NOREPINEPHRINE BITARTRATE- norepinephrine in sodium chloride injection, solution
Par Pharmaceutical, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NOREPINEPHRINE IN SODIUM CHLORIDE INJECTION safely and effectively. See full prescribing information for NOREPINEPHRINE IN SODIUM CHLORIDE INJECTION.

NOREPINEPHRINE IN SODIUM CHLORIDE INJECTION, for intravenous use
Initial U.S. Approval: 1950

INDICATIONS AND USAGE

Norepinephrine in Sodium Chloride Injection is a catecholamine indicated for restoration of blood pressure in adult patients with acute hypotensive states. (1)

DOSAGE AND ADMINISTRATION

- No further dilution prior to infusion is required (2.1)
- Initial intravenous infusion rate of 8 to 12 mcg per minute, adjust the rate of flow to establish and maintain a low to normal blood pressure (usually 80 to 100 mm Hg) sufficient to maintain the circulation of vital organs (2.2)
- The average maintenance dose ranges from 2 to 4 mcg per minute. (2.2)

DOSAGE FORMS AND STRENGTHS

- Injection: 250-mL single dose infusion bags with
  - 4 mg equivalent of norepinephrine (16 mcg /mL) in 0.9% sodium chloride
  - 8 mg equivalent of norepinephrine (32 mcg /mL) in 0.9% sodium chloride
  - 16 mg equivalent of norepinephrine (64 mcg /mL) in 0.9% sodium chloride

CONTRAINDICATIONS

• None. (4)

WARNINGS AND PRECAUTIONS

- Tissue Ischemia: Avoid extravasation into tissues, which can cause local necrosis (5.1)
- Hypotension After Abrupt Discontinuation: Sudden cessation of the infusion rate may result in marked hypotension. Reduce the Norepinephrine in Sodium Chloride Injection infusion rate gradually. (5.2)
- Cardiac Arrhythmias: Norepinephrine in Sodium Chloride Injection may cause arrhythmias. Monitor cardiac function in patients with underlying heart disease. (5.3)

ADVERSE REACTIONS

Most common adverse reactions are ischemic injury, bradycardia, anxiety, transient headache, respiratory difficulty, and extravasation necrosis at injection site. (6)
To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types may result in hypertension. (7.1)
- Cyclopropane and halothane anesthetics increase cardiac autonomic irritability. (7.4)

USE IN SPECIFIC POPULATIONS

- Elderly patients may be at greater risk of developing adverse reactions. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Norepinephrine in Sodium Chloride Injection is indicated to raise blood pressure in adult patients with severe, acute hypotension.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

Correct Hypovolemia

Address hypovolemia before initiation of Norepinephrine in Sodium Chloride Injection therapy. If the patient does not respond to therapy, suspect occult hypovolemia *[see Warnings and Precautions (5.1)]*.

Administration

Infuse Norepinephrine in Sodium Chloride Injection into a large vein. Avoid infusions into the veins of the leg in the elderly or in patients with occlusive vascular disease of the legs *[see Warnings and Precautions (5.1)]*. Avoid using a catheter-tie-in technique.

Inspect parenteral drug products for particulate matter and discoloration prior to use, whenever solution and container permit.

Do not open the aluminum foil pouch until time of use. The premixed, ready-to-use infusion bag has a single port for insertion of the infusion set only. Do not use this port to remove content from the bag or add another medication. Once the infusion bag has been connected to the infusion set, it is stable for 24 hours for intermittent or continuous use, as long as the bag stays connected to the infusion set.

Discontinuation

When discontinuing the infusion, reduce the flow rate gradually. Avoid abrupt withdrawal. Single dose only. Discard unused portion.

2.2 Dosage

After an initial dose of 8 to 12 mcg per minute via intravenous infusion, assess patient response and adjust dosage to maintain desired hemodynamic effect. Monitor blood pressure every two minutes or continuously until the desired hemodynamic effect is achieved, and then monitor blood pressure every five minutes for the duration of the infusion.

