To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Interactions that Augment the Pressor Effect: clonidine, oxytocin and oxytocic drugs, propofol, monoamine oxidase inhibitors (MAOIs), and atropine. Monitor blood pressure. (7)
- Interactions that Antagonize the Pressor Effect: Antagonistic effects with α-adrenergic antagonists, β-adrenergic antagonists, reserpine, quinidine, meperidine. Monitor blood pressure. (7)
- Guanethidine: Ephedrine may inhibit the neuron blockade produced by guanethidine, resulting in loss of antihypertensive effectiveness. Monitor blood pressure and adjust the dosage of pressor accordingly. (7)
- Rocuronium: 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 interacion. No treatment or other interventions are needed. (7)
- Epidural anesthesia: Ephedrine may decrease the efficacy of epidural blockade by hastening the regression of sensory analgesia. Monitor and treat the patient according to clinical practice. (7)
- Theophylline: Concomitant use of ephedrine may increase the frequency of nausea, nervousness, and insomnia. Monitor patient for worsening symptoms and manage symp- tomatic according to clinical practice. (7)
- Cardiac glycosides: 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. (7)

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

2.3 Preparation of 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 Sodium Chloride Injection. Withdraw an appropriate dose of the 5 mg/mL solution prior to bolus intravenous administration.

3 DOSAGE FORMS AND STRENGTHS Ephedrine sulfate injection is available as a single-dose 1 mL vial that contains 50 mg/mL ephedrine sulfate, equivalent to 30 mg ephedrine base.
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Limited published data on the use of ephedrine sulfate are insufficient to determine a drug associated risk of major birth defects or miscarriage. However, there are clinical considerations [see Clinical Considerations]. Animal reproduction studies have not been conducted with ephedrine sulfate. The estimated background risk of 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 clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.
Clinical Considerations
Fetal/neonatal adverse reactions
Cases of potential maternal acidosis in newborns at delivery with maternal ephedrine exposure have been reported in the literature. These reports describe uterine artery pH of 6.7 2 at the time of delivery [see Clinical Pharmacology 12.3]. Monitoring of the neonate for signs and symptoms of metabolic acidosis may be required. Monitoring of infant’s acid-base status is warranted to ensure that an episode of acidosis is acute and reversible.
8.2 Lactation
Risk Summary
Limited published literature reports that ephedrine is present in human milk. However, no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ephedrine sulfate injection and any potential adverse effects on the breastfed child from ephedrine sulfate injection or from the underlying maternal condition.
8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.
8.5 Geriatric Use
Clinical studies of ephedrine 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. However, no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ephedrine sulfate injection and any potential adverse effects on the breastfed child from ephedrine sulfate injection or from the underlying maternal condition.
8.6 Renal Impairment
Ephedrine and its metabolite are excreted in urine. In patients with renal impairment, excretion of ephedrine is likely to be affected with a corresponding increase in renal function. Therefore, elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

10 OVERDOSAGE
Overdose of ephedrine can cause a rapid rise in blood pressure. In the case of an overdose, careful monitoring of blood pressure is recommended. If blood pressure continues to rise to an unacceptable level, parenteral antihypertensive agents can be administered at the discretion of the clinician.

11 DESCRIPTION
Ephedrine sulfate is an alpha- and beta-adrenergic agonist and a norepinephrine-releasing agent. Ephedrine sulfate injection, USP is a clear, colorless, sterile solution for intravenous injection. Each mL contains ephedrine sulfate 50 mg in water for injection. The pH of the drug product is 6.5 to 7.1. The drug product must be diluted before intravenous administration. The chemical name of ephedrine sulfate is (1R,2S)-(+) -2-methylamine-1-phenylpropan-1-ol sulfate (2:1) (salt), its molecular weight is 428.54.

The structural formula is:

Ephedrine sulfate darkens on exposure to light. It is freely soluble in water and ethanol, very slightly soluble in chloroform, and practically insoluble in ether.

Ephedrine Sulfate Injection, USP, 50 mg/mL, is supplied as follows:

<table>
<thead>
<tr>
<th>NDC</th>
<th>Strength</th>
<th>How Supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>74203-216-25</td>
<td>50 mg/mL</td>
<td>1 mL clear glass vial for single use (supplied in packages of 25)</td>
</tr>
</tbody>
</table>

Vial stoppers are not manufactured with natural rubber latex.

Store ephedrine sulfate injection, 50 mg/mL, at 20° to 25°C (68° to 77°F), with excursions permitted to 15°C to 30°C (59°F 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.

Distributed by:
Par Pharmaceutical
Chestnut Ridge, New York 10977

801/17
OS216J-01-09-02
3003652A

Ephedrine is known to be metabolized primarily in the liver. Ephedrine is metabolized to both active and inactive metabolites. The active metabolite of ephedrine is known to be norephedrine. This metabolite is known to have similar activities to ephedrine. The inactive metabolite is known to be metabolized to norephedrine. The metabolism of ephedrine is known to be mediated by CYP2D6. The metabolism of ephedrine is known to be mediated by CYP2D6. The metabolism of ephedrine is known to be mediated by CYP2D6. The metabolism of ephedrine is known to be mediated by CYP2D6.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Ephedrine is a sympathomimetic amine that directly acts as an agonist at α- and β- 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 increases blood pressure. Stimulation of the α- and β-adrenergic receptors of smooth muscle cells in the bladder base may increase the resistance to the outflow of urine. Activation of β-adrenergic receptors in the lungs promotes bronchodilation. The overall cardiovascular effect from ephedrine is the result of a balance among α-1 adrenoceptor-mediated vasoconstriction, α-2 adrenoceptor-mediated vasoconstriction, and β-2 adrenoceptor-mediated vasodilation. Stimulation of the β-1 adrenoceptors results in positive inotrope and chronotropic 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 to 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 sulfate support similar observations of urinary excretion of drug and metabolite. The plasma elimination half-life of ephedrine following oral administration was about 9 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-neuraxial 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.