

ADRENALIN- epinephrine injection

Par Pharmaceutical, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ADRENALIN (epinephrine injection) 1 mg/mL, for intramuscular, subcutaneous, and intravenous use
Initial U.S. Approval: 1939

INDICATIONS AND USAGE

Adrenalin[®] is a non-selective alpha and beta adrenergic agonist indicated for:

- Emergency treatment of allergic reactions (Type 1), including anaphylaxis (1.1)
- To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock (1.2)

DOSAGE AND ADMINISTRATION

- Anaphylaxis:
 - *Adults and Children 30 kg (66 lbs) or more:* 0.3 mg to 0.5 mg (0.3 mL to 0.5 mL) intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary (2.2)
 - *Children 30 kg (66 lbs) or less:* 0.01 mg/kg (0.01 mL/kg), up to 0.3 mg (0.3 mL), intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary (2.2)
- Hypotension associated with septic shock:
 - Dilute epinephrine in dextrose solution prior to infusion (2.3)
 - Infuse epinephrine into a large vein (2.3)
 - Intravenous infusion rate of 0.05 mcg/kg/min to 2 mcg/kg/min, titrated to achieve desired mean arterial pressure (2.3)
 - Wean gradually (2.3)
 - See Full Prescribing Information for instructions on dilution and administration of the injection.

DOSAGE FORMS AND STRENGTHS

Injection: 30 mg/30 mL (1 mg/mL) multiple dose vial (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Do not inject into buttocks, digits, hands, or feet (5.1)
- Avoid extravasation into tissues, which can cause local necrosis (5.3)
- May aggravate angina pectoris or produce ventricular arrhythmias (5.7)

ADVERSE REACTIONS

Common adverse reactions to systemically administered epinephrine include anxiety, tremor, weakness, dizziness, sweating, palpitations and pallor (6)

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

- Drugs that counter the pressor effects of epinephrine include alpha blockers, vasodilators such as nitrates, diuretics, antihypertensives and ergot alkaloids. (7.1)
- Drugs that potentiate the effects of epinephrine include sympathomimetics, beta blockers, tricyclic antidepressants, MAO inhibitors, COMT inhibitors, clonidine, doxapram, oxytocin, levothyroxine sodium, quinidine and certain antihistamines. (7.2)
- Drugs that increase the arrhythmogenic potential of epinephrine include beta blockers, cyclopropane and halogenated hydrocarbon anesthetics, antihistamines, exogenous thyroid hormones, diuretics, and cardiac glycosides. Observe for development of cardiac arrhythmias. (7.3)
- Potassium-depleting drugs, including corticosteroids, diuretics, and theophylline, potentiate the hypokalemic effects of epinephrine. (7.4)

USE IN SPECIFIC POPULATIONS

- Elderly patients and pregnant women may be at greater risk of developing adverse reactions when epinephrine is administered parenterally (8.1,8.5)
- Pregnancy: May cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Anaphylaxis

Emergency treatment of allergic reactions (Type I), including anaphylaxis, which may result from insect stings or bites, foods, drugs, sera, diagnostic testing substances and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.

1.2 Hypotension associated with Septic Shock

Adrenalin is indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

Inspect visually for particulate matter and discoloration prior to administration; solution should be clear and colorless. Do not use if the solution is colored or cloudy, or if it contains particulate matter.

2.2 Anaphylaxis

Inject Adrenalin intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. When administering to a child, to minimize the risk of injection related injury, hold the leg firmly in place and limit movement prior to and during an injection. The injection may be repeated every 5 to 10 minutes as necessary. For intramuscular administration, use a needle long enough (at least 1/2 inch) to ensure the injection is administered into the muscle. Monitor the patient clinically for the severity of the allergic reaction and potential cardiac effects of the drug, and repeat as needed. Do not administer repeated injections at the same site, as the resulting vasoconstriction may cause tissue necrosis.

Adults and Children 30 kg (66 lbs) or more: 0.3 to 0.5 mg (0.3 to 0.5 mL) of undiluted Adrenalin administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, up to a maximum of 0.5 mg (0.5 mL) per injection, repeated every 5 to 10 minutes as necessary. Monitor clinically for reaction severity and cardiac effects.

