PRESCRIBING INFORMATION

NOREPINEPHRINE BITARTRATE in 5% Dextrose Injection

0.016 mg / mL and 0.032 mg / mL norepinephrine (as norepinephrine bitartrate)

Sterile Solution for Intravenous Infusion

Manufacturer Standard

Sympathomimetic Amine for Use in Hypotensive Emergencies

Baxter Corporation

Mississauga, Ontario
L5N 0C2

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DESCRIPTION

Norepinephrine (sometimes referred to as *l-arterenol/Levarterenol or l-norepinephrine)* is a sympathomimetic amine which differs from epinephrine by the absence of a methyl group on the nitrogen atom.

ACTIONS

Norepinephrine bitartrate functions as a powerful peripheral vasoconstrictor (alpha-adrenergic action) and as a potent inotropic stimulator of the heart and dilator of coronary arteries (beta-adrenergic action). Both of these actions result in an increase in systemic blood pressure and coronary artery blood flow. Cardiac output will vary reflexly in response to systemic hypertension but is usually increased in hypotensive man when the blood pressure is raised to an optimal level. In myocardial infarction accompanied by hypotension. Norepinephrine bitartrate usually increases aortic blood pressure, coronary artery blood flow, and myocardial oxygenation, thereby helping to limit the area of myocardial ischemia and infarction. Venous return is increased and the heart tends to resume a more normal rate and rhythm than in the hypotensive state.

In hypotension that persists after correction of blood volume deficits, norepinephrine bitartrate helps raise the blood pressure to an optimal level and establish a more adequate circulation.

In *myocardial infarction,* norepinephrine bitartrate has been shown to increase greatly the patient survival rate. Norepinephrine bitartrate not only corrects systemic shock (through cardiotonic and peripheral vasoconstrictor action), but also markedly dilates the coronary arteries, thereby increasing coronary blood flow, reducing the area of ischemia and promoting myocardial oxygenation. There is increased venous return and the heart tends to resume a more normal rate and rhythm.

On the coronary arteries, norepinephrine bitartrate causes about two and one half times the degree of vasodilatation that epinephrine produces and therefore has a greater effect in increasing coronary flow. It has only a slight effect on sugar metabolism, its hyperglycemic action being far less pronounced than epinephrine, and is not contraindicated in diabetic patients.

NOTE: With norepinephrine bitartrate administration, bradycardia sometimes occurs, probably as a direct result of the rise in blood pressure to normal levels.

INDICATIONS

Norepinephrine Bitartrate in 5% Dextrose Injection is recommended for the restoration and maintenance of blood pressure in all acute hypotensive or shock states which may result from surgery, trauma, hemorrhage, myocardial infarction, pheochromocytomectomy, sympathectomy, spinal anesthesia, septicemia, drug reactions, poliomyelitis and blood transfusion reactions.

Because of the selective peripheral vasoconstrictive action of norepinephrine bitartrate, pooled or stagnant blood in the dilated capillaries is driven into the central circulation, thus maintaining vital functions (e.g.-brain, heart, kidneys, etc.).

It may also be useful as an adjunct in the treatment of cardiac arrest and profound hypotension.

CONTRAINDICATIONS

Norepinephrine Bitartrate in 5% Dextrose Injection should not be given to patients who are hypotensive from blood volume deficits except as an emergency measure to maintain coronary and cerebral artery perfusion until blood volume replacement therapy can be completed. If Norepinephrine Bitartrate in 5% Dextrose Injection is continuously administered to maintain blood pressure in the absence of blood volume replacement, the following may occur: severe peripheral and visceral vasoconstriction, decreased renal perfusion and urine output, poor systemic blood flow despite "normal" blood pressure, tissue hypoxia, and lactate acidosis.

Norepinephrine Bitartrate in 5% Dextrose Injection should also not be given to patients with mesenteric or peripheral vascular thrombosis (because of the risk of increasing ischemia and extending the area of infarction) unless, in the opinion of the attending physician, the administration of Norepinephrine Bitartrate in 5% Dextrose Injection is necessary as a life-saving procedure.

Cyclopropane and halothane anesthetics increase cardiac autonomic irritability and therefore seem to sensitize the myocardium to the action of intravenously administered epinephrine or levarterenol. Hence, the use of Norepinephrine Bitartrate in 5% Dextrose Injection during cyclopropane and halothane anesthesia is generally considered contraindicated because of the risk of producing ventricular tachycardia or fibrillation. The same type of cardiac arrhythmias may result from the use of Norepinephrine Bitartrate in 5% Dextrose Injection in patients with

profound hypoxia or hypercarbia.

