CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

007513Orig1s038

Trade Name:	**LEVOPHED**
Generic or Proper Name:	norepinephrine bitartrate
Sponsor:	HOSPIRA, INC
Approval Date:	June 15, 2020
Indication:	**LEVOPHED** is a catecholamine indicated for restoration of blood pressure in adult patients with acute hypotensive states.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

NDA 007513/S-038

SUPPLEMENT APPROVAL

Hospira, Inc
Attention: Emily Schmidt
Senior Associate, Pfizer Essential Health Global Regulatory Affaris
275 North Field Drive
Bldg. H1
Lake Forest, IL, 60045

Dear Ms. Schmidt:

Please refer to your supplemental new drug application (sNDA) dated November 6, 2018, received November 6, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Levophed (norepinephrine bitartrate) injection.

This Prior Approval supplemental new drug application provides for revision of the prescribing information to comply with the Physician Labeling Rule.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Michael Monteleone, Associate Director for Labeling, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD
Deputy Director for Safety
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Content of Labeling
  - Prescribing Information

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY R SOUTHWORTH
06/15/2020 04:33:07 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

007513Orig1s038

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LEVOPHED safely and effectively. See full prescribing information for LEVOPHED.

LEVOPHED® (norepinephrine bitartrate) injection, for intravenous use
Initial U.S. Approval: 1950

---------- INDICATIONS AND USAGE----------
LEVOPHED is a catecholamine indicated for restoration of blood pressure in adult patients with acute hypotensive states. (1)

----------DOSAGE AND ADMINISTRATION----------
- Initial dose of 0.25 mL to 0.375 mL (from 8 mcg to 12 mcg of base) per minute, adjust the rate of flow to establish and maintain a low to normal blood pressure (usually 80 mm Hg to 100 mm Hg systolic) sufficient to maintain the circulation of vital organs. (2.2)
- The average maintenance dose ranges from 0.0625 mL to 0.125 mL per minute (from 2 mcg to 4 mcg of base). (2.2)

---------- DOSAGE FORMS AND STRENGTHS----------
Injection: 4 mg/4 mL (1 mg/mL) norepinephrine base in single-dose glass vial or ampule. (3)

---------- CONTRAINDICATIONS ----------
None. (4)

---------- WARNINGS AND PRECAUTIONS----------
- Tissue Ischemia: Avoid extravasation of LEVOPHED into the tissues, as local necrosis might ensue due to the vasoconstrictive action of the drug. Infuse LEVOPHED into a large vein. To prevent sloughing and necrosis in areas in which extravasation has taken place, the area should be infiltrated as soon as possible with 10 mL to 15 mL of saline solution containing from 5 mg to 10 mg of an adrenergic blocking agent. (5.1)
- Hypotension After Abrupt Discontinuation: Sudden cessation of the infusion rate may result in marked hypotension. Reduce the LEVOPHED infusion rate gradually. (5.2)
- Cardiac Arrhythmias: LEVOPHED may cause arrhythmias. Monitor cardiac function in patients with underlying heart disease. (5.3)
- Allergic Reactions with Sulfite: LEVOPHED contains sodium metabisulfite. Sulfite may cause allergic-type-reactions. (5.4)

---------- 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 Pfizer Inc. at 1-800-438-1985, 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: 6/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Administration

Dilute LEVOPHED prior to use *[see Dosage and Administration (2.3)]*.

Infuse LEVOPHED 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 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 to 4 mcg per minute.

2.3 Preparation of Diluted Solution

Visually inspect LEVOPHED 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 LEVOPHED vial or ampule (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 LEVOPHED solution for up to 24 hours at room temperature [20°C to 25°C (68°F 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, colorless solution in a single-dose amber glass vial.

Injection: 4 mg/4 mL (1 mg/mL norepinephrine base) sterile, colorless solution in a single-dose clear glass ampule.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Tissue Ischemia

Administration of LEVOPHED 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 LEVOPHED *[see Dosage and Administration (2.1)]*. Avoid LEVOPHED 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 LEVOPHED 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 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 LEVOPHED infusion rate while expanding blood volume with intravenous fluids.

