

# EPHEDRINE SULFATE - ephedrine sulfate injection

## Gland Pharma Limited

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### 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

- This is a pre-mixed formulation. Do not dilute before administration. (2)
- 5 mg to 10 mg administered by intravenous bolus. Additional boluses as needed, not to exceed a total dose of 50 mg. (2)

### DOSAGE FORMS AND STRENGTHS

Injection: 50 mg/10 mL ephedrine sulfate, equivalent to 38 mg/10 mL ephedrine base in a single-dose vial (5 mg/mL ephedrine sulfate, equivalent to 3.8 mg/mL ephedrine base). (3)

### CONTRAINDICATIONS

None (4)

### WARNINGS AND PRECAUTIONS

- Pressor Effects with Concomitant Use with Oxytocic Drugs: Pressor effect of sympathomimetic pressor amines is potentiated (5.1)
- Tachyphylaxis and Tolerance: Repeated administration of ephedrine sulfate injection may cause tachyphylaxis (5.2)

### ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS contact Gland Pharma Limited at 609-250-7990 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Interactions that Augment 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  $\alpha$ -adrenergic antagonists,  $\beta$ -adrenergic antagonists, reserpine, quinidine, mephentermine. Monitor blood pressure. (7)
- Guanethidine: Ephedrine sulfate injection may inhibit the neuron blockage produced by guanethidine, resulting in loss of antihypertensive effectiveness. Monitor blood pressure and adjust the dosage of pressor accordingly.
- Rocuronium: Ephedrine sulfate injection 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.
- Epidural anesthesia: Ephedrine sulfate injection may decrease the efficacy of epidural blockade by hastening the regression of sensory analgesia. Monitor and treat the patient according to clinical practice.
- Theophylline: Concomitant use of ephedrine sulfate injection may increase the frequency of nausea, nervousness, and insomnia. Monitor patient for worsening symptoms and manage symptoms according to clinical practice
- Cardiac glycosides: Giving ephedrine sulfate injection with a cardiac glycoside, such as digitalis, may increase the possibility of arrhythmias. Carefully monitor patients on cardiac glycosides who are also administered ephedrine sulfate injection.

Revised: 6/2024

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## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

## **2 DOSAGE AND ADMINISTRATION**

2.1 General Dosage and Administration Instructions

2.2 Dosing for the Treatment of Clinically Important Hypotension in the Setting of Anesthesia

## **3 DOSAGE FORMS AND STRENGTHS**

## **4 CONTRAINDICATIONS**

## **5 WARNINGS AND PRECAUTIONS**

5.1 Pressor Effect with Concomitant Oxytocic Drugs

5.2 Tolerance and Tachyphylaxis

5.3 Risk of Hypertension When Used Prophylactically

## **6 ADVERSE REACTIONS**

## **7 DRUG INTERACTIONS**

## **8 USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

## **10 OVERDOSAGE**

## **11 DESCRIPTION**

## **12 CLINICAL PHARMACOLOGY**

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

## **13 NONCLINICAL TOXICOLOGY**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

## **14 CLINICAL STUDIES**

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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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**

- This is a premixed formulation. Do not dilute prior to use.
- Discard any unused portion of Ephedrine sulfate injection.
- Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Ephedrine sulfate injection is a clear, colorless solution. Do not use if the solution is not clear or if particulate matter is present

#### **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 mg 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., titrate to effect).

### 3 DOSAGE FORMS AND STRENGTHS

Ephedrine Sulfate Injection, USP is a clear, colorless solution available as:

- A single-dose vial that contains 50 mg/10 mL (5 mg/mL) ephedrine sulfate, equivalent to 38 mg/10 mL (3.8 mg/mL) 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 sulfate injection and an oxytocic.

#### 5.2 Tolerance and Tachyphylaxis

Data indicate that repeated administration of ephedrine can result in tachyphylaxis. Be aware of this possibility when treating anesthesia-induced hypotension with ephedrine sulfate injection and 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.