Recommended Average Maintenance Dosage:

Typical maintenance intravenous dosage is 2 to 4 mcg of per minute.

2.3 Drug Incompatibilities

Avoid contact with iron salts and alkalizing and oxidizing agents.

Whole blood or plasma, if indicated to increase blood volume, should be administered separately.

3 DOSAGE FORMS AND STRENGTHS

Injection: Three concentrations of norepinephrine, a clear, colorless sterile solution in 250 mL of 0.9% sodium chloride, available in the premixed, ready-to-use single dose intravenous infusion bags:

- 4 mg equivalent of norepinephrine (16 mcg/mL)
- 8 mg equivalent of norepinephrine (32 mcg/mL)
- 16 mg equivalent of norepinephrine (64 mcg/mL)

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Tissue Ischemia

Administration of Norepinephrine in Sodium Chloride Injection to patients who are hypotensive from hypovolemia can result in severe peripheral and visceral vasoconstriction, decreased renal perfusion and reduced urine output, tissue hypoxia, lactic acidosis, and reduced systemic blood flow despite “normal” blood pressure. Address hypovolemia prior to initiating Norepinephrine in Sodium Chloride Injection *[see Dosage and Administration (2.1)]*. Avoid Norepinephrine in Sodium Chloride Injection in patients with mesenteric or peripheral vascular thrombosis, as this may increase ischemia and extend the area of infarction.

Gangrene of the extremities has occurred in patients with occlusive or thrombotic vascular disease or who received prolonged or high dose infusions. Monitor for changes to the skin of the extremities in susceptible patients.

Extravasation of Norepinephrine in Sodium Chloride Injection may cause necrosis and sloughing of surrounding tissue. To reduce the risk of extravasation, infuse into a large vein, check the infusion site frequently for free flow, and monitor for signs of extravasation *[see Dosage and Administration (2.1)]*.

Emergency Treatment of Extravasation

To prevent sloughing and necrosis in areas in which extravasation has occurred, infiltrate the ischemic area as soon as possible, using a syringe with a fine hypodermic needle with 5 to 10 mg of phentolamine mesylate in 10 mL to 15 mL of 0.9% Sodium Chloride Injection in adults.

Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours.

5.2 Hypotension after Abrupt Discontinuation

Sudden cessation of the infusion rate may result in marked hypotension. When discontinuing the infusion, gradually reduce the Norepinephrine in Sodium Chloride Injection infusion rate while expanding blood volume with intravenous fluids.

5.3 Cardiac Arrhythmias

Norepinephrine in Sodium Chloride Injection elevates intracellular calcium concentrations and may cause arrhythmias, particularly in the setting of hypoxia or hypercarbia. Perform continuous cardiac monitoring of patients with arrhythmias.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Tissue Ischemia *[seeWarnings and Precautions (5.1)]*
- Hypotension *[see Warnings and Precautions (5.2)]*

- Cardiac Arrhythmias *[see Warnings and Precautions (5.3)]*

The most common adverse reactions are hypertension and bradycardia.

The following adverse reactions can occur:

Nervous system disorders: Anxiety, headache

Respiratory disorders: Respiratory difficulty, pulmonary edema

7 DRUG INTERACTIONS

7.1 MAO-Inhibiting Drugs

Co-administration of Norepinephrine in Sodium Chloride Injection with monoamine oxidase (MAO) inhibitors or other drugs with MAO-inhibiting properties (e.g., linezolid) can cause severe, prolonged hypertension.

If administration of Norepinephrine in Sodium Chloride Injection cannot be avoided in patients who recently have received any of these drugs and in whom, after discontinuation, MAO activity has not yet sufficiently recovered, monitor for hypertension.

7.2 Tricyclic Antidepressants

Co-administration of Norepinephrine in Sodium Chloride Injection with tricyclic antidepressants (including amitriptyline, nortriptyline, protriptyline, clomipramine, desipramine, imipramine) can cause severe, prolonged hypertension. If administration of Norepinephrine in Sodium Chloride Injection cannot be avoided in these patients, monitor for hypertension.