5.3 Cardiac Arrhythmias

LEVOPHED 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

LEVOPHED 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 LEVOPHED with monoamine oxidase (MAO) inhibitors or other drugs with MAO-inhibiting properties (e.g., linezolid) can cause severe, prolonged hypertension.

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

7.3 Antidiabetics

LEVOPHED can decrease insulin sensitivity and raise blood glucose. Monitor glucose and consider dosage adjustment of antidiabetic drugs.

7.4 Halogenated Anesthetics

Concomitant use of LEVOPHED 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^3 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 2-4% 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 LEVOPHED 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 LEVOPHED into the veins in the leg in elderly patients *[see Warnings and Precautions (5.1)]*.

10 OVERDOSAGE

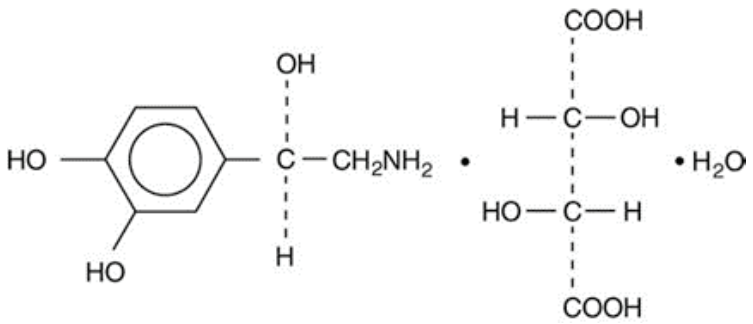
Overdosage with LEVOPHED may result in headache, severe hypertension, reflex bradycardia, marked increase in peripheral resistance, and decreased cardiac output.

In case of overdosage, discontinue LEVOPHED until the condition of the patient stabilizes.

11 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.

LEVOPHED is (-)-α-(aminomethyl)-3,4-dihydroxybenzyl alcohol tartrate (1:1) (salt) monohydrate (molecular weight 337.3 g/mol) and has the following structural formula:



LEVOPHED is supplied in a sterile aqueous solution in the form of the bitartrate salt to be administered by intravenous infusion. Norepinephrine is sparingly soluble in water, very slightly soluble in alcohol and ether, and readily soluble in acids. Each mL contains 1 mg of norepinephrine base (equivalent to 1.89 mg of

norepinephrine bitartrate, anhydrous basis), sodium chloride for isotonicity, not more than 0.2 mg (vials) or 2 mg (ampules) of sodium metabisulfite as an antioxidant, and may contain sodium hydroxide and/or hydrochloric acid for pH adjustment to 3.0-4.5. The air in the containers has been displaced by nitrogen gas.

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 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 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-methoxyl-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

LEVOPHED (norepinephrine bitartrate) injection, USP, is a sterile, colorless 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/4 mL in single-dose amber glass vials and in single-dose clear glass ampules. Supplied as:

Unit of Sale	Concentration
NDC 0409-3375-04 10 vials in a Carton	4 mg/4 mL (1 mg/mL)
NDC 0409-1443-04 10 ampules in a Carton	4 mg/4 mL (1 mg/mL)

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.]

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.pfizer.com.

Distributed by Hospira, Inc., Lake Forest, IL 60045 USA

LAB-1150-1.2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

007513Orig1s038

OTHER REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Labeling Review

NDA:	007513/S-038
Date of submission:	November 6, 2018
Review date:	June 2, 2020
Applicant:	Hospira, Inc
Product:	Levophed (norepinephrine) 1 mg/mL injection
Reviewers:	Michael Monteleone, MS, RAC Associate Director for Labeling

Background: On November 6, 2018 the applicant submitted a labeling supplement providing for revisions in the drug interactions, pregnancy and adverse reactions sections of labeling. In the course of review, the Division requested the firm to convert their label into the Physician Labeling Rule format and they agreed.

Review:
This supplement is the subject of a review by the Office of Pharmaceutical Quality [Zimmermann, 2020-05-21].

