HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use REZIPRES® safely and effectively. See full prescribing information for REZIPRES®.

REZIPRES® injection for intravenous use

Initial U.S. Approval: 2016

INDICATIONS AND USAGE

REZIPRES® 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

- REZIPRES® is injected intravenously as a bolus.
- REZIPRES® 47 mg/mL must be diluted before administration; (2)
- REZIPRES® 9.4 mg/mL can be either used as provided or it can be diluted; (2)
- REZIPRES® 4.7 mg/mL is a premixed formulation. Do not dilute prior to use; (2)
- Bolus intravenous injection: 4.7 mg to 9.4 mg as needed, not to exceed 47 mg. (2)

DOSAGE FORMS AND STRENGTHS

- Injection: 47 mg/mL ephedrine hydrochloride (equivalent to 38 mg ephedrine base) in single-dose ampule. (3)
- Injection: 47 mg/5 mL (9.4 mg/mL) ephedrine hydrochloride (equivalent to 7.7 mg ephedrine base) in single-dose ampule. (3)
- Injection: 23.5 mg/5 mL (4.7 mg/mL) ephedrine hydrochloride (equivalent to 3.8 mg ephedrine base) in single-dose ampule. (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 REZIPRES® may cause tachyphylaxis. (5.2)

ADVERSE REACTION

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

To report SUSPECTED ADVERSE REACTIONS, contact Eton Pharmaceuticals at 1-888-450-0568 or FDA at 1-800-FDA-1088 or *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. (7.1)
- Interactions that Antagonize the Pressor Effect: Antagonistic effects with α-adrenergic antagonists, β-adrenergic antagonists, reserpine, quinidine, mephentermine. Monitor blood pressure. (7.2)
- Guanethidine: REZIPRES® may inhibit the neuron blockage produced by guanethidine, resulting in loss of antihypertensive effectiveness. Monitor blood pressure and adjust the dosage of pressor accordingly. (7.3)
- Rocuronium: REZIPRES® 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. (7.3)
- Epidural anesthesia: REZIPRES® may decrease the efficacy of epidural blockade by hastening the regression of sensory analgesia. Monitor and treat the patient

  according to clinical practice. (7.3)
- Theophylline: Concomitant use of REZIPRES® may increase the frequency of nausea, nervousness, and insomnia. Monitor patient for worsening symptoms and manage symptoms according to clinical practice. (7.3)
- Cardiac glycosides: Giving REZIPRES® with a cardiac glycoside, such as digitalis, may increase the possibility of arrhythmias. Carefully monitor patients on cardiac glycosides who are also administered REZIPRES®. (7.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

REZIPRES® 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

REZIPRES® 47 mg/mL must be diluted before administration as an intravenous bolus to achieve the desired concentration. Dilute with normal saline or 5% dextrose in water.

REZIPRES® 9.4 mg/mL can be either used as provided at 9.4 mg/mL or it can be diluted, with 5% Dextrose Injection or 0.9% Sodium Chloride Injection, to achieve the desired concentration, before administration as an intravenous bolus.

REZIPRES® 4.7 mg/mL is a premixed formulation. Do not dilute prior to use.

- REZIPRES® is a clear, colorless solution. Discard any unused portion.
- Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution is not clear or if particulate matter is present.

2.2 Dosing for 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 4.7 mg to 9.4 mg administered by intravenous bolus. Administer additional boluses as needed, not to exceed a total dosage of 47 mg.

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

2.3 Prepare a 4.7 mg/mL Solution for Bolus Intravenous Administration

REZIPRES® 47 mg/mL

- Withdraw 47 mg (1 mL of 47 mg/mL) of REZIPRES® 47 mg/mL and dilute with 9 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection.
- Withdraw an appropriate dose of the 4.7 mg/mL solution prior to bolus intravenous administration.

