**Levophed**

Norepinephrine Bitartrate

Injection

Reference market : USPI

AfME Markets using same as LPD:  Saudi Arabia

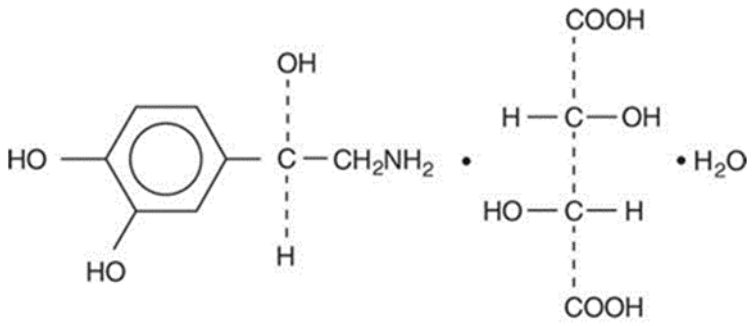
# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Norepinephrine Bitartrate
Injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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 of sodium metabisulfite as an antioxidant. It has a pH of 3.0 to 4.5. The air in the containers has been displaced by nitrogen gas.

## 3. PHARMACEUTICAL FORM

Injection: 4 mg/4 mL (1 mg/mL norepinephrine base) sterile, Colorless or practically colorless liquid; may gradually turn dark on exposure to air and light.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

LEVOPHED is indicated to raise blood pressure in adult patients with severe, acute hypotension.

### 4.2 Posology and method of administration

**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 Special Warnings and Precautions for use (4.4*)]*.

Administration

Dilute LEVOPHED prior to use [See Posology and methods of admistration (4.2)].

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 Special Warnings and Precautions for use (4.4)]. Avoid using a catheter-tie-in technique.

Discontinuation

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

***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.

**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 (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.

**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.

## 4.3 Contraindications

None.

## 4.4 Special warnings and precautions for use

**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 Posology and methods of administration (4.2)]. 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 Posology and methods of administration (4.2)].

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.

**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.

**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.

**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.

**Pediatric Use**

Safety and effectiveness in pediatric patients have 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.
Avoid administration of LEVOPHED into the veins in the leg in elderly patients *[See Special Warnings and Precautions for use (4.4)]*.

## 4.5 Interaction with other medicinal products and other forms of interaction

**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.

**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.

**Antidiabetics**

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

**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.

## 4.6 Fertility, pregnancy and lactation

**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).

**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.

## 4.7 Effects on ability to drive and use machines

Not applicable.

## 4.8 Undesirable effects

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

- Tissue Ischemia [See Special Warnings and Precautions for use (4.4)]
- Hypotension [See Special Warnings and Precautions for use (4.4)]
- Cardiac Arrhythmias [See Special Warnings and Precautions for use (4.4)]

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

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after marketing authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions according to their local country requirements.

**To report side effects:**

National Pharmacovigilance Centre ( NPC )
- Call Center: 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: www.sfda.gov.sa/npc

## 4.9 Overdose

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.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**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).

**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.

**Pharmacokinetic properties**

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.

### 5.3 Preclinical safety data

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium Metabisulfite, Sodium Chloride, Carbon Dioxide, Nitrogen, Water for Injection

### 6.2 Incompatibilities

Not Applicable

### 6.3 Shelf life

18 months.

Do not use Levophed after the expiry date which is stated on the label after EXP:. The expiry date refers to the last day of that month.

### 6.4 Special precautions for storage

Store below 25°C. Protect from light.

### 6.5 Nature and contents of container

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

Supplied as:
vials of 4 mL in boxes of 10.

### 6.6 Special precautions for disposal

Keep out of the sight and reach of children.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 7. FURTHER INFORMATION

**MARKETING AUTHORISATION HOLDER**
Hospira, Inc., Lake Forest, IL 60045, USA

**MANUFACUTRED BY**

HOSPIRA INC., 1776 North Centennial Drive, McPherson, KS 67460-1247, MCPHERSON, United states.

## 8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of latest renewal: 10-07-2018

## 9. DATE OF REVISION OF THE TEXT

October 2020