Ephedrine Sulfate Injection

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

EPHEDRINE SULFATE injection, for intravenous use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE
Ephedrine Sulfate Injection is an alpha- and beta-adrenergic agonist and a norepinephrine-releasing agent that is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia. (1)

DOSAGE AND ADMINISTRATION
Bolus intravenous injection: 5 to 10 mg as needed, not to exceed 50 mg. Dilute before use. See Full Prescribing Information for instructions on administration and preparation for injection. (2)

DOSE FORMS AND STRENGTHS
Injection: 50 mg/mL ephedrine sulfate in an ampule (3)
Injection: 50 mg/mL ephedrine sulfate in a vial (3)

CONTRAINDICATIONS
None (4)

WARNINGS AND PRECAUTIONS
• Pressor Effect with Concomitant Oxytocic Drugs: Pressor effect of sympathomimetic pressor amines is potentiated. (5.1)
• Tolerance and Tachyphylaxis: Repeated administration of ephedrine may cause tachyphylaxis. (5.2)

FULL PRESCRIBING INFORMATION:
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FULL PRESCRIBING INFORMATION
1 INDICATIONS AND USAGE
Ephedrine Sulfate Injection is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia.

2 DOSAGE AND ADMINISTRATION
2.1 General Dosage and Administration Instructions
Ephedrine Sulfate Injection must be diluted before administration as an intravenous bolus to achieve the desired concentration. Dilute with normal saline or 5% dextrose in water.

Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if solution is colored or cloudy, or if it contains particulate matter.

2.2 Dosing for the Treatment of Clinically Important Hypotension in the Setting of Anesthesia
The recommended dosages for the treatment of clinically important hypotension in the setting of anesthesia is an initial dose of 5 to 10 mg administered by intravenous bolus. Administer additional boluses as needed, not to exceed a total dosage of 50 mg.

• Adjust dosage according to the blood pressure goal (i.e., target to effect).

2.3 Prepare a 5 mg/mL Solution for Bolus Intravenous Administration
For bolus intravenous administration, prepare a solution containing a final concentration of 5 mg/mL of Ephedrine Sulfate Injection:
• Withdraw 50 mg (1 mL of 50 mg/mL) of Ephedrine Sulfate Injection and dilute with 9 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection and maintain at room temperature. Discard diluted solution after 24 hours.
• Withdraw an appropriate dose of the 5 mg/mL solution prior to bolus intravenous administration.

3 DOSAGE FORMS AND STRENGTHS
Ephedrine Sulfate Injection, USP is supplied as a 1 mL ampule that contains 50 mg/mL ephedrine sulfate equivalent to 38 mg ephedrine base.

Ephedrine Sulfate Injection, USP is supplied as 1 mL vial that contains 50 mg/mL ephedrine sulfate equivalent to 38 mg ephedrine base.

4 CONTRAINDICATIONS
None

5 WARNINGS AND PRECAUTIONS
5.1 Pressor Effect with Concomitant Oxytocic Drugs
Serious postpartum hypertension has been described in patients who received both a vasopressor (i.e., methoxamine, phenylephrine, ephedrine) and an oxytocic (i.e., methylergonovine, ergonovine) [see Drug Interactions (7)]. Some of these patients experienced a stroke. Carefully monitor the blood pressure of individuals who have received both ephedrine and an oxytocic.

5.2 Tolerance and Tachyphylaxis
Data indicate that repeated administration of ephedrine can result in tachyphylaxis. Clinicians treating anesthesia-induced hypotension with Ephedrine Sulfate Injection should be aware of the possibility of tachyphylaxis and should be prepared with an alternative pressor to mitigate unacceptable responsiveness.

5.3 Risk of Hypertension When Used Prophylactically
When used to prevent hypotension, ephedrine has been associated with an increased incidence of hypertension compared with when ephedrine is used to treat hypotension.

ADVERSE REACTIONS
The following adverse reactions associated with the use of ephedrine were identified in the clinical literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Gastrointestinal disorders: Nausea, vomiting
Cardiac disorders: Tachycardia, palpitations (thumping heart), reactive hyperpnea, arrhythmia, ventricular ejection, R-R variability
Nervous system disorders: Dizziness
Psychiatric disorders: Restlessness

7 DRUG INTERACTIONS

Interactions that Augment the Pressor Effect

<table>
<thead>
<tr>
<th>Oxytocin and oxytoxic drugs</th>
<th>Clinical Impact</th>
<th>Intervention</th>
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Clonidine, propofol, monoamine oxidase inhibitors (MAOIs), atropine

Clinical Impact: These drugs augment the pressor effect of ephedrine.

| Intervention | Carefully monitor the blood pressure of individuals who have received both ephedrine and any of these drugs. |

Interactions that Antagonize the Pressor Effect

<table>
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</tr>
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These drugs antagonize the pressor effect of ephedrine.

| Intervention | Carefully monitor the blood pressure of individuals who have received both ephedrine and any of these drugs. |

Most common adverse reactions during treatment: nausea, vomiting, and tachycardia. (6).