7.3 Antidiabetics

Norepinephrine in Sodium Chloride Injection can decrease insulin sensitivity and raise blood glucose. Monitor glucose and consider dosage adjustment of antidiabetic drugs.

7.4 Halogenated Anesthetics

Concomitant use of Norepinephrine in Sodium Chloride Injection with halogenated anesthetics (e.g., cyclopropane, desflurane, enflurane, isoflurane, and sevoflurane) may lead to ventricular tachycardia or ventricular fibrillation. Monitor cardiac rhythm in patients receiving concomitant halogenated anesthetics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published data consisting of a small number of case reports and multiple small trials involving the use of norepinephrine in pregnant women at the time of delivery have not identified an increased risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and fetus from hypotension associated

with septic shock, myocardial infarction and stroke which are medical emergencies in pregnancy and can be fatal if left untreated *(see Clinical Considerations)*. In animal reproduction studies, using high doses of intravenous norepinephrine resulted in lowered maternal placental blood flow. Clinical relevance to changes in the human fetus is unknown since the average maintenance dose is ten times lower *(see Data)*. Increased fetal reabsorptions were observed in pregnant hamsters after receiving daily injections at approximately 2 times the maximum recommended dose on a mg/m^2 basis for four days during organogenesis *(see Data)*.

The estimated background risk for 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 U.S. 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

Disease-associated maternal and/or embryo/fetal risk

Hypotension associated with septic shock, myocardial infarction, and stroke are medical emergencies in pregnancy which can be fatal if left untreated. Delaying treatment in pregnant women with hypotension associated with septic shock, myocardial infarction and stroke 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 norepinephrine on the fetus.

Data

Animal Data

A study in pregnant sheep receiving high doses of intravenous norepinephrine (40 mcg/min, at approximately 10 times the average maintenance dose of 2-4 mcg/min in human, on a mg/kg basis) exhibited a significant decrease in maternal placental blood flow. Decreases in fetal oxygenation, urine and lung liquid flow were also observed.

Norepinephrine administration to pregnant rats on Gestation Day 16 or 17 resulted in cataract production in rat fetuses.

In hamsters, an increased number of resorptions (29.1% in study group vs. 3.4% in control group), fetal microscopic liver abnormalities and delayed skeletal ossification were observed at approximately 2 times the maximum recommended intramuscular or subcutaneous dose (on a mg/m^2 basis at a maternal subcutaneous dose of 0.5 mg/kg/day from Gestation Day 7-10).

8.2 Lactation

Risk Summary

There are no data on the presence of norepinephrine in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. Clinically relevant exposure to the infant is not expected based on the short half-life and poor oral bioavailability of norepinephrine.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of Norepinephrine in Sodium Chloride Injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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 other drug therapy.

Avoid administration of Norepinephrine in Sodium Chloride Injection into the veins in the leg in elderly patients *[see Warnings and Precautions (5.1)].*