Children less than 30 kg (66 lbs): 0.01 mg/kg (0.01 mL/kg) of undiluted Adrenalin administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, up to a maximum of 0.3 mg (0.3 mL) per injection, repeated every 5 to 10 minutes as necessary. Monitor clinically for reaction severity and cardiac effects.

2.3 Hypotension associated with Septic Shock

Dilute 1 mL (1 mg) of epinephrine from its vial to 1,000 mL of a 5 percent dextrose or 5 percent dextrose and sodium chloride solution to produce a 1 mcg per mL dilution. Administration in saline solution alone is not recommended. If indicated, administer whole blood or plasma separately.

Whenever possible, give infusions of epinephrine into a large vein. Avoid using a catheter tie-in technique, because the obstruction to blood flow around the tubing may cause stasis and increased local concentration of the drug. Avoid the veins of the leg in elderly patients or in those suffering from occlusive vascular diseases.

To provide hemodynamic support in septic shock associated hypotension in adult patients, the suggested dosing infusion rate of intravenously administered epinephrine is 0.05 to 2 mcg/kg/min, and is titrated to achieve a desired mean arterial pressure (MAP). The dosage may be adjusted periodically, such as every 10 to 15 minutes, in increments of 0.05 to 0.2 mcg/kg/min, to achieve the desired blood pressure goal.

After hemodynamic stabilization, wean incrementally over time, such as by decreasing doses of epinephrine every 10 minutes to determine if the patient can tolerate gradual withdrawal.

Adrenalin diluted in 5 percent dextrose solutions or 5 percent dextrose and sodium chloride solutions are stable for 4 hours at room temperature or 24 hours under refrigerated conditions.

3 DOSAGE FORMS AND STRENGTHS

Adrenalin injection: clear, colorless solution supplied as 30 mg/30 mL (1 mg/mL) in a multiple dose amber glass vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Incorrect Locations of Injection for Anaphylaxis

Injection into the anterolateral aspect of the thigh (vastus lateralis muscle) is the most appropriate location for administration because of its location, size, and available blood flow. Injection into (or near) smaller muscles, such as in the deltoid, is not recommended.

Do not administer repeated injections of epinephrine at the same site, as the resulting vasoconstriction may cause tissue necrosis.

Do not inject into buttock. Injection into the buttock may not provide effective treatment of anaphylaxis and has been associated with the development of Clostridial infections (gas gangrene).

Do not inject into digits, hands, or feet. Epinephrine is a strong vasoconstrictor. Accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area and tissue necrosis.

5.2 Serious Infections at the Injection Site

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported at the injection site following epinephrine injection for anaphylaxis. Advise patients to seek medical care if they develop signs or symptoms of infection, such as persistent redness, warmth, swelling, or tenderness, at the epinephrine injection site.

5.3 Extravasation and Tissue Necrosis with Intravenous Infusion

Avoid extravasation of epinephrine into the tissues, to prevent local necrosis. When Adrenalin is administered intravenously, check the infusion site frequently for free flow. Blanching along the course of the infused vein, sometimes without obvious extravasation, may be attributed to vasa vasorum constriction with increased permeability of the vein wall, permitting some leakage. This also may progress on rare occasions to superficial slough. Hence, if blanching occurs, consider changing the infusion site at intervals to allow the effects of local vasoconstriction to subside.

There is potential for gangrene in a lower extremity when infusions of catecholamine are given in an ankle vein.

Antidote for Extravasation Ischemia: To prevent sloughing and necrosis in areas in which extravasation has taken place, infiltrate the area with 10 mL to 15 mL of saline solution containing from 5 mg to 10 mg of **phentolamine**, an adrenergic blocking agent. Use a syringe with a fine hypodermic needle, with the solution being infiltrated liberally throughout the area, which is easily identified by its cold, hard, and pallid appearance. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours.

5.4 Hypertension

Because individual response to epinephrine may vary significantly, monitor blood pressure frequently and titrate to avoid excessive increases in blood pressure.

Patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types may experience severe, prolonged hypertension when given epinephrine.

5.5 Pulmonary Edema

Epinephrine increases cardiac output and causes peripheral vasoconstriction, which may result in pulmonary edema.