WARNING

Norepinephrine Bitartrate in 5% Dextrose Injection should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Norepinephrine Bitartrate in 5% Dextrose Injection should be used with caution in the context of aneurysmal subarachnoid hemorrhage (SAH) due to the risk of overdose and associated adverse events. Whenever clinical symptoms rather worsen after the augmentation of blood pressure, reverse hypertensive therapy is advised.

PRECAUTIONS

Avoid Hypertension: Because of the potency of Norepinephrine Bitartrate in 5% Dextrose Injection and because of varying response to pressor substances, the possibility always exists that dangerously high blood pressure may be produced with overdoses of this pressor agent. It is desirable, therefore, to record the blood pressure every two minutes from the time administration is started until the desired blood pressure is obtained, then every five minutes if administration is to be continued. The rate of flow must be watched constantly, and the patient should never be left unattended while receiving Norepinephrine Bitartrate in 5% Dextrose Injection. Headache may be a symptom of hypertension due to overdosage.

Site of infusion: Whenever possible, Norepinephrine Bitartrate in 5% Dextrose Injection should be given into a large vein, particularly an antecubital vein because, when administered into this vein, the risk of necrosis of the overlying skin from prolonged vasoconstriction is apparently very slight**.** Some authors have indicated that the femoral vein is also an acceptable route of administration. A catheter tie-in technique should be avoided, if possible, since the obstruction to blood flow around the tubing may cause stasis and increased local concentration of the drug. Occlusive vascular diseases (for example, atherosclerosis, arteriosclerosis, diabetic endarteritis, Buerger's disease) are more likely to occur in the lower than in the upper extremity. Therefore, one should avoid the veins of the leg or dorsum of the hand in elderly patients, or in those suffering from such disorders. Gangrene has been reported in a lower extremity when norepinephrine bitartrate was given in an ankle vein.

Extravasation: **The infusion site should be checked frequently for free flow.** Care should be taken to avoid extravasation of Norepinephrine Bitartrate in 5% Dextrose Injection into the tissues, as local necrosis might ensue due to the vasoconstrictive action of the drug. **Blanching along the course of the infused vein**, sometimes without obvious extravasation, has been attributed to vasa vasorum constriction with increased permeability of the vein wall, permitting some leakage. This also may progress on rare occasions to superficial slough, particularly during infusion into leg veins, in elderly patients or in those suffering from obliterative vascular disease. Hence, if blanching occurs, consideration should be given to the advisability of changing the infusion site at intervals to allow the effects of local vasoconstriction to subside.

Norepinephrine administration was reported to induce fetal bradycardia most likely as a result of uterine/peripheral vasoconstriction by norepinephrine, however transplacental passage cannot be excluded. It was shown to exert a contractile effect on the pregnant uterus and may lead to fetal hypoxia in late pregnancy. These possible risks to the fetus should therefore be weighed against the potential benefit to the mother.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Norepinephrine Bitartrate in 5% Dextrose Injection is administered to a nursing woman.

IMPORTANT: Antidote for Extravasation Ischemia: To prevent sloughing and necrosis in areas in which extravasation has taken place, the area should be infiltrated as soon as possible with 10 to 15 mL of saline solution containing from 5 to 10 mg of phentolamine, an adrenergic blocking agent. A syringe with a fine hypodermic needle is used, and the solution is infiltrated liberally throughout the area, which is easily identified by its cold, hard, and pallid appearance. Sympathetic blockage with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, **phentolamine should be given as soon as possible after the extravasation is noted.**

Although investigators have described addition of other medications such as phentolamine and heparin to diluted norepinephrine solutions prior to infusion to prevent potential adverse events, the container design of Norepinephrine Bitartrate in 5% Dextrose Injection prohibits addition of other medications to the container. Manipulation of the product by addition of other medications would negate the benefit of the product design as a ready to use solution that does not require

admixture steps that could lead to possible preparation errors or contamination during preparation. If addition of other medications to norepinephrine is desired, a norepinephrine product that is designed for admixture should be used.

Sympathetic nerve block has also been suggested.

ADVERSE REACTIONS

The following reactions can occur:

Body As A Whole: Ischemic injury due to potent vasoconstrictor action and tissue hypoxia.

Cardiovascular System: Cardiogenic shock, arrhythmia, bradycardia, probably as a reflex result of a rise in blood pressure, stress cardiomyopathy.