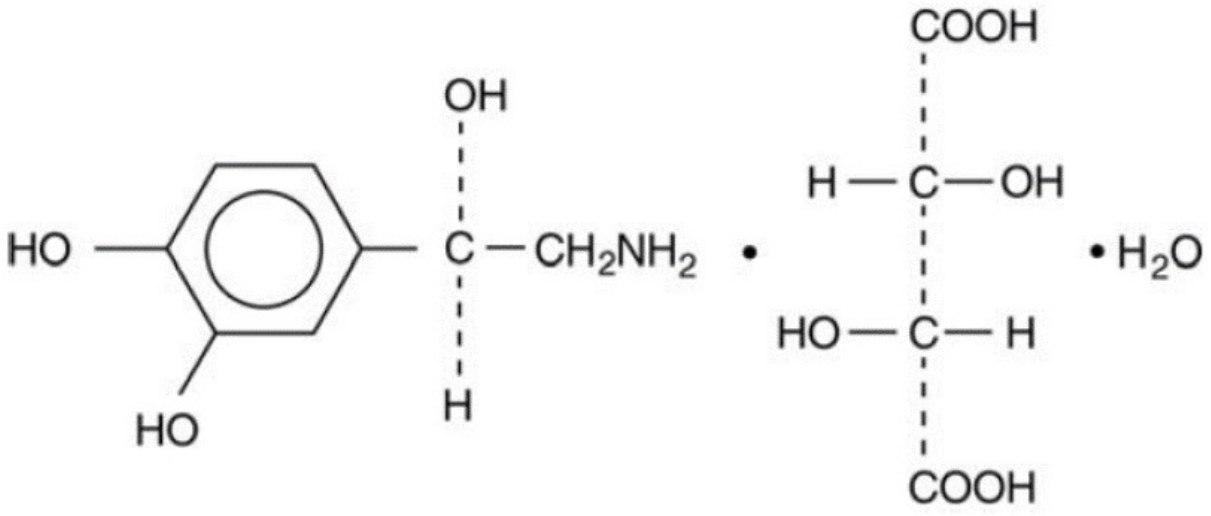
10 OVERDOSAGE

Overdosage with Norepinephrine in Sodium Chloride Injection may result in headache, severe hypertension, reflex bradycardia, marked increase in peripheral resistance, and decreased cardiac output.

In case of accidental overdosage, discontinue Norepinephrine in Sodium Chloride Injection until the condition of the patient stabilizes.

11 DESCRIPTION

Norepinephrine (sometimes referred to as l-arterenol/Levarterenol or l-norepinephrine) is a catecholamine which differs from epinephrine by the absence of a methyl group on the nitrogen atom.
Chemically, Norepinephrine Bitartrate is (-)-α-(aminomethyl)-3,4-dihydroxybenzyl alcohol tartrate (1:1) (salt) monohydrate (molecular weight 337.3 g/mol) and has the following structural formula:



Norepinephrine in Sodium Chloride Injection is a clear, colorless, single dose sterile

solution supplied as a ready-to-use intravenous infusion bag for intravenous use and does not require further dilution. Each mL contains the equivalent of 16 or 32 or 64 micrograms of norepinephrine base supplied as 31.90 or 63.80 or 127.6 micrograms per mL of norepinephrine bitartrate monohydrate. In addition, each mL of solution contains 0.01 mg edetate disodium dihydrate as a metal chelator and 9.0 mg sodium chloride for isotonicity. It has a pH of 3.5 to 4.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Norepinephrine is a peripheral vasoconstrictor (alpha-adrenergic action) and an inotropic stimulator of the heart and dilator of coronary arteries (beta-adrenergic action).

12.2 Pharmacodynamics

The primary pharmacodynamic effects of norepinephrine are cardiac stimulation and vasoconstriction. Cardiac output is generally unaffected, although it can be decreased, and total peripheral resistance is also elevated. The elevation in resistance and pressure result in reflex vagal activity, which slows the heart rate and increases stroke volume. The elevation in vascular tone or resistance reduces blood flow to the major abdominal organs as well as to skeletal muscle. Coronary blood flow is substantially increased secondary to the indirect effects of alpha stimulation. After intravenous administration, a pressor response occurs rapidly and reaches steady state within 5 minutes. The pharmacologic actions of norepinephrine are terminated primarily by uptake and metabolism in sympathetic nerve endings. The pressor action stops within 1-2 minutes after the infusion is discontinued.

12.3 Pharmacokinetics

Absorption

Following intravenous administration, the steady state plasma concentration is achieved in 5 min.

Distribution

Plasma protein binding of norepinephrine is approximately 25%. It is mainly bound to plasma albumin and to a smaller extent to prealbumin and alpha 1-acid glycoprotein. The volume of distribution is 8.8 L. Norepinephrine localizes mainly in sympathetic nervous tissue. It crosses the placenta but not the blood-brain barrier.