REZIPRES® 9.4 mg/mL

- Withdraw 5 mL of REZIPRES® 9.4 mg/mL and dilute with 5 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection.
- Withdraw an appropriate dose of the 4.7 mg/mL solution prior to bolus intravenous administration.

2.4 Direct Administration of 9.4 mg/mL Solution for Bolus Intravenous

REZIPRES® if used as provided at 9.4 mg/ml:

- withdraw an appropriate dose of REZIPRES® 9.4 mg/mL solution prior to bolus intravenous administration.

3 DOSAGE FORMS AND STRENGTHS

REZIPRES® 47 mg/mL

REZIPRES® 47 mg/mL is a clear, colorless solution available in a one point cut clear colorless glass 2 mL single-dose ampule that contains 1 mL of solution, corresponding to 47 mg of ephedrine hydrochloride, equivalent to 38 mg of ephedrine base.

REZIPRES® 47 mg/5 mL (9.4 mg/mL)

REZIPRES® 47 mg/5mL is a clear, colorless solution available in a one point cut clear colorless glass single-dose ampule equivalent to 38 mg/5 mL ephedrine base (9.4 mg/mL ephedrine hydrochloride, equivalent to 7.7 mg/mL ephedrine base)

REZIPRES® 23.5 mg/5 mL (4.7 mg/mL)

REZIPRES® 23.5 mg/ 5mL is a clear, colorless solution, available in a one point cut clear colorless glass single-dose ampule, equivalent to 19 mg/5 mL of ephedrine base (4.7 mg/mL ephedrine hydrochloride, equivalent to 3.8 mg/mL of 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 REZIPRES® 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 REZIPRES® 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.

6 ADVERSE REACTIONS

The following adverse reactions associated with the use of ephedrine 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 Pressor Effect	
Oxytocin and oxytocic drugs	
Clinical Impact:	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.
Intervention:	Carefully monitor the blood pressure of individuals who have received both REZIPRES® and an oxytocic.
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 REZIPRES® and any of these drugs.

Interactions that Antagonize the Pressor Effect	
Clinical Impact:	These drugs antagonize the pressor effect of ephedrine.
Intervention:	Carefully monitor the blood pressure of individuals who have received both REZIPRES® and any of these drugs.
Examples:	α-adrenergic antagonists, β-adrenergic receptor antagonists, reserpine, quinidine, mephentermine.

Other Drug Interaction	
Guanethidine	
Clinical Impact:	REZIPRES® may inhibit the neuron blockage produced by guanethidine, resulting in loss of antihypertensive effectiveness
Intervention:	Clinician should monitor patient for blood pressor response and adjust the dosage or choice of pressor accordingly.
Rocuronium	
Clinical Impact:	REZIPRES® may reduce the onset time of neuromuscular blockade when used for intubation with rocuronium if administered simultaneously with anesthetic induction.
Intervention	Be aware of this potential interaction. No treatment or other interventions are needed.
Epidural anesthesia	
Clinical Impact:	REZIPRES® may decrease the efficacy of epidural blockade by hastening the regression of sensory analgesia
Intervention:	Monitor and treat the patient according to clinical practice.
Theophylline	
Clinical Impact:	Concomitant use of REZIPRES® may increase the frequency of nausea, nervousness, and insomnia.
Intervention:	Monitor patient for worsening symptoms and manage symptoms according to clinical practice.
Cardiac glycosides	
Clinical Impact:	Giving REZIPRES® with a cardiac glycoside, such as digitalis, may increase the possibility of arrhythmias.

Intervention:	Carefully monitor patients on cardiac glycosides who are also administered REZIPRES®.

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 *[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 47 mg/day of ephedrine hydrochloride). 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 are 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 ≤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) based on body surface area) from Gestation Day 6-17. 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).