5.6 Renal Impairment

Epinephrine constricts renal blood vessels, which may result in oliguria or renal impairment.

5.7 Cardiac Arrhythmias and Ischemia

Epinephrine may induce cardiac arrhythmias and myocardial ischemia in patients, especially patients suffering from coronary artery disease, or cardiomyopathy.

5.8 Allergic Reactions Associated with Sulfite

Adrenalin contains sodium bisulfite which may cause mild to severe allergic reactions including anaphylaxis or asthmatic episodes in susceptible individuals. However, the presence of bisulfite in this product should not preclude its use for the treatment of serious allergic or other emergency situations even if the patient is sulfite-sensitive, as the alternatives to using epinephrine in a life-threatening situation may not be satisfactory.

6 ADVERSE REACTIONS

Common adverse reactions to systemically administered epinephrine include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and respiratory difficulties. These symptoms occur in some persons receiving therapeutic doses of epinephrine, but are more likely to occur in patients with heart disease, hypertension, or hyperthyroidism [see *Warnings and Precautions (5.7)*].

The true incidence of adverse reactions associated with the systemic use of epinephrine is difficult to determine. Adverse reactions reported in observational trials, case reports, and studies are listed below by body system:

Cardiovascular: angina, arrhythmias, hypertension, pallor, palpitations, tachyarrhythmia, tachycardia, vasoconstriction, ventricular ectopy and stress cardiomyopathy.

Rapid rises in blood pressure associated with epinephrine use have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease [see *Warnings and Precautions (5.7)*].

Neurological: disorientation, impaired memory, panic, psychomotor agitation, sleepiness, tingling.

Psychiatric: anxiety, apprehensiveness, restlessness.

Other:

Patients with Parkinson's disease may experience psychomotor agitation or a temporary worsening of symptoms [see *Warnings and Precautions (5.7)*].

Diabetic patients may experience transient increases in blood sugar.

Injection into the buttock has resulted in cases of gas gangrene [see *Warnings and Precautions (5.1)*].

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported following epinephrine injection in the thigh [see *Warnings and Precautions (5.2)*].

7 DRUG INTERACTIONS

7.1 Drugs Antagonizing Pressor Effects of Epinephrine

- α -blockers, such as phentolamine
- Vasodilators, such as nitrates
- Diuretics

- Antihypertensives
- Ergot alkaloids
- Phenothiazine antipsychotics

7.2 Drugs Potentiating Pressor Effects of Epinephrine

- Sympathomimetics
- β -blockers, such as propranolol
- Tricyclic anti-depressants
- Monoamine oxidase (MAO) inhibitors
- Catechol-O-methyl transferase (COMT) inhibitors, such as entacapone
- Clonidine
- Doxapram
- Oxytocin

7.3 Drugs Potentiating Arrhythmogenic Effects of Epinephrine

Cardiac arrhythmias are more common among patients receiving any of the following drugs [see *Warnings and Precautions (5.7)* and *Adverse Reactions (6)*].

- β -blockers, such as propranolol
- Cyclopropane or halogenated hydrocarbon anesthetics, such as halothane
- Antihistamines
- Thyroid hormones
- Diuretics
- Cardiac glycosides, such as digitalis glycosides
- Quinidine

7.4 Drugs Potentiating Hypokalemic Effects of Epinephrine

- Potassium depleting diuretics
- Corticosteroids
- Theophylline

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged experience with epinephrine use in pregnant women over several decades, based on published literature, do not identify a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. However, there are risks to the mother and fetus associated with epinephrine use during labor or delivery (see *Clinical Considerations*). In animal reproduction studies, epinephrine administered by the subcutaneous route to pregnant rabbits, mice, and hamsters, during the period of organogenesis, resulted in adverse developmental effects (including gastroschisis, and embryonic lethality, and delayed skeletal ossification) at doses approximately 2 times the maximum recommended daily intramuscular, subcutaneous, or intravenous dose (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 United States 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 embryo/fetal risk

During pregnancy, anaphylaxis can be catastrophic and can lead to hypoxic-ischemic encephalopathy and permanent central nervous system damage or death in the mother and, more commonly, in the fetus or neonate. The prevalence of anaphylaxis occurring during pregnancy is reported to be approximately 3 cases per 100,000 deliveries.