Elimination

The mean half-life of norepinephrine is approximately 2.4 min. The average metabolic clearance is 3.1 L/min.

Metabolism

Norepinephrine is metabolized in the liver and other tissues by a combination of reactions involving the enzymes catechol-O-methyltransferase (COMT) and MAO. The major metabolites are normetanephrine and 3-methoxy-4-hydroxy mandelic acid (vanillylmandelic acid, VMA), both of which are inactive. Other inactive metabolites include 3-methoxy-4-hydroxyphenylglycol, 3,4-dihydroxymandelic acid, and 3,4-

dihydroxyphenylglycol.

Excretion

Noradrenaline metabolites are excreted in urine primarily as sulphate conjugates and, to a lesser extent, as glucuronide conjugates. Only small quantities of norepinephrine are excreted unchanged.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, mutagenesis, and fertility studies have not been performed.

16 HOW SUPPLIED/STORAGE AND HANDLING

Norepinephrine in Sodium Chloride Injection (norepinephrine bitartrate) is supplied as a clear, colorless sterile solution in a 250 mL non-PVC infusion bag with single function connector system consisting of a port and cap, packaged individually in an aluminum foil pouch with an oxygen scavenger. Supplied as:

Unit of Sale	Concentration	Package Size
NDC 42023-245-10	4 mg/250 mL (16 mcg/mL)	10 bags
NDC 42023-246-10	8 mg/250 mL (32 mcg/mL)	10 bags
NDC 42023-247-10	16 mg/250 mL (64 mcg/mL)	10 bags

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature.] Protect from light. Keep in sealed overwrap until ready to use. Discard after 24 hours of opening overwrap.

17 PATIENT COUNSELING INFORMATION

Risk of Tissue Damage

Advise the patient, family, or caregiver to report signs of extravasation urgently *[see Warnings and Precautions (5.1)]*.

Distributed by:

Par Pharmaceutical, Inc.

Chestnut Ridge, NY 10977

I10/2022
OS245-01-23-01

PRINCIPAL DISPLAY PANEL - 4 mg/250 mL non-PVC infusion bag

NDC 42023-245-01

Rx Only

Norepinephrine in 0.9% Sodium Chloride Injection

4 mg/250 mL (16 mcg/mL)

For Intravenous Infusion Only

Discard if overwrap has been previously opened or damaged.
Stable out of overwrap for 24 hours.
Do not use if solution is discolored.
Ready-To-Use. Sterile.
Dosage: See prescribing information.
Contains 0.01 mg/mL of edetate disodium dihydrate.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
Single dose container. Discard unused portion.
Vesicant. Use optimal intravenous access (largest vein possible) to minimize risk of extravasation.