In addition, revised labeling for norepinephrine has been reviewed by;

Kris Raman	Chemistry
Mariappan Chelliah	Chemistry
James Willard	Pharmacology/Toxicology
Albert Defelice	Lead, Pharmacology/Toxicology
Xuan Chi	Lead, Pharmacology/Toxicology
Jane Liedtka	Division of Pediatric and Maternal Health
Miriam Dinatale	Division of Pediatric and Maternal Health
Sreedharan Sabarinath	Clinical Pharmacology
Venki Chithambaram	Clinical Pharmacology
Sudharshan Hariharan	Lead, Clinical Pharmacology
Martin Rose	Lead, Clinical
Fortunato Senatore	Lead, Clinical

Michael Monteleone	Associate Director for Labeling
Mary Ross Southworth	Deputy Director for Safety
Norman Stockbridge	Director, Division of Cardiology and Nephrology

Extensive organizational and editorial revisions have been made throughout the label in accordance with conversion to the Physician Labeling Rule formatting of labeling. In addition, the following notable revisions have been made;

Under Indications and Usage;

The indication has been revised to remove examples of specific hypotensive states and to include 'adults' as the indicated population.

Reviewer's Note: Revisions to the indication statement are consistent with the Division's approach to labeling of this indication in similar products. These revisions are intended for clarity and consistency with good labeling practices and are not intended to alter the approved indication. See Guidance for Industry: Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format Guidance for Industry (July 2018).

Under Dosage and Administration;

The Dosage and Administration section of the prescribing information has been revised for clarity and concision. Language considered to be practice of medicine considerations has been removed.

Under Warnings and Precautions;

This section has generally been revised and reorganized for clarity and concision.

A new subsection has been added, Hypotension after Abrupt Discontinuation.

Reviewer's Note: The new subsection regarding hypotension after abrupt discontinuation is consistent with the current approved labeling in the Dosage and Administration section advising that Levophed be reduced gradually, avoiding abrupt withdrawal.

Under Drug Interactions;

A new subsection on antidiabetics has been added.

Under Use in Specific Populations;

This section has been revised consistent with the Pregnancy Lactation and Labeling Rule, (PLLR).

Reviewer's Note: Revisions in this section are consistent with other products in this class.

Under Clinical Pharmacology;

Pharmacodynamic and ADME information has been added in subsections 12.2 and 12.3.

Reviewer's Note: Inclusion of this information is consistent with the Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (December 2016). Information for these subsections was drawn from the following sources.

Catecholamine Metabolism: A Contemporary View with Implications for Physiology and Medicine, Eisenhofer et al. Pharmacology Reviews Vol 56 No 3 2004

Placental Transporters Relevant to Drug Distribution across the Maternal-Fetal Interface, Ganapathy et al, The Journal of Pharmacology and Experimental Therapeutics, Vol 294 No 2, 2000

Recommendation: This supplement is recommended for approval.

Attachments:
Currently marketed SPL in 'old' format (June 2, 2020)
Final draft labeling in PLR format

LEVOPHED®

Norepinephrine Bitartrate

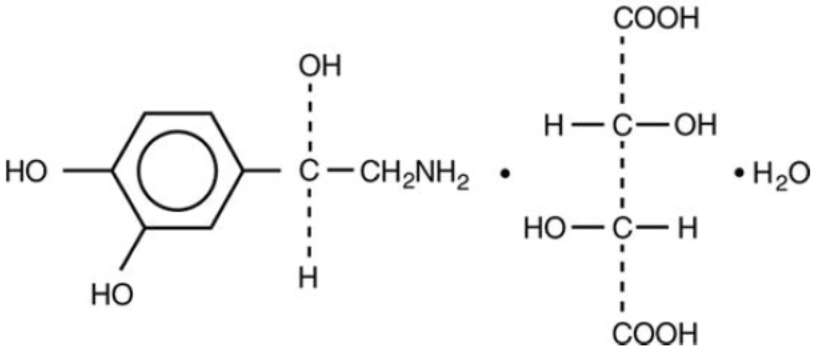
Injection, USP

R_x only

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.