Management of anaphylaxis during pregnancy is similar to management in the general population. Epinephrine is the first line-medication of choice for treatment of anaphylaxis; it should be used in the same manner in pregnant and non-pregnant patients. In conjunction with the administration of epinephrine, the patient should seek immediate medical or hospital care.

Hypotension associated with septic shock is a medical emergency in pregnancy which can be fatal if left untreated. Delaying treatment in pregnant women with hypotension associated with septic shock 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 epinephrine on the fetus.

Labor or Delivery

Epinephrine usually inhibits spontaneous or oxytocin induced contractions of the pregnant human uterus and may delay the second stage of labor. Avoid epinephrine during the second stage of labor. In dosage sufficient to reduce uterine contractions, the drug may cause a prolonged period of uterine atony with hemorrhage. Avoid epinephrine in obstetrics when maternal blood pressure exceeds 130/80 mmHg.

Although epinephrine may improve maternal hypotension associated with septic shock and anaphylaxis, it may result in uterine vasoconstriction, decreased uterine blood flow, and fetal anoxia.

Data

Animal Data

In an embryofetal development study with pregnant rabbits dosed during the period of organogenesis (on days 3 to 5, 6 to 7 or 7 to 9 of gestation), epinephrine caused teratogenic effects (including gastroschisis) at doses approximately 15 times the maximum recommended intramuscular, subcutaneous, or intravenous dose (on a mg/m² basis at a maternal subcutaneous dose of 1.2 mg/kg/day for two to three days). Animals treated on days 6 to 7 had decreased number of implantations.

In an embryofetal development study, pregnant mice were administered epinephrine (0.1 to 10 mg/kg/day) on Gestation Days 6 to 15. Teratogenic effects, embryonic lethality, and delays in skeletal ossification were observed at approximately 3 times the maximum recommended intramuscular, subcutaneous, or intravenous dose (on a mg/m² basis at maternal subcutaneous dose of 1 mg/kg/day for 10 days). These effects were not seen in mice at approximately 2 times the maximum recommended daily intramuscular or subcutaneous dose (on a mg/m² basis at a subcutaneous maternal dose of 0.5 mg/kg/day for 10 days).

In an embryofetal development study with pregnant hamsters dosed during the period of organogenesis from gestation days 7 to 10, epinephrine produced reductions in litter size and delayed skeletal ossification at doses approximately 2 times the maximum recommended intramuscular, subcutaneous, or intravenous dose (on a mg/m² basis at a maternal subcutaneous dose of 0.5 mg/kg/day).

8.2 Lactation

Risk Summary

There is no information regarding the presence of epinephrine in human milk or the effects of epinephrine on the breastfed infant or on milk production. However, due to its poor oral bioavailability and short half-life, epinephrine exposure is expected to be very low in the breastfed infant.

Epinephrine is the first-line medication of choice for treatment of anaphylaxis; it should be used in the same manner for anaphylaxis in breastfeeding and non-breastfeeding patients.

8.4 Pediatric Use

Clinical use data support weight-based dosing for treatment of anaphylaxis in pediatric patients, and other reported clinical experience with the use of epinephrine suggests that the adverse reactions seen in children are similar in nature and extent to those both expected and reported in adults.

Safety and effectiveness of epinephrine in pediatric patients with septic shock have not been established.

8.5 Geriatric Use

Clinical studies for the treatment of anaphylaxis have not been performed in subjects aged 65 and over to determine whether they respond differently from younger subjects. However, other reported clinical experience with use of epinephrine for the treatment of anaphylaxis has identified that geriatric patients may be particularly sensitive to the effects of epinephrine. Therefore, for the treatment of anaphylaxis, consider starting with a lower dose to take into account potential concomitant disease or other drug therapy.

Clinical studies of epinephrine for the treatment of hypotension associated with septic shock 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.