Nervous System: Anxiety, transient headache.

Respiratory System: Respiratory difficulty.

Skin and Appendages: Extravasation necrosis at injection site.

Prolonged administration of any potent vasopressor may result in plasma volume depletion which should be continuously corrected by appropriate fluid and electrolyte replacement therapy. If plasma volumes are not corrected, hypotension may recur when Norepinephrine Bitartrate in 5% Dextrose Injection is discontinued, or blood pressure may be maintained at the risk of severe peripheral and visceral vasoconstriction (e.g., decreased renal perfusion) with diminution in blood flow and tissue perfusion with subsequent tissue hypoxia and lactic acidosis and possible ischemic injury. Gangrene of extremities has been rarely reported.

Overdoses or conventional doses in hypersensitive persons {eg. hyperthyroid patients) cause severe hypertension with violent headache, photophobia, stabbing retrosternal pain, pallor, intense sweating and vomiting.

DRUG INTERACTIONS

Cyclopropane and halothane anesthetics increase cardiac autonomic irritability and therefore seem to sensitize the myocardium to the action of intravenously administered epinephrine or levarterenol. Hence, the use of Norepinephrine Bitartrate in 5% Dextrose Injection during cyclopropane and halothane anesthesia is generally considered contraindicated because of the risk of producing ventricular tachycardia or fibrillation. The same type of cardiac arrhythmias may result from the use of Norepinephrine Bitartrate in 5% Dextrose Injection in patients with profound hypoxia or hypercarbia.

Norepinephrine Bitartrate in 5% Dextrose Injection should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

OVERDOSAGE

Overdosage with norepinephrine bitartrate was shown to be associated with severe hypertension, reflex bradycardia, marked increase in peripheral resistance, and decreased cardiac output. These may be accompanied by violent headache, pulmonary edema, photophobia, retrosternal pain, pallor, intense sweating and vomiting. Stress cardiomyopathy was also reported in the context of norepinephrine overdose. In case of accidental overdosage, as evidenced by excessive blood pressure elevation, treatment with Norepinephrine Bitartrate in 5% Dextrose Injection should be withdrawn and appropriate corrective measures initiated until the condition of the patient stabilizes.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

DOSAGE AND ADMINISTRATION

Restoration of Blood Pressure in **Acute Hypotensive States**

Blood volume depletion should always be corrected as fully as possible before any vasopressor is administered. When, as an emergency measure, intraaortic pressures must be maintained to prevent cerebral or coronary artery ischemia, Norepinephrine Bitartrate in 5% Dextrose Injection can be administered before and concurrently with blood volume replacement.

Norepinephrine Bitartrate in 5% Dextrose Injection is a ready to administer product that requires

no further dilution prior to infusion. It comes in a VIAFLO flexible plastic container with foil overpouch and a single administration port. An infusion of Norepinephrine Bitartrate in 5% Dextrose Injection should be given into a large vein [see **PRECAUTIONS**].

Whole blood or plasma, if indicated to increase blood volume, should be administered separately (for example by use of a Y-tube and individual flasks if given simultaneously).

Average Dosage: Give this solution intravenously. Insert a plastic intravenous catheter through a suitable bore needle well advanced centrally into the vein and securely fixed with adhesive tape, avoiding if possible, a catheter tie-in technique as this promotes stasis. A drip bulb or administration via a rate controlled infusion pump is necessary to permit an accurate estimation of the rate of flow in drops per minute. Electromechanical infusion pumps are designed to accurately deliver intravenous infusions at specified rates and are therefore recommended for use in the administration of Norepinephrine Bitartrate in 5% Dextrose Injection.

After observing the response to an initial dose of 8 to 12 mcg of base per minute, adjust the rate of flow to establish and maintain a low normal blood pressure (usually 80 to 100 mm Hg systolic) sufficient to maintain the circulation to vital organs. In previously hypertensive patients, it is recommended that the blood pressure should be raised no higher than 40 mm Hg below the preexisting systolic pressure. The average maintenance dose ranges from 2 to 4 mcg of base per minute.

High Dosage: Great individual variation occurs in the dose required to attain and maintain adequate blood pressure. In all cases, dosage of Norepinephrine Bitartrate in 5% Dextrose Injection should be titrated according to response of the patient. Occasionally much larger or even enormous daily doses (as high as 68 mg norepinephrine base) may be necessary if the patient remains hypotensive, but occult blood volume depletion should always be suspected and corrected when present. Central venous pressure monitoring is usually helpful in detecting and treating this situation. Due to the large volume of Norepinephrine Bitartrate in 5% Dextrose Injection that would be required to meet these enormous doses, this product may not meet the needs of all patients and a more concentrated product (greater than 32 mcg / mL) should be used.