Norepinephrine Bitartrate is (-)-α-(aminomethyl)-3,4-dihydroxybenzyl alcohol tartrate (1:1) (salt) monohydrate and has the following structural formula:



LEVOPHED is supplied in sterile aqueous solution in the form of the bitartrate salt to be administered by intravenous infusion following dilution. Norepinephrine is sparingly soluble in water, very slightly soluble in alcohol and ether, and readily soluble in acids. Each mL contains the equivalent of 1 mg base of norepinephrine, sodium chloride for isotonicity, and not more than 0.2 mg of sodium metabisulfite as an antioxidant. It has a pH of 3 to 4.5. The air in the vials has been displaced by nitrogen gas.

CLINICAL PHARMACOLOGY

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

INDICATIONS AND USAGE

For blood pressure control in certain acute hypotensive states (e.g., pheochromocytomectomy, sympathectomy, poliomyelitis, spinal anesthesia, myocardial infarction, septicemia, blood transfusion, and drug reactions).

As an adjunct in the treatment of cardiac arrest and profound hypotension.

CONTRAINDICATIONS

LEVOPHED 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 LEVOPHED 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.

LEVOPHED 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 LEVOPHED 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 norepinephrine. Hence, the use of LEVOPHED 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 LEVOPHED in patients with profound hypoxia or hypercarbia.

WARNINGS

LEVOPHED should be used with extreme caution in patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

LEVOPHED 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 nonasthmatic people.

PRECAUTIONS

General

Avoid Hypertension: Because of the potency of LEVOPHED 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 LEVOPHED. Headache may be a symptom of hypertension due to overdosage.

Site of Infusion: Whenever possible, infusions of LEVOPHED 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 in elderly patients or in those suffering from such disorders. Gangrene has been reported in a lower extremity when infusions of LEVOPHED were given in an ankle vein.

Extravasation: The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation of LEVOPHED 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.

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 mL to 15 mL of saline solution containing from 5 mg to 10 mg of **Regitine® (brand of phentolamine)**, an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, with the solution being infiltrated liberally throughout the area, which is easily identified by its cold, hard, and pallid appearance. Sympathetic blockade 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.

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 norepinephrine. Hence, the use of LEVOPHED 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 LEVOPHED in patients with profound hypoxia or hypercarbia.

LEVOPHED should be used with extreme caution in patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies have not been performed.

Pregnancy: Animal reproduction studies have not been conducted with LEVOPHED. It is also not known whether LEVOPHED can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. LEVOPHED should be given to a pregnant woman only if clearly needed.

Nursing Mothers: 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 LEVOPHED is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients has not been established.

Geriatric Use: Clinical studies of LEVOPHED 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.

LEVOPHED infusions should not be administered into the veins in the leg in elderly patients (see PRECAUTIONS, General).

ADVERSE REACTIONS

The following reactions can occur:

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

Cardiovascular System: Bradycardia, probably as a reflex result of a rise in blood pressure, arrhythmias.

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 LEVOPHED 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 (e.g., hyperthyroid patients) cause severe hypertension with violent headache, photophobia, stabbing retrosternal pain, pallor, intense sweating, and vomiting.

OVERDOSAGE

Overdosage with LEVOPHED may result in headache, severe hypertension, reflex bradycardia, marked increase in peripheral resistance, and decreased cardiac output. In case of accidental overdosage, as evidenced by excessive blood pressure elevation, discontinue LEVOPHED until the condition of the patient stabilizes.

DOSAGE AND ADMINISTRATION

Norepinephrine Bitartrate Injection is a concentrated, potent drug which must be diluted in dextrose containing solutions prior to infusion. An infusion of LEVOPHED should be given into a large vein (see PRECAUTIONS).

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, LEVOPHED can be administered before and concurrently with blood volume replacement.

Diluent: LEVOPHED should be diluted in 5 percent dextrose injection or 5 percent dextrose and sodium chloride injections. These dextrose containing fluids are protection against significant loss of potency due to oxidation. **Administration in saline solution alone is not recommended.** Whole blood or plasma, if indicated to increase blood volume, should be administered separately (for example, by use of a Y-tube and individual containers if given simultaneously).