### 6 ADVERSE REACTIONS

The following adverse reactions associated with the use of ephedrine sulfate were identified in the 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 hypertension, bradycardia, ventricular ectopics, R-R variability

Nervous system disorders: Dizziness

Psychiatric disorders: Restlessness

### 7 DRUG INTERACTIONS

Interactions that Augment the Pressor Effect	
<b>Oxytocin and oxytocic drugs</b>	
<i>Clinical Impact:</i>	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). Some of these patients experienced a stroke.
<i>Intervention:</i>	Carefully monitor the blood pressure of individuals who have received both ephedrine sulfate injection and an oxytocic.
<b>Clonidine, propofol, monoamine oxidase inhibitors (MAOIs), atropine</b>	
<i>Clinical Impact:</i>	These drugs augment the pressor effect of ephedrine.
<i>Intervention:</i>	Carefully monitor the blood pressure of individuals who have received both ephedrine sulfate injection and any of these drugs.
<b>Drugs that Antagonize the Pressor Effect</b>	
<b><math>\alpha</math>-adrenergic antagonists, <math>\beta</math>-adrenergic receptor antagonists, reserpine, quinidine, mephentermine</b>	
<i>Clinical Impact:</i>	These drugs antagonize the pressor effect of ephedrine.
<i>Intervention:</i>	Carefully monitor the blood pressure of individuals who have received both ephedrine sulfate injection and any of these drugs.
<b>Other Drug Interactions</b>	
<b>Guanethidine</b>	
<i>Clinical Impact:</i>	Ephedrine sulfate injection may inhibit the neuron blockage produced by guanethidine, resulting in loss of antihypertensive effectiveness.
<i>Intervention:</i>	Clinician should monitor patient for blood pressor response and adjust the dosage or choice of pressor accordingly.
<b>Rocuronium</b>	
<i>Clinical Impact:</i>	Ephedrine sulfate injection may reduce the onset time of neuromuscular blockade when used for intubation with rocuronium if administered simultaneously with anesthetic induction.
<i>Intervention:</i>	Be aware of this potential interaction. No treatment or other interventions are needed.
<b>Epidural anesthesia</b>	
<i>Clinical Impact:</i>	Ephedrine sulfate injection may decrease the efficacy of epidural blockade by hastening the regression of sensory analgesia.
<i>Intervention:</i>	Monitor and treat the patient according to clinical practice.
<b>Theophylline</b>	
<i>Clinical Impact:</i>	Concomitant use of ephedrine sulfate injection may increase the frequency of nausea, nervousness, and insomnia.
<i>Intervention:</i>	Monitor patient for worsening symptoms and manage symptoms according to clinical practice.
<b>Cardiac glycosides</b>	
<i>Clinical Impact:</i>	Giving ephedrine sulfate injection with a cardiac glycoside, such as digitalis, may increase the possibility of arrhythmias.
<i>Intervention:</i>	Carefully monitor patients on cardiac glycosides who are also administered ephedrine.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Available data from randomized studies, case series, and reports of ephedrine sulfate use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. However, there are clinical considerations due to underlying conditions

[see *Clinical Considerations*]. In animal reproduction studies, decreased fetal survival and

fetal body weights were observed in the presence of maternal toxicity after normotensive pregnant rats were administered 60 mg/kg intravenous ephedrine sulfate (12 times the maximum recommended human dose (MRHD) of 50 mg/day). No malformations or embryofetal adverse effects were observed when pregnant rats or rabbits were treated with intravenous bolus doses of ephedrine sulfate during organogenesis at doses 1.9 and 7.7 times the MRHD, respectively [See data]. 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

### *Disease-associated maternal and/or embryofetal risk*

Untreated hypotension associated with spinal anesthesia for cesarean section is associated with an increase in maternal nausea and vomiting. A decrease in uterine blood flow due to maternal hypotension may result in fetal bradycardia and acidosis.

### *Fetal/Neonatal Adverse Reactions*

Cases of potential metabolic acidosis in newborns at delivery with maternal ephedrine exposure have been reported in the literature. These reports describe umbilical artery pH of  $\leq 7.2$  at the time of delivery [see *Clinical Pharmacology 12.3*]. Monitoring of the newborn 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.

## Data

### *Animal Data*

Decreased fetal body weights were observed when pregnant rats were administered intravenous bolus doses of 60 mg/kg ephedrine sulfate (12 times the maximum recommended human dose (MRHD) of 50 mg based on body surface area) from Gestation Day 6 to 17. This dose was associated with evidence of maternal toxicity (decreased body weight of dams and abnormal head movements). No malformations or fetal deaths were noted at this dose. No effects on fetal body weight were noted at 10 mg/kg (1.9 times the MRHD of 50 mg).

No evidence of malformations or embryo-fetal toxicity were noted in pregnant rabbits administered intravenous bolus doses up to 20 mg/kg ephedrine sulfate (7.7 times the maximum recommended human dose (MRHD) of 50 mg based on body surface area) from Gestation Day 6 to 20. This dose was associated with expected pharmacological maternal effects (increased respiration rate, dilated pupils, piloerection).