Fluid Intake: The choice of appropriate concentration of Norepinephrine Bitartrate in 5% Dextrose Injection depends on clinical fluid volume requirements. If large volumes of fluid (dextrose) are needed at a flow rate that would involve an excessive dose of the pressor agent per

unit of time, a concentration lower than the 16 mcg / mL Norepinephrine Bitartrate in 5% Dextrose Injection product should be used. On the other hand, when large volumes of fluid are clinically undesirable, a concentration greater than 32 mcg per mL may be necessary.

Duration of Therapy: The infusion should be continued until adequate blood pressure and tissue perfusion are maintained without therapy. Norepinephrine Bitartrate in 5% Dextrose Injection infusion should be reduced gradually, avoiding abrupt withdrawal. In some of the reported cases of vascular collapse due to acute myocardial infarction, treatment was required for up to six days.

Adjunctive Treatment in Cardiac Arrest

Norepinephrine Bitartrate in 5% Dextrose Injection is usually administered intravenously during cardiac resuscitation to restore and maintain an adequate blood pressure after an effective heartbeat and ventilation have been established by other means. Norepinephrine's powerful beta-adrenergic stimulating action is also thought to increase the strength and effectiveness of systolic contractions once they occur.)

Average Dosage: To maintain systemic blood pressure during the management of cardiac arrest. Norepinephrine Bitartrate in 5% Dextrose Injection is used in the same manner as described under Restoration of Blood Pressure in Acute Hypotensive States.

Directions for Use of Norepinephrine Bitartrate in 5% Dextrose Injection in VIAFLO Container

WARNINGS: Do NOT add supplementary medication. Do NOT use VIAFLO containers in series connections. Such use could result in air embolism due to residual air being drawn from the first container before administration of the fluid from the second container is complete. Do NOT remove VIAFLO container from overwrap until ready to use. Discard if expired.

To Open

Tear overwrap down side at slit and remove VIAFLO container. Discard the oxygen absorbing sachet. Visually inspect the container. If the outlet port protector is damaged, detached, or not present, discard container as solution path sterility may be impaired. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and

does not affect the solution quality or safety. The opacity will diminish gradually. Do not use if the solution is pinkish or darker than slightly yellow or contains a precipitate. Check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired.

1. Remove the VIAFLO container from the overwrap just before use. The VIAFLO container should be used within 30 days.
2. Check for minute leaks by squeezing the VIAFLO container firmly. If leaks are found, discard solution, as sterility may be impaired.
3. Check solution for clarity and absence of foreign matter. If solution is not clear or contains foreign matter, discard the solution.

Preparation for Administration

1. Suspend VIAFLO container from eyelet support.
2. Identify correct port.
3. Remove plastic protector from outlet port at bottom of container.
    - Grip the small wing on the neck of the port with one hand,
    - Grip the large wing on the cap with the other hand and twist,
    - The cap will pop off.
4. NEVER use non-accessible secondary port.
5. Use an aseptic method to set up the infusion.
6. Attach administration set. Refer to directions accompanying the administration set for connection, priming of the set, and administration of the solution.
7. For single use only – discard unused portion. Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required.

HOW SUPPLIED

Norepinephrine Bitartrate in 5% Dextrose Injection for intravenous infusion is available as a sterile aqueous solution in single-dose, ready-to-use VIAFLO containers. The ready to use container is protected from light and oxygen using an amber/foil overwrap containing an oxygen absorbing sachet. Each 250 mL of Norepinephrine Bitartrate in 5% Dextrose Injection contains the equivalent of 4 mg and 8 mg base of norepinephrine, respectively (as norepinephrine bitartrate, USP). Each mL contains the equivalent of 0.016 or 0.032 milligrams base of norepinephrine and as non-medicinal ingredients: 50 mg dextrose hydrous for isotonicity; sodium hydroxide and hydrochloric acid for pH adjustment; and water for injection. It has a pH of 3.0 – 4.5. The air in the solution has been displaced by nitrogen gas.

Caution -Destroy when expired and do not use if the solution is pinkish or darker than slightly yellow or contains a precipitate. Protect from light.

Store at room temperature (15°C to 25°C). It is recommended that the containers be kept in the overwrap until ready to use.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

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