10 OVERDOSAGE

Overdosage of epinephrine may produce extremely elevated arterial pressure, which may result in cerebrovascular hemorrhage, particularly in elderly patients. Overdosage may also result in pulmonary edema because of peripheral vascular constriction

together with cardiac stimulation. Epinephrine overdosage can also cause transient bradycardia followed by tachycardia and these may be accompanied by potentially fatal cardiac arrhythmias. Premature ventricular contractions may appear within one minute after injection and may be followed by multifocal ventricular tachycardia (prefibrillation rhythm). Subsidence of the ventricular effects may be followed by atrial tachycardia and occasionally by atrioventricular block. Myocardial ischemia and infarction, cardiomyopathy, extreme pallor and coldness of the skin, metabolic acidosis due to elevated blood lactic acid levels, and renal insufficiency have also been reported.

Epinephrine is rapidly inactivated in the body and treatment following overdose with epinephrine is primarily supportive. Treatment of pulmonary edema consists of a rapidly acting alpha-adrenergic blocking drug (such as phentolamine mesylate) and respiratory support. Treatment of arrhythmias consists of administration of a beta-adrenergic blocking drug (such as propranolol). If necessary, pressor effects may be counteracted by rapidly acting vasodilators or α -adrenergic blocking drugs. If prolonged hypotension follows such measures, it may be necessary to administer another pressor drug.

11 DESCRIPTION

Adrenalin (epinephrine injection, USP) is a clear, colorless, sterile solution containing 1 mg/mL epinephrine, packaged as 30 mL of solution in a multiple dose amber glass vial. In the 30 mL vial, each 1 mL of Adrenalin solution contains 1 mg epinephrine, 6.15 mg sodium chloride, 0.457 mg sodium metabisulfite, 0.920 mg sodium hydroxide, 2.25 mg tartaric acid, 0.20 mg disodium edetate dihydrate, hydrochloric acid to adjust pH, 5.25 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.

Epinephrine is a sympathomimetic catecholamine. The chemical name of epinephrine is: 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (-)-3,4-Dihydroxy- α -[2-(methylamino)ethyl]benzyl alcohol.

The chemical structure of epinephrine is:

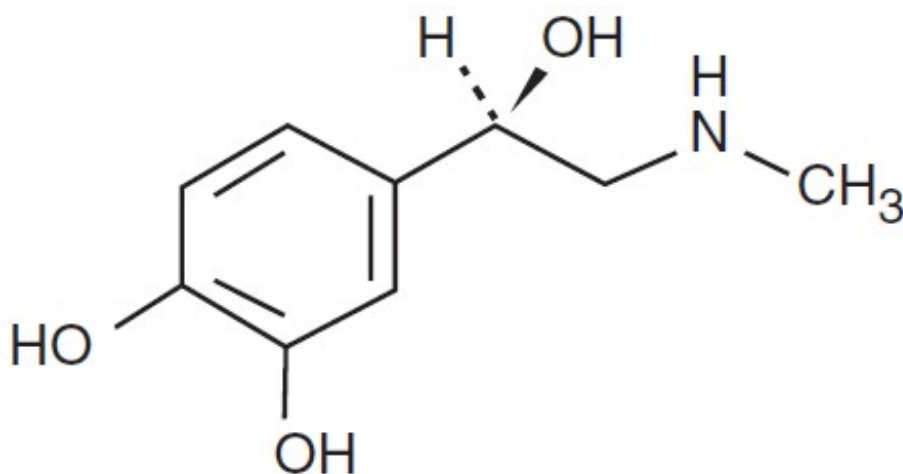


Image 1

The molecular weight of epinephrine is 183.2.

Epinephrine solution deteriorates rapidly on exposure to air or light, turning pink from

oxidation to adrenochrome and brown from the formation of melanin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Epinephrine acts on both alpha and beta-adrenergic receptors. The mechanism of the rise in blood pressure is 3-fold: a direct myocardial stimulation that increases the strength of ventricular contraction (positive inotropic action), an increased heart rate (positive chronotropic action), and peripheral vasoconstriction.

12.2 Pharmacodynamics

Epinephrine increases glycogenolysis, reduces glucose up take by tissues, and inhibits insulin release in the pancreas, resulting in hyperglycemia and increased blood lactic acid.

Intramuscular and subcutaneous use for anaphylaxis

Through its action on alpha-adrenergic receptors, epinephrine lessens the vasodilation and increased vascular permeability that occurs during anaphylaxis, which can lead to loss of intravascular fluid volume and hypotension.

Through its action on beta-adrenergic receptors, epinephrine causes bronchial smooth muscle relaxation and helps alleviate bronchospasm, wheezing and dyspnea that may occur during anaphylaxis.