Average Dosage: Add the content of the vial (4 mg/4 mL) of LEVOPHED to 1,000 mL of a 5 percent dextrose containing solution. Each mL of this dilution contains 4 mcg of the base of LEVOPHED. Give this solution by intravenous infusion. 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. An IV drip chamber or other suitable metering device is essential to permit an accurate estimation of the rate of flow in drops per minute. After observing the response to an initial dose of 2 mL to 3 mL (from 8 mcg to 12 mcg of base) per minute, adjust the rate of flow to establish and maintain a low normal blood pressure (usually 80 mm Hg 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 0.5 mL to 1 mL per minute (from 2 mcg to 4 mcg of base).

High Dosage: Great individual variation occurs in the dose required to attain and maintain an adequate blood pressure. In all cases, dosage of LEVOPHED should be titrated according to the response of the patient. Occasionally much larger or even enormous daily doses (as high as 68 mg base or 17 vials) 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.

Fluid Intake: The degree of dilution 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 solution more dilute than 4 mcg per mL should be used. On the other hand, when large volumes of fluid are clinically undesirable, a concentration greater than 4 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. Infusions of LEVOPHED 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

Infusions of LEVOPHED are 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. [LEVOPHED'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, LEVOPHED is used in the same manner as described under Restoration of Blood Pressure in Acute Hypotensive States.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use, whenever solution and container permit.

Do not use the solution if its color is pinkish or darker than slightly yellow or if it contains a precipitate.

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

HOW SUPPLIED

LEVOPHED (norepinephrine bitartrate) injection, USP, contains the equivalent of 1 mg base of LEVOPHED per 1 mL (4 mg/4 mL).

Supplied as:

Unit of Sale	Concentration

NDC 0409-3375-04 10 in a Carton	4 mg/4 mL (1 mg/mL)

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

Protect from light.

Regitine, trademark, CIBA Pharmaceuticals Company.

Hospira

Distributed by Hospira, Inc., Lake Forest, IL 60045 USA

LAB-1150-1.0

Revised: 03/2018

PRINCIPAL DISPLAY PANEL - 4 mL Vial Label

4 mL Fill in 5 mL Vial
NDC 0409-3375-14
Single dose Fliptop Vial
Rx only

Levophed®
norepinephrine bitartrate
injection, USP
4 mg/4mL (1 mg/mL)

FOR INTRAVENOUS INFUSION ONLY
Warning: Contains Sulfites.
Distributed by Hospira, Inc., Lake Forest, IL 60045 USA

PRINCIPAL DISPLAY PANEL - 4 mL Vial Carton

4 mL
10 Single dose Fliptop Vials
STERILE INJECTION
NDC 0409-3375-04
Contains 10 of NDC 0409-3375-14