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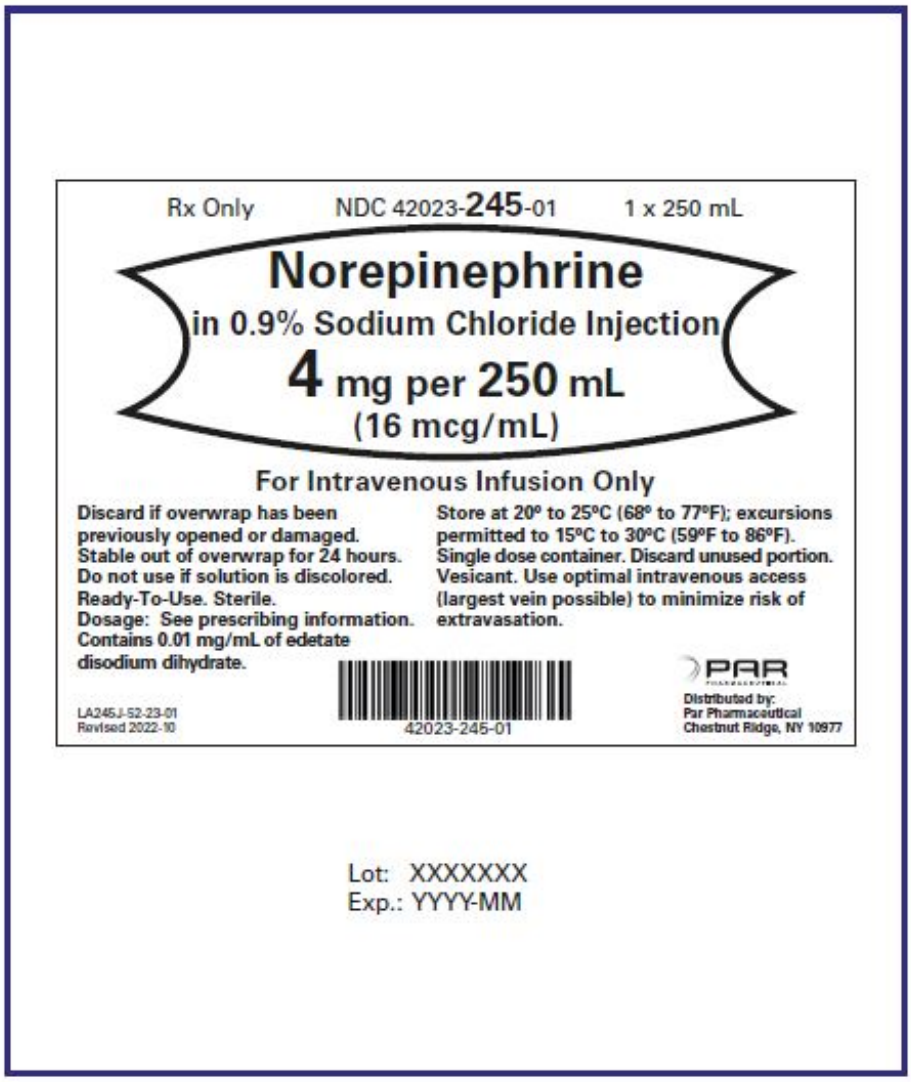

PRINCIPAL DISPLAY PANEL - 8 mg/250 mL non-PVC infusion bag

NDC 42023-246-01

Rx Only

Norepinephrine in 0.9% Sodium Chloride Injection

8 mg/250 mL
(32 mcg/mL)

For Intravenous Infusion Only

Discard if overwrap has been previously opened or damaged.
Stable out of overwrap for 24 hours.
Do not use if solution is discolored.
Ready-To-Use. Sterile.
Dosage: See prescribing information.
Contains 0.01 mg/mL of edetate disodium dihydrate.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
Single dose container. Discard unused portion.

Vesicant. Use optimal intravenous access (largest vein possible) to minimize risk of extravasation.