Epinephrine also alleviates pruritus, urticaria, and angioedema and may relieve gastrointestinal and genitourinary symptoms associated with anaphylaxis because of its relaxer effects on the smooth muscle of the stomach, intestine, uterus and urinary bladder.

Intravenous use for hypotension associated with septic shock

When administered parenterally, epinephrine has a rapid onset and short duration of action.

Following intravenous administration of epinephrine, increases in systolic blood pressure and heart rate are observed. Decreases in systemic vascular resistance and diastolic blood pressure are observed at low doses of epinephrine because of β_2 -mediated vasodilation, but are overtaken by α_1 -mediated peripheral vasoconstriction at higher doses leading to increase in diastolic blood pressure. The onset of blood pressure increase following an intravenous dose of epinephrine is < 5 minutes and the time to offset blood pressure response occurs within 15 minutes. Most vascular beds are constricted including renal, splanchnic, mucosal and skin.

Epinephrine causes mydriasis when administered parenterally.

12.3 Pharmacokinetics

Following intravenous injection, epinephrine is rapidly cleared from the plasma with an effective half-life of < 5 minutes. A pharmacokinetic steady state following continuous intravenous infusion is achieved within 10-15 minutes. In patients with septic shock, epinephrine displays dose-proportional pharmacokinetics in the infusion dose range of

0.03 to 1.7 mcg/kg/min.

Epinephrine is extensively metabolized with only a small amount excreted unchanged.

Epinephrine is rapidly degraded to vanillylmandelic acid, an inactive metabolite, by monoamine oxidase and catechol-O-methyltransferase that are abundantly expressed in the liver, kidneys and other extraneuronal tissues. The tissues with the highest contribution to removal of circulating exogenous epinephrine are the liver (32%), kidneys (25%), skeletal muscle (20%), and mesenteric organs (12%).

Specific Populations

Elderly

In a pharmacokinetic study of 45-minute epinephrine infusions given to healthy men aged 20 to 25 years and healthy men aged 60 to 65 years, the mean plasma metabolic clearance rate of epinephrine at steady state was greater among the older men (144.8 versus 78 mL/kg/min for a 0.0143 mcg/kg/min infusion).

Body Weight

Body weight has been found to influence epinephrine pharmacokinetics. Higher body weight was associated with a higher plasma epinephrine clearance and a lower concentration plateau.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to evaluate the carcinogenic potential of epinephrine have not been conducted.

Epinephrine and other catecholamines have been shown to have mutagenic potential *in vitro*. Epinephrine was positive in the *Salmonella* bacterial reverse mutation assay, positive in the mouse lymphoma assay, and negative in the *in vivo* micronucleus assay. Epinephrine is an oxidative mutagen based on the *E. coli* WP2 Mutoxitest bacterial reverse mutation assay. This should not prevent the use of epinephrine under the conditions noted under *Indications and Usage (1)*.

The potential for epinephrine to impair reproductive performance has not been evaluated, but epinephrine has been shown to decrease implantation in female rabbits dosed subcutaneously with 1.2 mg/kg/day (15-fold the highest human intramuscular or subcutaneous daily dose) during gestation days 3 to 9.

16 HOW SUPPLIED/STORAGE AND HANDLING

Adrenalin 30 mg/30 mL (1 mg/mL) Multiple Dose Vials:

Each carton contains 1 multiple dose vial containing 30 mg/30 mL (1 mg/mL) Adrenalin (epinephrine injection, USP) solution in a 36 mL amber glass vial.

NDC 42023-168-89 30 mL Multiple Dose Vial

Vial and contents must be discarded 30 days after initial use.

Store between 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Epinephrine is light sensitive. Protect from light and freezing.

Inspect visually for particulate matter and discoloration prior to administration. Do not use the solution if it is colored or cloudy, or if it contains particulate matter.

17 PATIENT COUNSELING INFORMATION

Advise patients or their caregivers about common adverse reactions associated with the use of epinephrine including an increase in heart rate, the sensation of a more forceful heartbeat, palpitations, sweating, nausea and vomiting, difficulty breathing, pallor, dizziness, weakness or shakiness, headache, apprehension, nervousness, or anxiety. These symptoms and signs usually subside rapidly, especially with rest, quiet and recumbent positioning.

