympathetic neurons to the same extent as are epinephrine and norepinephrine. The duration of action of isoproterenol may therefore be longer than that of epinephrine but is still brief.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of isoproterenol hydrochloride have not been done. Mutagenic potential and effect on fertility have not been determined. There is no evidence from human experience that isoproterenol hydrochloride injection may be carcinogenic or mutagenic or that it impairs fertility.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC Number	Container	Concentration	Fill	Quantity
68083-585-25	Single-Dose Vial	0.2 mg/mL	1 mL	Pack of 25
68083-586-10	Single-Dose Vial	1 mg/5 mL (0.2 mg/mL)	5 mL	Pack of 10

Protect from light. Keep in opaque container until used.

Store at 20º to 25ºC (68º to 77ºF). [See USP Controlled Room Temperature.]

Do not use if the injection is pinkish or darker than slightly yellow or contains a precipitate.

Discard unused portion.

Manufactured by:
Gland Pharma Limited
Hyderabad -502307, INDIA

Revised: 07/2024

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

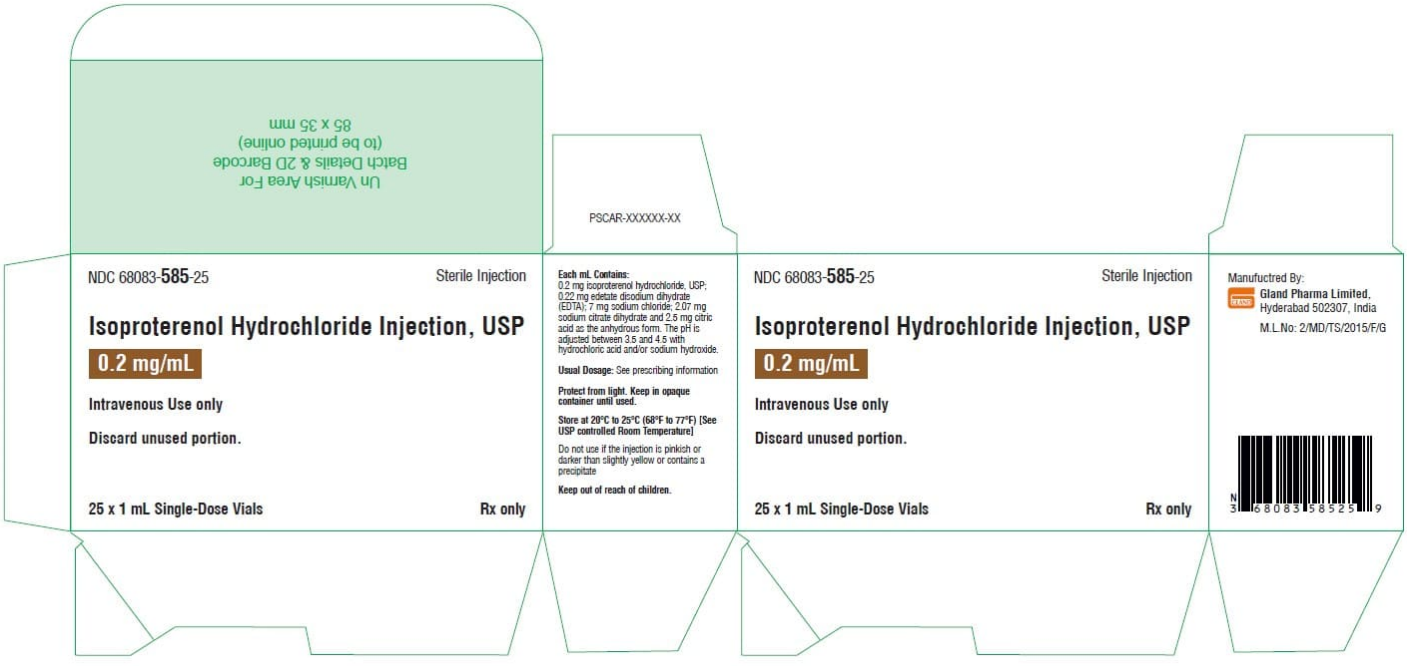
Carton Label 0.2 mg/mL:

NDC 68083-**585-**25 Sterile Injection

Isoproterenol Hydrochloride Injection, USP
0.2 mg/mL

Intravenous Use Only

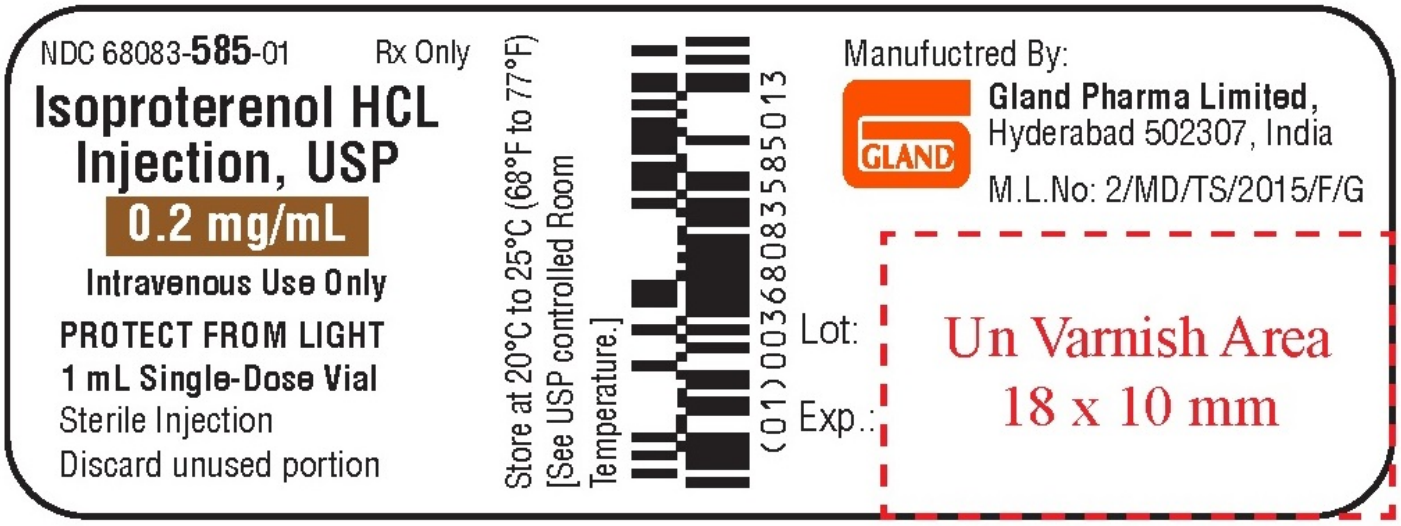
Discard unused portion.
25 x 1 mL Single-Dose Vials **Rx only**



Vial Label 0.2 mg/mL:

NDC 68083-**585**-01 Rx Only
Isoproterenol HCL Injection, USP
0.2 mg/mL
Intravenous Use Only
PROTECT FROM LIGHT
1 mL Single-Dose Vial
Sterile Injection

Discard unused portion

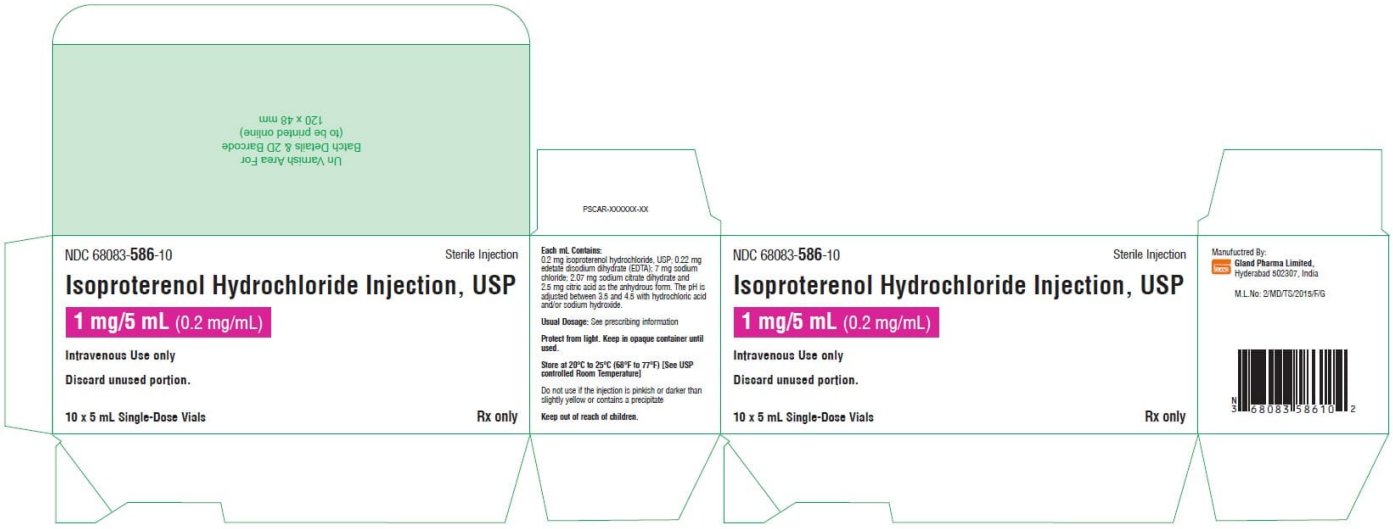


<u>Carton Label</u> 1 <u>mg/5 mL</u>:

NDC 68083-**586**-10 Sterile Injection

Isoproterenol Hydrochloride Injection, USP
1 mg/5 mL (0.2 mg/mL)
Intravenous Use Only

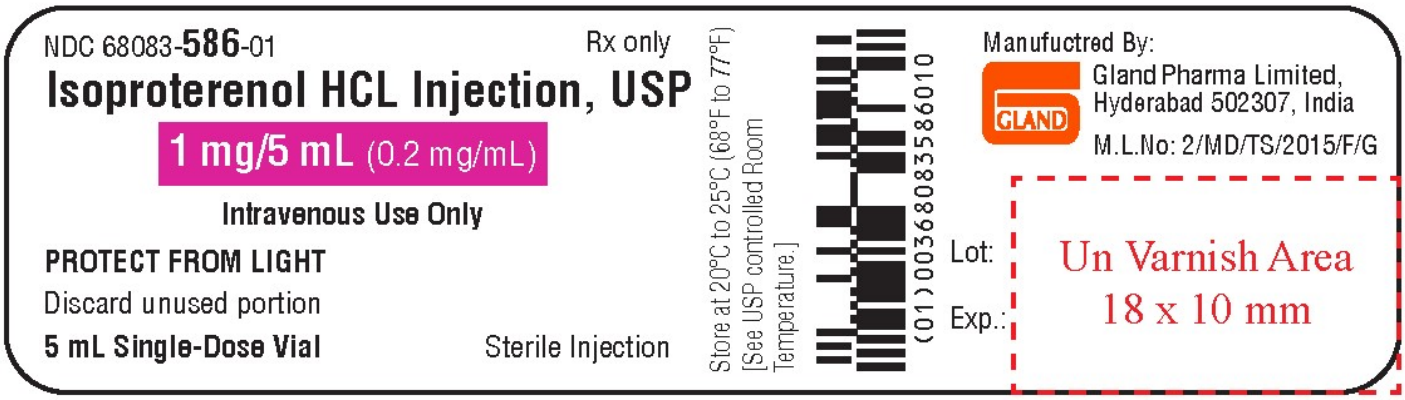
Discard unused portion.
10 X 5 mL Single-Dose Vials Rx only



Vial Label 1 mg/5 mL:

NDC 68083-**586-**01 Rx only
Isoproterenol HCL Injection, USP
1 mg/5 mL (0.2 mg/mL)
Intravenous Use Only
PROTECT FROM LIGHT

Discard unused portion
5 mL Single-Dose Vial
Sterile Injection



ISOPROTERENOL HYDROCHLORIDE

isoproterenol hydrochloride injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68083-585

Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ISOPROTERENOL HYDROCHLORIDE (UNII: DIA2A74855) (ISOPROTERENOL - UNII:L628TT009W)	ISOPROTERENOL HYDROCHLORIDE	0.2 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
EDETATE DISODIUM (UNII: 7FLD91C86K)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
TRISODIUM CITRATE DIHYDRATE (UNII: B22547B95K)	
ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)	
WATER (UNII: 059QF0KO0R)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68083-585-25	25 in 1 CARTON	10/03/2024	
1		1 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
ANDA	ANDA217648	10/03/2024	

ISOPROTERENOL HYDROCHLORIDE

isoproterenol hydrochloride injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68083-586
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ISOPROTERENOL HYDROCHLORIDE (UNII: DIA2A74855) (ISOPROTERENOL - UNII:L628TT009W)	ISOPROTERENOL HYDROCHLORIDE	1 mg in 5 mL

Inactive Ingredients

Ingredient Name	Strength
EDETATE DISODIUM (UNII: 7FLD91C86K)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
TRISODIUM CITRATE DIHYDRATE (UNII: B22547B95K)	
ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)	
WATER (UNII: 059QF0KO0R)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68083-586-10	10 in 1 CARTON	10/03/2024	
1		5 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
ANDA	ANDA217648	10/03/2024	

Labeler - Gland Pharma Limited (918601238)

Establishment

Name	Address	ID/FEI	Business Operations
GLAND PHARMA LIMITED		858971074	ANALYSIS(68083-585, 68083-586) , LABEL(68083-585, 68083-586) , MANUFACTURE(68083-585, 68083-586) , PACK(68083-585, 68083-586)

Revised: 10/2024 Gland Pharma Limited