Decreased fetal survival and body weights in the presence of maternal toxicity (increased mortality) were noted when pregnant dams were administered intravenous bolus doses of 60 mg/kg epinephrine sulfate (approximately 12 times the MRHD based on body surface area) from GD 6 through Lactation Day 20. No adverse effects were noted at 10 mg/kg (1.9 times the MRHD).

## **8.2 Lactation**

### Risk Summary

A single published case report indicates 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 of ephedrine sulfate injection in pediatric patients have not been established.

### Animal Toxicity Data

In a study in which juvenile rats were administered intravenous bolus doses of 2, 10, or 60 mg/kg ephedrine sulfate daily from Postnatal Day 35 to 56, an increased incidence of mortality was noted at the high dose of 60 mg/kg. The no-adverse-effect level was 10 mg/kg (approximately 1.9 times a maximum daily dose of 50 mg in a 60 kg person based on body surface area).

### **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, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because 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.

### **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 elimination half-life, which will lead to slow elimination of ephedrine and consequently prolonged pharmacological effect and potentially adverse reactions. Monitor patients with renal impairment carefully after the initial bolus dose for adverse events.

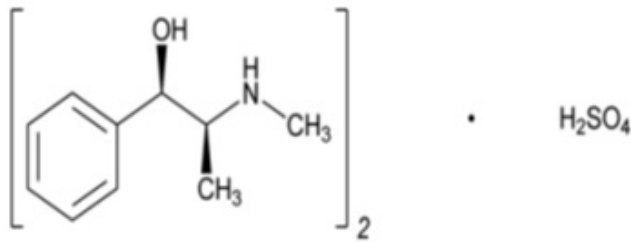
## **10 OVERDOSAGE**

Overdose of ephedrine sulfate injection 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 a sympathomimetic amine. Ephedrine Sulfate Injection, USP is a clear, colorless, sterile solution for intravenous injection. The chemical name of

ephedrine sulfate is benzenemethanol,  $\alpha$ -[1-(methylamino) ethyl]-, [R-(R\*, S\*)]-, sulfate (2:1) (salt), and the molecular weight is 428.5 g/mol. Its structural formula is depicted below:



Ephedrine sulfate is freely soluble in water and ethanol, very slightly soluble in chloroform, and practically insoluble in ether. Each mL contains ephedrine sulfate, USP 5 mg (equivalent to 3.8 mg ephedrine base), 0.9% sodium chloride, USP in water for injection. The pH range is 4.5 to 7.0.

## 12 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  $\beta$ -1 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/m<sup>2</sup> 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, the *in vitro* chromosomal aberration assay, and the *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility: There was no impact on fertility or early embryonic development in a study in which male rats were administered intravenous bolus doses of 0, 2, 10, or 60 mg/kg ephedrine sulfate (up to 12 times the maximum recommended human dose of 50 mg based on body surface area) for 28 days prior to mating and through gestation and females were treated for 14 days prior to mating through Gestation Day 7.

## 14 CLINICAL STUDIES

The evidence for the efficacy of ephedrine sulfate 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.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Ephedrine sulfate injection, USP is a clear, colorless solution available as a single-dose vial that contains 50 mg/10 mL (5 mg/mL) ephedrine sulfate, equivalent to 38 mg/10 mL (3.8 mg/mL) ephedrine base and is supplied as follows:

<b>NDC</b>	<b>Presentation</b>
68083-610-10	10 mL clear glass, single-dose vials; strength 50 mg/10 mL (5 mg/mL) packaged in a carton of 10

Ephedrine Sulfate Injection, USP 50 mg/10 mL (5 mg/mL) is not made with natural rubber latex.

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].

Store in carton until time of use. For single dose only. Discard unused portion.

Manufactured by:

**Gland Pharma Limited**



D.P.Pally, Dundigal Post  
Hyderabad-500 043, India.