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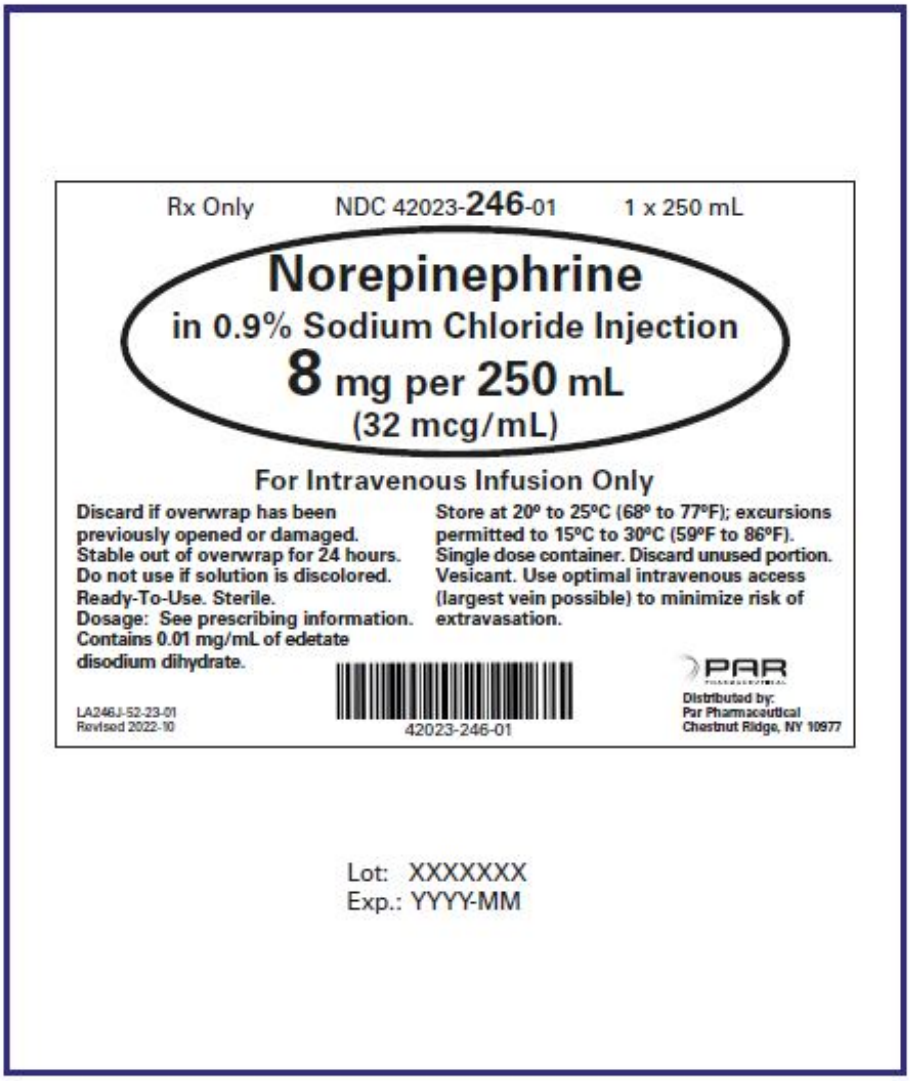

PRINCIPAL DISPLAY PANEL - 16 mg/250 mL non-PVC infusion bag

NDC 42023-247-01

Rx Only

Norepinephrine in 0.9% Sodium Chloride Injection

16 mg/250 mL
(64 mcg/mL)

For Intravenous Infusion Only

Discard if overwrap has been previously opened or damaged.
Stable out of overwrap for 24 hours.
Do not use if solution is discolored.
Ready-To-Use. Sterile.
Dosage: See prescribing information.
Contains 0.01 mg/mL of edetate disodium dihydrate.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
Single dose container. Discard unused portion.
Vesicant. Use optimal intravenous access (largest vein possible) to minimize risk of extravasation.