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 MRHD

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 REZIPRES® and any potential adverse effects on the breastfed child from REZIPRES® or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness 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 47 mg ephedrine hydrochloride 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

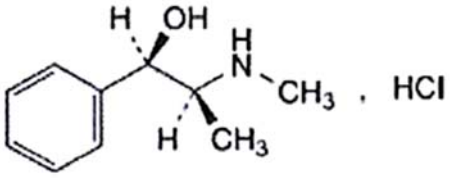
Ephedrine and its metabolite are excreted in urine. In patients with renal impairment, excretion of ephedrine is likely to be affected with a corresponding increase in elimination half-life, which will lead to slow elimination of ephedrine and consequently prolonged pharmacological effect and potentially adverse reactions. Monitor patients with renal impairment carefully after the initial bolus dose for adverse events.

10 OVERDOSAGE

Overdose of REZIPRES® 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

REZIPRES® is an alpha- and beta-adrenergic agonist and a norepinephrine-releasing agent. The chemical name of ephedrine hydrochloride is (1R,2S)-(-)-2-methylamino-1-phenyl-1-propanol hydrochloride, and the molecular weight is 201.7 g/mol. Its structural formula is depicted below:



Ephedrine hydrochloride is freely soluble in water, soluble in ethanol and stable in aqueous solution.

REZIPRES® 47 mg/mL

REZIPRES® 47 mg/ml is a clear, colorless, sterile solution for intravenous injection. It must be diluted before intravenous administration.

Each mL contains ephedrine hydrochloride 47 mg (equivalent to 38 mg ephedrine base) in water for injection. The pH is adjusted with sodium hydroxide and hydrochloric acid if necessary. The pH range is 5.0 to 6.5.

REZIPRES® 47 mg/5 mL (9.4 mg/mL)

REZIPRES® 9.4 mg/ml is a clear, colorless, sterile solution for intravenous injection. It can either be used as provided or diluted at 4.7 mg/mL, before intravenous administration.

Each mL contains ephedrine hydrochloride 9.4 mg (equivalent to 7.7 mg ephedrine base) and sodium chloride 6.0 mg in water for injection. The pH is adjusted with sodium hydroxide and hydrochloric acid if necessary. The pH range is 5.0 to 6.5.

REZIPRES® 23.5 mg/5 mL (4.7 mg/mL)

REZIPRES® 4.7 mg/ml is a clear, colorless, sterile solution for intravenous injection. It must not be diluted prior to use.

Each mL contains ephedrine hydrochloride 4.7 mg (equivalent to 3.8 mg ephedrine base) and sodium chloride 7.5 mg in water for injection. The pH is adjusted with sodium hydroxide and hydrochloric acid if necessary. The pH range is 5.0 to 6.5.

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 usually increases blood pressure. Stimulation of the α-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, β-2 adrenoceptor-mediated vasoconstriction, and β-2 adrenoceptor-mediated vasodilatation. Stimulation of the β-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^2 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 MRHD of 47 mg of ephedrine hydrochloride 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 REZIPRES® 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

REZIPRES® is a clear, colorless solution supplied as follows:

NDC Number	Strength	Presentation
71863-212-01	47 mg/ml	2 mL clear glass, single-dose ampule filled with 1 mL
71863-212-02		2 mL ampules filled with 1 mL packaged in a carton of 10
71863-211-05	47 mg/5 mL (9.4 mg/ml)	5 mL clear glass, single-dose ampule
71863-211-06		5 mL ampules packaged in a carton of 10
71863-210-05	23.5 mg/5 mL (4.7 mg/ml)	5 mL clear glass, single-dose ampule
71863-210-06		5 mL ampules packaged in a carton of 10

Store REZIPRES® 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].
For single-dose only. The diluted solution should not be held for more than 4 hours at room temperature or for more than 24 hours under refrigerated conditions. Discard any unused portion.

17 PATIENT COUNSELING INFORMATION

If applicable, inform patient, family member, or caregiver that certain medical conditions and medications might influence how REZIPRES® works.

Manufactured for:
Eton Pharmaceuticals, Inc.
Deer Park, IL 60010
USA

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