Levophed® norepinephrine bitartrate injection, USP

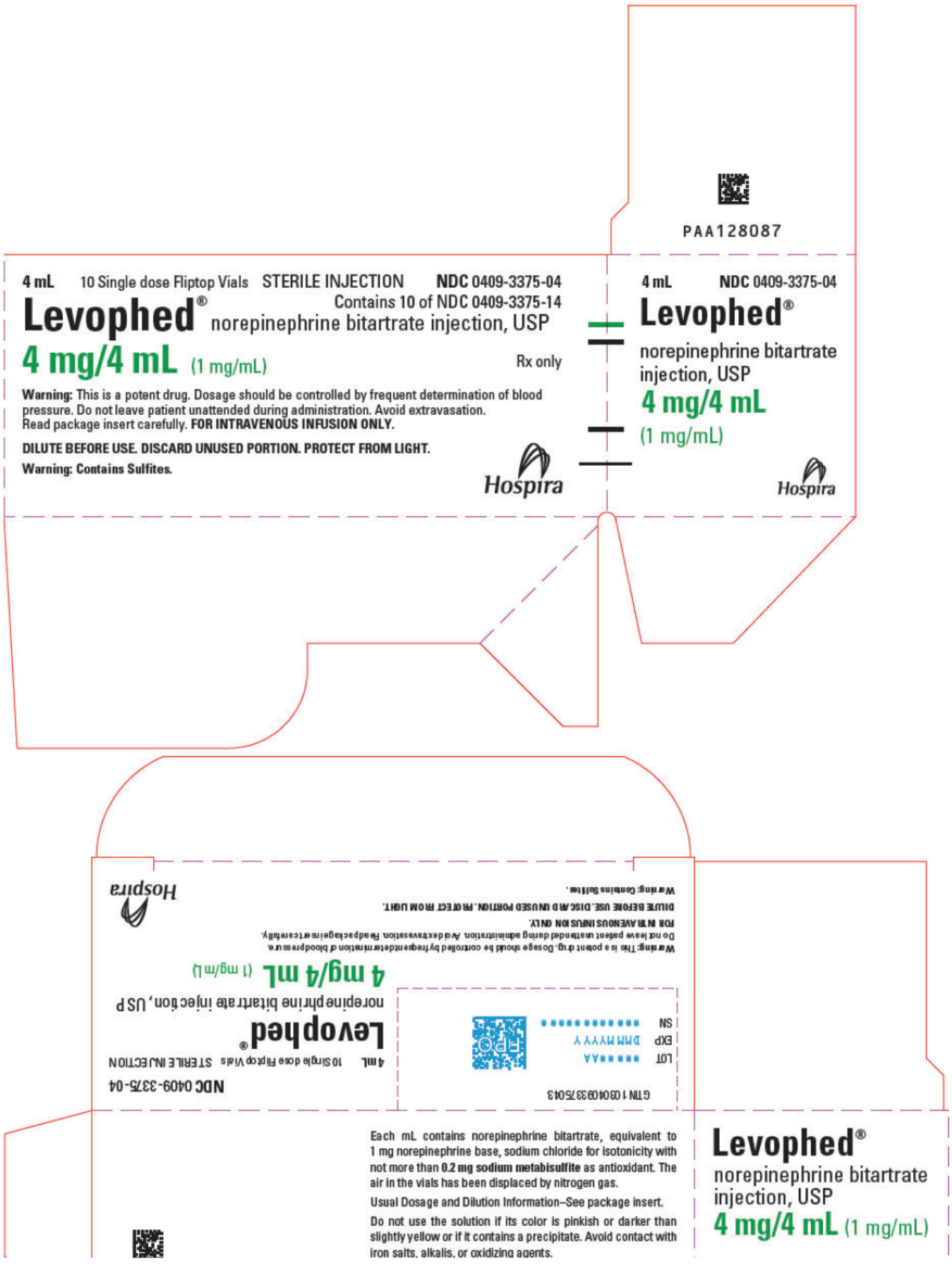
4 mg/4 mL (1 mg/mL)
Rx only

Warning: This is a potent drug. Dosage should be controlled by frequent determination of blood pressure. Do not leave patient unattended during administration. Avoid extravasation.
Read package insert carefully. FOR INTRAVENOUS INFUSION ONLY.

DILUTE BEFORE USE. DISCARD UNUSED PORTION. PROTECT FROM LIGHT.

Warning: Contains Sulfites.

