Norepinephrine Bitartrate Injection, USP

4 mg/4 mL* (1 mg/mL)

See accompanying full Prescribing Information

*Each mL contains norepinephrine bitartrate USP, equivalent to 1 mg norepinephrine base, sodium chloride for isotonicity with not more than 0.2 mg sodium metabisulfite as antioxidant.
NOREPINEPHRINE BITARTRATE injection, for intravenous use
Initial U.S. Approval: 1950

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Norepinephrine bitartrate 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 bitartrate injection therapy. If the patient does not respond to therapy, suspect occult hypovolemia [see Warnings and Precautions (5.1)].

Administration

Dilute norepinephrine bitartrate injection prior to use [see Dosage and Administration (2.3)].

Infuse norepinephrine bitartrate 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.

Discontinuation

When discontinuing the infusion, reduce the flow rate gradually. Avoid abrupt withdrawal.

2.2 Dosage

After an initial dosage of 8 mcg 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 until the desired hemodynamic effect is achieved, and then monitor blood pressure every five minutes for the duration of the infusion.

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

2.3 Preparation of Diluted Solution

Visually inspect norepinephrine bitartrate injection for particulate matter and discoloration prior to administration (the solution is colorless). Do not use the solution if its color is pinkish or darker than slightly yellow or if it contains a precipitate.

Add the content of one norepinephrine bitartrate injection vial (4 mg in 4 mL) to 1,000 mL of 5% Dextrose Injection, USP or Sodium Chloride Injection solutions that contain 5% dextrose to produce a 4 mcg per mL dilution. Dextrose reduces loss of potency due to oxidation. Administration in saline solution alone is not recommended.

Use higher concentration solutions in patients requiring fluid restriction. Prior to use, store the diluted norepinephrine bitartrate injection solution for up to 24 hours at room temperature (20° to 25°C (68° to 77°F)) and protect from light.

2.4 Drug Incompatibilities

Avoid contact with iron salts, alkalis, or oxidizing agents.

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

3 DOSAGE FORMS AND STRENGTHS

Injection: 4 mg/4 mL (1 mg/mL norepinephrine base) sterile, clear, colorless or practically colorless to slightly yellow color solution in a single-dose amber glass vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Tissue Ischemia

Administration of norepinephrine to patients who are hypotensive from hypovolemia can result in severe peripheral and visceral vasconstriction, 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 [see Dosage and Administration (2.1)]. Avoid norepinephrine 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 disease or who received prolonged or high dose infusions. Monitor for changes to the skin.

Extravasation of norepinephrine 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 mg to 10 mg of phenolamine mesylate in 10 mL to 15 mL of 0.9% Sodium Chloride Injection in adults.

Sympathetic blockade with phenolamine 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 infusion rate while expanding blood volume with intravenous fluids.

5.3 Cardiac Arrhythmias

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

5.4 Allergic Reactions Associated with Sulfite

Norepinephrine bitartrate injection contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

6 ADVERSE REACTIONS

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

- Tissue Ischemia [see Warnings 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 with monoamine oxidase (MAO) inhibitors or other drugs with MAO-inhibiting properties (e.g., linezolid) can cause severe, prolonged hypertension.

If administration of norepinephrine 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 with tricyclic antidepressants (including amitriptyline, norپropitline, protriptyline, clomipramine, desipramine, imipramine) can cause severe, prolonged hypertension. If administration of norepinephrine cannot be avoided in these patients, monitor for hypertension.

7.3 Antidiabetics

Norepinephrine can increase insulin sensitivity and raise blood glucose. Monitor glucose and consider dosage adjustment of antidiabetic drugs.

7.4 Halogenated Anesthetics

Concomitant use of norepinephrine 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/m² 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 the clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

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 vasocostruction. 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 to 2 minutes after the infusion is discontinued.

12.3 Pharmacokinetics

Absorption
Following initiation of intravenous infusion, 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 lesser extent to prealbumin and alpha 1-acid glycoprotein. The volume of distribution is 8.1 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 monoamine oxidase (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 Bitartrate Injection, USP is a sterile, colorless or practically colorless to slightly yellow color solution for injection intended for intravenous use. It contains the equivalent of 1 mg of norepinephrine base per 1 mL (4 mg/4 mL). It is available as 4 mg/mL in single-dose amber glass vials supplied as:

- 4 mg/4 mL (1 mg/mL):
  10 x 4 mL Single-Dose Vials in a Carton: NDC 70121-1576-7

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature.]

Store in original carton until time of administration to protect from light. Discard unused portion.

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)].

This product’s labeling may have been updated. For the most recent prescribing information, please visit www.amneal.com.

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