Revised: 06/2024

## PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

### Carton Label

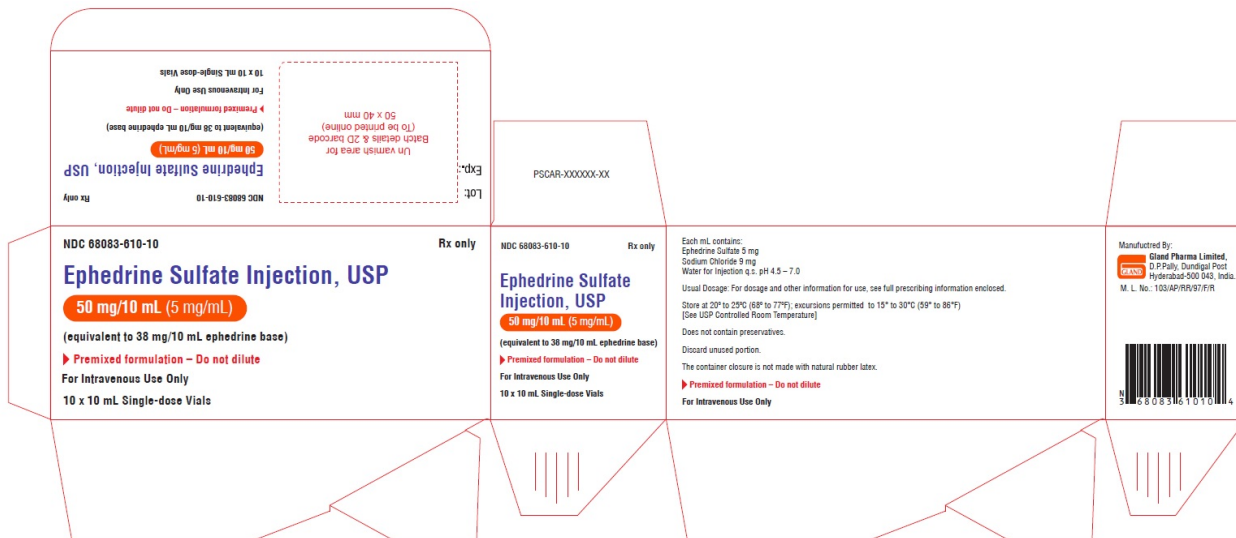
NDC 68083-610-10 **Rx only**  
**Ephedrine Sulfate Injection, USP**

**50 mg/10 mL** (5 mg/mL)

(equivalent to 38 mg/10 mL ephedrine base)  
Premixed formulation – Do not dilute

For Intravenous Use Only

10 x 10 mL Single-dose Vials



### Container Label

NDC 68083-610-01 **Rx only**  
**Ephedrine Sulfate Injection, USP**

**50 mg/10 mL** (5 mg/mL)

(equivalent to 38 mg/10 mL ephedrine base)  
Premixed formulation – Do not dilute

For Intravenous Use Only

10 mL Single-dose Vial

NDC 68083-610-01

Rx only

# Ephedrine Sulfate Injection, USP

**50 mg/10 mL (5 mg/mL)**

(equivalent to 38 mg/10 mL ephedrine base)

**Premixed formulation – Do not dilute****For Intravenous Use Only****10 mL Single-dose Vial**
 Store at 20° to 25°C (68° to 77°F)  
 [See USP Controlled Room Temperature].

 Usual Dosage: See Full Prescribing  
 Information

Does not contain preservative.

Discard unused portion.



Manufactured By:


**Gland Pharma Limited,**  
 D.P.Pally, Dundigal Post  
 Hyderabad-500 043, India.

M. L. No.: 103/AP/RR/97/F/R

1311XXXXXX-XX

Lot:

Exp.:

 Un Varnish Area  
 18 x 12 mm

## EPHEDRINE SULFATE

ephedrine sulfate injection

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:68083-610
<b>Route of Administration</b>	INTRAVENOUS		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>EPHEDRINE SULFATE</b> (UNII: U6X61U5ZEG) (EPHEDRINE - UNII:GN83C131XS)	EPHEDRINE SULFATE	5 mg in 1 mL

### Inactive Ingredients

Ingredient Name	Strength
<b>SODIUM CHLORIDE</b> (UNII: 451W47IQ8X)	
<b>WATER</b> (UNII: 059QF0K0OR)	

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68083-610-10	10 in 1 CARTON	01/16/2025	
1		10 mL in 1 VIAL; Type 0: Not a Combination Product		

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA218211	01/16/2025	

**Labeler - Gland Pharma Limited (918601238)**

## Establishment

Name	Address	ID/FEI	Business Operations
GLAND PHARMA LIMITED		918601238	ANALYSIS(68083-610) , LABEL(68083-610) , MANUFACTURE(68083-610) , PACK(68083-610)

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Gland Pharma Limited