Hospira


PAA128087
4 mL 10 Single dose Fliptop Vials STERILE INJECTION NDC 0409-3375-04
Contains 10 of NDC 0409-3375-14
Levophed®
norepinephrine bitartrate injection, USP
4 mg/4 mL (1 mg/mL)
Rx only
Warning: This is a potent drug. Dosage should be controlled by frequent determination of blood pressure. Do not leave patient unattended during administration. Avoid extravasation.
Read package insert carefully. FOR INTRAVENOUS INFUSION ONLY.
DILUTE BEFORE USE. DISCARD UNUSED PORTION. PROTECT FROM LIGHT.
Warning: Contains Sulfites.
Hospira
4 mL NDC 0409-3375-04
Levophed®
norepinephrine bitartrate injection, USP
4 mg/4 mL
(1 mg/mL)
Hospira
Hospira
Warning: This is a potent drug. Dosage should be controlled by frequent determination of blood pressure.
Do not leave patient unattended during administration. Avoid extravasation. Read package insert carefully.
FOR INTRAVENOUS INFUSION ONLY.
DILUTE BEFORE USE. DISCARD UNUSED PORTION. PROTECT FROM LIGHT.
Warning: Contains Sulfites.
4 mL 10 Single dose Fliptop Vials STERILE INJECTION
NDC 0409-3375-04
Levophed®
norepinephrine bitartrate injection, USP
4 mg/4 mL (1 mg/mL)
GTIN 10304093375043
LOT ******AA
EXP DMM MYYYY
SN **********
Each mL contains norepinephrine bitartrate, equivalent to 1 mg norepinephrine base, sodium chloride for isotonicity with not more than 0.2 mg sodium metabisulfite as antioxidant. The air in the vials has been displaced by nitrogen gas.
Usual Dosage and Dilution Information–See package insert.
Do not use the solution if its color is pinkish or darker than slightly yellow or if it contains a precipitate. Avoid contact with iron salts, alkalis, or oxidizing agents.
Levophed®
norepinephrine bitartrate injection, USP
4 mg/4 mL (1 mg/mL)

LEVOPHED
norepinephrine bitartrate injection, solution, concentrate

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0409-3375
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NOREPINEPHRINE BITARTRATE (UNII: IFY5PE3ZRW) (NOREPINEPHRINE - UNII:X4W3ENH1CV)	NOREPINEPHRINE	1 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
SODIUM METABISULFITE (UNII: 4VON5FNS3C)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0409-3375-04	10 in 1 CARTON	04/27/2009	
1	NDC:0409-3375-14	4 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA007513	04/27/2009	

Labeler – Hospira, Inc. (141588017)

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c4de72a8-2a75-4984-ce90-e4870226dc12

Establishment

Name	Address	ID/FEI	Business Operations
Hospira, Inc.		030606222	ANALYSIS(0409-3375) , LABEL(0409-3375) , MANUFACTURE(0409-3375) , PACK(0409-3375)

Revised: 7/2019

Hospira, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LEVOPHED safely and effectively. See full prescribing information for LEVOPHED.

LEVOPHED® (norepinephrine bitartrate) injection, for intravenous use
Initial U.S. Approval: 1950

---------- INDICATIONS AND USAGE----------
LEVOPHED is a catecholamine indicated for restoration of blood pressure in adult patients with acute hypotensive states. (1)

----------DOSAGE AND ADMINISTRATION----------
- Initial dose of 0.25 mL to 0.375 mL (from 8 mcg to 12 mcg of base) per minute, adjust the rate of flow to establish and maintain a low to normal blood pressure (usually 80 mm Hg to 100 mm Hg systolic) sufficient to maintain the circulation of vital organs. (2.2)
- The average maintenance dose ranges from 0.0625 mL to 0.125 mL per minute (from 2 mcg to 4 mcg of base). (2.2)

---------- DOSAGE FORMS AND STRENGTHS----------
Injection: 4 mg/4 mL (1 mg/mL) norepinephrine base in single-dose glass vial or ampule. (3)

---------- CONTRAINDICATIONS ----------
None. (4)

---------- WARNINGS AND PRECAUTIONS----------
- Tissue Ischemia: Avoid extravasation of LEVOPHED into the tissues, as local necrosis might ensue due to the vasoconstrictive action of the drug. Infuse LEVOPHED into a large vein. To prevent sloughing and necrosis in areas in which extravasation has taken place, the area should be infiltrated as soon as possible with 10 mL to 15 mL of saline solution containing from 5 mg to 10 mg of an adrenergic blocking agent. (5.1)
- Hypotension After Abrupt Discontinuation: Sudden cessation of the infusion rate may result in marked hypotension. Reduce the LEVOPHED infusion rate gradually. (5.2)
- Cardiac Arrhythmias: LEVOPHED may cause arrhythmias. Monitor cardiac function in patients with underlying heart disease. (5.3)
- Allergic Reactions with Sulfite: LEVOPHED contains sodium metabisulfite. Sulfite may cause allergic-type-reactions. (5.4)

---------- 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 Pfizer Inc. at 1-800-438-1985, 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: 6/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Administration

Dilute LEVOPHED prior to use *[see Dosage and Administration (2.3)]*.