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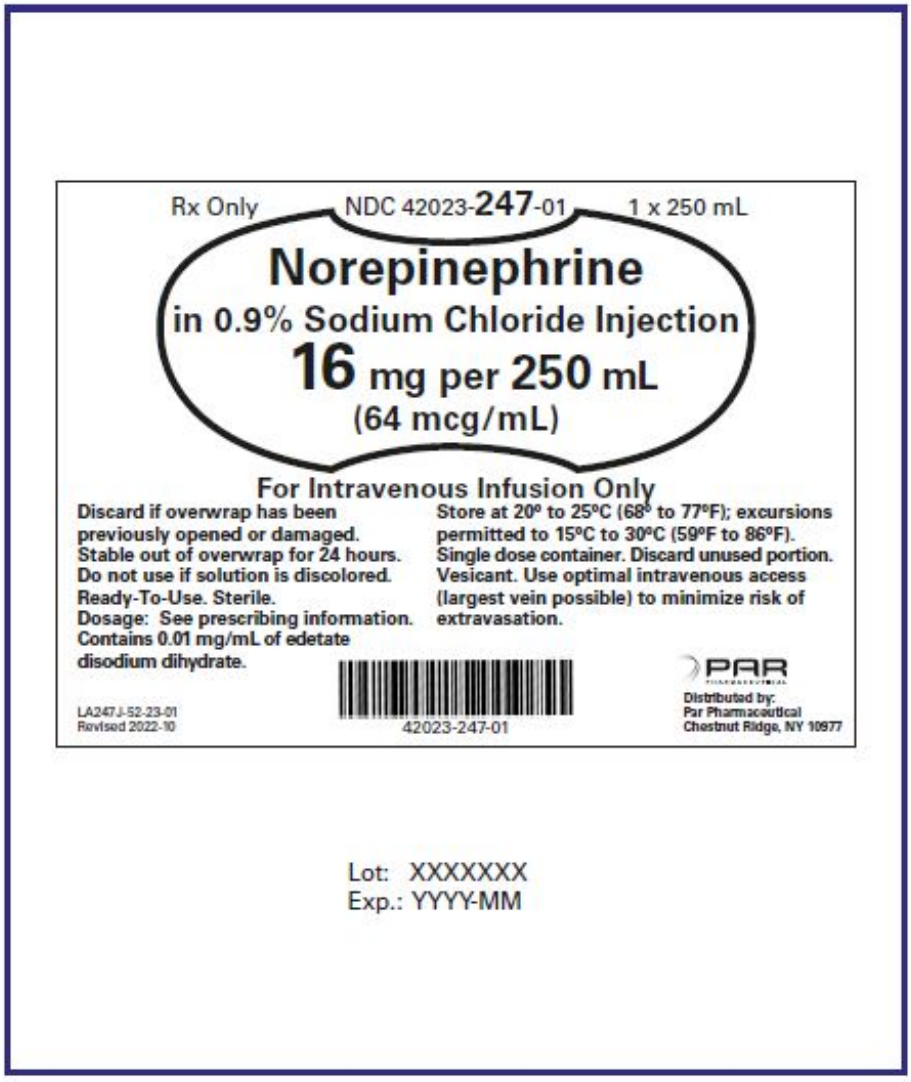

NORepinephrine BITARTRATE

norepinephrine in sodium chloride injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:42023-245
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**

NOREPINEPHRINE BITARTRATE (UNII: IFY5PE3ZRW) (NOREPINEPHRINE - UNII:X4W3ENH1CV)	NOREPINEPHRINE	4 mg in 250 mL

Inactive Ingredients	
Ingredient Name	**Strength**
SODIUM CHLORIDE (UNII: 451W47IQ8X)	2.25 g in 250 mL
EDETATE DISODIUM (UNII: 7FLD91C86K)	2.5 mg in 250 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42023-245-10	10 in 1 CARTON	01/04/2023	
1		250 mL in 1 BAG; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA214628	01/04/2023	

NOREPINEPHRINE BITARTRATE

norepinephrine in sodium chloride injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:42023-246
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NOREPINEPHRINE BITARTRATE (UNII: IFY5PE3ZRW) (NOREPINEPHRINE - UNII:X4W3ENH1CV)	NOREPINEPHRINE	8 mg in 250 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	2.25 g in 250 mL
EDETATE DISODIUM (UNII: 7FLD91C86K)	2.5 mg in 250 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42023-246-10	10 in 1 CARTON	01/04/2023	
1		250 mL in 1 BAG; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA214628	01/04/2023	

NOREPINEPHRINE BITARTRATE

norepinephrine in sodium chloride injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:42023-247
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
NOREPINEPHRINE BITARTRATE (UNII: IFY5PE3ZRW) (NOREPINEPHRINE - UNII:X4W3ENH1CV)	NOREPINEPHRINE	16 mg in 250 mL

Inactive Ingredients	
Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	2.25 g in 250 mL
EDETATE DISODIUM (UNII: 7FLD91C86K)	2.5 mg in 250 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42023-247-10	10 in 1 CARTON	01/04/2023	
1		250 mL in 1 BAG; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA214628	01/04/2023	

Labeler - Par Pharmaceutical, Inc. (092733690)

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