To report SUSPECTED ADVERSE REACTIONS, contact Akorn, Inc. at 1-800-932-5676 or FDA at 1-800-FDA-1088 or http://www.fda.gov/medwatch.
### Carefully monitor the blood pressure of individuals who have received both ephedrine and any of these drugs.

### Giving ephedrine with a cardiac glycoside, such as digitalis, may increase see Clinical Pharmacology (12.3)

### Carefully monitor patients on cardiac glycosides who are also administered Ephedrine may decrease the efficacy of epidural blockade by hastening the regression of sensory anesthesia.

### Monitor patient for worsening symptoms and manage symptoms according to clinical practice. Ephedrine Sulfate Injection may inhibit the neuron blockage produced by guanethidine, resulting in loss of antihypertensive effectiveness. Be aware of this potential interaction. No treatment or other interventions are needed.

### Ephedrine may reduce the onset time of neuromuscular blockade when used for intubation with rocuronium if administered simultaneously with anesthetic induction.

### Be aware of this potential interaction. No treatment or other interventions are needed.

### Ephedrine may make the efficacy of epidural blockade by hastening the regression of sensory anesthesia.

### Monitor patient for worsening symptoms and manage symptoms according to clinical practice.

### Giving ephedrine with a cardiac glycoside, such as digitals, may increase the possibility of arrhythmias.

### Carefully monitor patients on cardiac glycosides who are also administered ephedrine.

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### Clinical Pharmacology

#### 12.1 Mechanism of Action

Ephedrine sulfate is a sympathomimetic amine that directly acts as an agonist at \( \alpha \)- and \( \beta \)-adrenergic receptors and indirectly causes the release of norepinephrine from sympathetic neurons. Pressor effects by direct alpha- and beta-adrenergic receptor activation are mediated by increases in arterial pressures, cardiac output, and peripheral resistance. Indirect adrenergic stimulation is caused by norepinephrine release from sympathetic nerves.

#### 12.2 Pharmacodynamics

Ephedrine stimulates heart rate and cardiac output and variably increases peripheral resistance; as a result, ephedrine usually increases blood pressure. Stimulation of the \( \alpha \)-adrenergic receptors of smooth muscle cells in the bladder base may increase the resistance to the outflow of urine. Activation of \( \beta \)-adrenergic receptors in the lungs promotes bronchodilation.

The overall cardiovascular effect from ephedrine is the result of a balance among \( \alpha \)-1 adrenoceptor-mediated vasoconstriction, \( \beta \)-2 adrenoceptor-mediated vasoconstriction, and \( \beta \)-2 adrenoceptor-mediated vasodilatation. Stimulation of the \( \beta \)-adrenoceptors results in positive inotrope and chronotrope action.

Tachyphylaxis to the pressor effects of ephedrine may occur with repeated administration [see Warnings and Precautions (5.2)].

#### 12.3 Pharmacokinetics

Publications studying pharmacokinetics of oral administration of (-)-ephedrine support that (+)-ephedrine is metabolized into norephedrine. However, the metabolism pathway is unknown. Both the parent drug and the metabolite are excreted in urine. Limited data after IV administration of ephedrine support similar observations of urinary excretion of drug and metabolite. The plasma elimination half-life of ephedrine following oral administration was about 6 hours.

Ephedrine crosses the placental barrier [see Use in Specific Populations (8.1)].

#### 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Two-year feeding studies in rats and mice conducted under the National Toxicology Program (NTP) demonstrated no evidence of carcinogenic potential with ephedrine sulfate at doses up to 10 mg/kg/day and 27 mg/kg/day (approximately 2 times and 3 times the maximum human recommended dose on a mg/m² basis, respectively).

Mutagenesis: Ephedrine sulfate tested negative in the in vitro bacterial reverse mutation assay, the in vitro mouse lymphoma assay, the in vitro sister chromatid exchange, and the in vitro chromosomal aberration assay.

Impairment of Fertility: Studies to evaluate the effect of ephedrine on fertility have not been conducted.

### 14 CLINICAL STUDIES

The evidence for the efficacy of ephedrine injection is derived from the published literature. Increases in blood pressure following administration of ephedrine were observed in 14 studies, including 9 where ephedrine was used in pregnant women undergoing neuraxial anesthesia during Cesarean delivery, 1 study in non-obstetric surgery under neuraxial anesthesia, and 4 studies in patients undergoing surgery under general anesthesia. Ephedrine has been shown to raise systolic and mean blood pressure when administered as a bolus dose following the development of hypotension during anesthesia.

### 15 HOW SUPPLIED/STORAGE AND HANDLING

Ephedrine Sulfate Injection, USP, 50 mg/mL, is a clear, colorless, sterile solution supplied as follows:

- **NDC 17478-415-10**: 1 mL clear, glass ampules supplied in packages of 10
- **NDC 17478-517-01**: 1 mL Single-dose Vials supplied in packages of 10

This container closure is not made with natural rubber latex.

Store at 20° to 25°C (68° to 77°F), with excursions permitted from 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from light. Store in carton until time of use.

For single use only. Discard unused portion.

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**Ephedrine Sulfate Injection**

Manufactured by: Akorn, Inc.

Lake Forest, IL 60045

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