Warn patients with a good response to initial treatment about the possibility of recurrence of symptoms and instruct patients to obtain proper medical attention if symptoms return.

Warn patients with diabetes that they may develop increased blood glucose levels following epinephrine administration.

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported at the injection site following epinephrine injection for anaphylaxis. Advise patients to seek medical care if they develop signs or symptoms of infection, such as persistent redness, warmth, swelling, or tenderness, at the epinephrine injection site [see *Warnings and Precautions (5.2)*].

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Registered Trademark No. 53,934

Distributed by:

Par Pharmaceutical

Chestnut Ridge, NY 10977

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PRINCIPLE DISPLAY PANEL - 30ML VIAL LABEL

PRINCIPAL DISPLAY PANEL - 30 mL Vial Label

NDC 42023-168-89

Rx Only

Adrenalin®
(epinephrine
injection, USP)

30 mg/30 mL

(1 mg/mL)

For Intravenous Infusion, Intramuscular and Subcutaneous Use

NOT for Ophthalmic Use

30 mL Multiple Dose Vial

NDC 42023-168-89

Adrenalin®
(epinephrine injection, USP)
30 mg/30 mL
(1 mg/mL)

**For Intravenous Infusion,
Intramuscular and Subcutaneous Use**

Dilute Before Intravenous Infusion

NOT for Ophthalmic Use

30 mL Multiple Dose Vial

Rx Only


Each mL contains 1 mg Adrenalin (epinephrine) dissolved in Water for Injection, USP with sodium chloride, sodium hydroxide, tartaric acid, disodium edetate, 0.5% Chlorobutanol as a preservative and not more than 0.05% sodium bisulfite as an antioxidant.

Prior to intravenous infusion, dilute 1 mL (1 mg) of epinephrine in 1,000 mL of a 5% Dextrose Solution or 5% Dextrose and Sodium Chloride Solution to produce a resulting concentration of 1 mcg/mL.

Usual Dose, Storage, and Dilution Information: See full Prescribing Information. Store between 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.) Protect from light and freezing. Discard 30 days after initial use: Discard on ___/___/___

Distributed by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

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107/2020



(01)00342023168894

3 0 0 3 8 8 6

LOT
EXP

Image 2

ADRENALIN

epinephrine injection

Product Information

Product Type

HUMAN PRESCRIPTION DRUG

**Item Code
(Source)**

NDC:42023-168

Route of Administration

INTRAMUSCULAR, INTRAVENOUS,
SUBCUTANEOUS

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|--|-------------------|--------------|
| EPINEPHRINE (UNII: YKH834O4BH) (EPINEPHRINE - UNII:YKH834O4BH) | EPINEPHRINE | 1 mg in 1 mL |

Inactive Ingredients

| Ingredient Name | Strength |
|-----------------|----------|
|-----------------|----------|

| | |
|--|------------------|
| SODIUM CHLORIDE (UNII: 451W47IQ8X) | 6.15 mg in 1 mL |
| SODIUM METABISULFITE (UNII: 4VON5FNS3C) | 0.457 mg in 1 mL |
| SODIUM HYDROXIDE (UNII: 55X04QC32I) | 0.920 mg in 1 mL |
| TARTARIC ACID (UNII: W4888I119H) | 2.25 mg in 1 mL |
| EDETATE DISODIUM (UNII: 7FLD91C86K) | 0.20 mg in 1 mL |
| CHLOROBUTANOL (UNII: HM4YQM8WRC) | 5.25 mg in 1 mL |
| HYDROCHLORIC ACID (UNII: QTT17582CB) | |
| WATER (UNII: 059QF0KO0R) | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|------------------|--|----------------------|--------------------|
| 1 | NDC:42023-168-89 | 1 in 1 CARTON | 12/04/2020 | |
| 1 | | 30 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 |
|--------------------|--|----------------------|--------------------|
| NDA | NDA204640 | 12/04/2020 | |

Labeler - Par Pharmaceutical, Inc. (092733690)

Registrant - Par Pharmaceutical Inc. (092733690)

Revised: 8/2020

Par Pharmaceutical, Inc.