Infuse LEVOPHED 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 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 to 4 mcg per minute.

2.3 Preparation of Diluted Solution

Visually inspect LEVOPHED 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 LEVOPHED vial or ampule (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 LEVOPHED solution for up to 24 hours at room temperature [20°C to 25°C (68°F 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, colorless solution in a single-dose amber glass vial.

Injection: 4 mg/4 mL (1 mg/mL norepinephrine base) sterile, colorless solution in a single-dose clear glass ampule.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Tissue Ischemia

Administration of LEVOPHED 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 LEVOPHED *[see Dosage and Administration (2.1)]*. Avoid LEVOPHED 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 LEVOPHED 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 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 LEVOPHED infusion rate while expanding blood volume with intravenous fluids.

5.3 Cardiac Arrhythmias

LEVOPHED 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

LEVOPHED 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 LEVOPHED with monoamine oxidase (MAO) inhibitors or other drugs with MAO-inhibiting properties (e.g., linezolid) can cause severe, prolonged hypertension.

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

7.3 Antidiabetics

LEVOPHED can decrease insulin sensitivity and raise blood glucose. Monitor glucose and consider dosage adjustment of antidiabetic drugs.

7.4 Halogenated Anesthetics

Concomitant use of LEVOPHED 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^3 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 2-4% 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 LEVOPHED 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 LEVOPHED into the veins in the leg in elderly patients *[see Warnings and Precautions (5.1)]*.

10 OVERDOSAGE

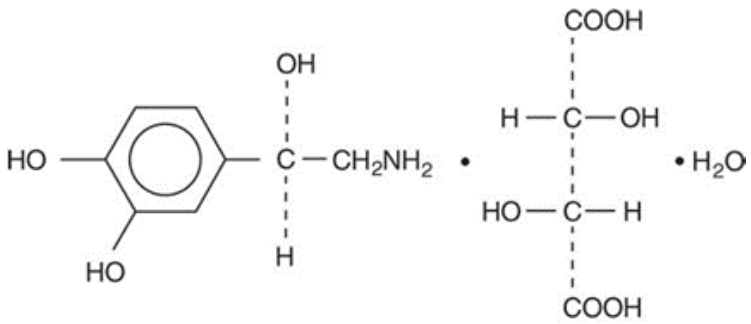
Overdosage with LEVOPHED may result in headache, severe hypertension, reflex bradycardia, marked increase in peripheral resistance, and decreased cardiac output.

In case of overdosage, discontinue LEVOPHED until the condition of the patient stabilizes.

11 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.

LEVOPHED is (-)-α-(aminomethyl)-3,4-dihydroxybenzyl alcohol tartrate (1:1) (salt) monohydrate (molecular weight 337.3 g/mol) and has the following structural formula:



LEVOPHED is supplied in a sterile aqueous solution in the form of the bitartrate salt to be administered by intravenous infusion. Norepinephrine is sparingly soluble in water, very slightly soluble in alcohol and ether, and readily soluble in acids. Each mL contains 1 mg of norepinephrine base (equivalent to 1.89 mg of

norepinephrine bitartrate, anhydrous basis), sodium chloride for isotonicity, not more than 0.2 mg (vials) or 2 mg (ampules) of sodium metabisulfite as an antioxidant, and may contain sodium hydroxide and/or hydrochloric acid for pH adjustment to 3.0-4.5. The air in the containers has been displaced by nitrogen gas.

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 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 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-methoxyl-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

LEVOPHED (norepinephrine bitartrate) injection, USP, is a sterile, colorless 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/4 mL in single-dose amber glass vials and in single-dose clear glass ampules. Supplied as:

Unit of Sale	Concentration
NDC 0409-3375-04 10 vials in a Carton	4 mg/4 mL (1 mg/mL)
NDC 0409-1443-04 10 ampules in a Carton	4 mg/4 mL (1 mg/mL)

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.]

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.pfizer.com.

Distributed by Hospira, Inc., Lake Forest, IL 60045 USA

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