ADRENALIN (epinephrine) injection
1 mg/mL (1:1000) 1 mL single-use vial for intramuscular, subcutaneous, and intracutaneous use
30 mL vial: for intramuscular and subcutaneous 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 I), including anaphylaxis
- Induction and maintenance of mydriasis during intraocular surgery

CONTRAINdications
Do not use Adrenalin® if:
- The solution is colored or cloudy, or if it contains particulate matter.
- The vial contains sodium bisulfite, which may cause mild to severe allergic reactions in some individuals.

DRUG INTERACTIONS
Caution should be exercised in administering Adrenalin® with drugs that:
- May cause additive cardiovascular effects
- May potentiate cardiovascular effects of epinephrine
- Block the effects of epinephrine

ADVERSE REACTIONS
Adrenalin® may cause:
- Hypertensive effects
- Cardiac arrhythmias
- Headache
- Jessicin
- Palpitations

WARNINGS AND PRECAUTIONS
Patients with:
- Hyperthyroidism
- Parkinson's disease
- Diabetes mellitus
- Pheochromocytoma
- Elderly individuals
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PATIENT COUNSELING INFORMATION
- Do not use Adrenalin® if the solution is colored or cloudy, or if it contains particulate matter.
- Do not use Adrenalin® if it contains sodium bisulfite.
- Do not use Adrenalin® if it contains beta-blockers.

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FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE
Adrenalin® is available as a single-use 1 mL vial and a multiple-use 30 mL vial.

- For the treatment of anaphylaxis
- For the treatment of ventricular arrhythmias

2 DOSAGE AND ADMINISTRATION

2.1 Anaphylaxis (Adrenalin® 1 mL single-use and 30 mL multiple-use vials)
Emergency treatment of allergic reactions (Type I), including anaphylaxis, which may result from allergic reactions to insect stings, biting insects, foods, drugs, sera, diagnostic testing substances and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis. The signs and symptoms associated with anaphylaxis include flushing, apprehension, syncope, tachycardia, tachypnea, urticaria, or atypical urticaria, angioedema of the eyelids, lips, and tongue.

2.2 Induction and Maintenance of Mydriasis during Intraocular Surgery

Dosage and Administration

Adrenalin® is given parenterally by injection only. Adrenalin® contains sodium bisulfite which may cause mild to severe allergic reactions in some individuals.

Adrenalin® is contraindicated in patients who are on drugs that may sensitize the heart to arrhythmias, epinephrine should be administered with caution in patients who have heart disease, including patients with cardiac arrhythmias, coronary artery or organic heart disease, or hypertension. In such patients, or in patients who are on drugs that may sensitize the heart to arrhythmias, epinephrine may precipitate or aggravate arrhythmias as well as other cardiovascular effects. In patients with underlying organic heart disease or patients receiving drugs that sensitize the heart to arrhythmias, intravenous epinephrine should be administered with caution. Adverse reactions reported in observational trials, case reports, and studies listed below by body system:

Cardiovascular: Angina, arrhythmias, hypertension, palpitations, tachycardia, tachycardia, xanthomata, ventricular ectopy.

CNS: Anxiety, apprehension, restlessness, tremor, and weakness.

Gastrointestinal: Nausea, vomiting.

Respiratory: respiratory difficulties.

Neurological: dizziness, disorientation, excitability, headache, impaired memory, nervousness, panic, psychomotor agitation, sleepiness, tingling, tremor, and weakness.

Psychiatric: anxiety, apprehensiveness, restlessness.

Rapid rises in blood pressure associated with epinephrine use have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease.

Adrenalin® may be diluted prior to intravenous use. Dilute 1 mL of Adrenalin® (1 mg/mL) with 10 mL of saline or 10 mL of dextrose solution. Adrenalin® may also be injected intramuscularly as a bolus dose of 1 mL at a dilution of 1 vial of 1:1000 to 1:4000 (10 mg/mL to 2.5 mg/mL).

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: December 2013

WARNINGs AND PRECAUTIONs

5.1 Potential for Organic Heart Disease from Adrenalin® 30 mL multiple-use vial

Adrenalin® 30 mL multiple-use vial may be used only for epinephrine use because it contains chlorobutanol which may be harmful to the corneal endothelium.

5.2 Injury with Undiluted Intracutaneous Solution

The Adrenalin® 30 mL single-use vial, while it does not contain chlorobutanol, must be diluted before intracutaneous use. Epinephrine containing sodium bisulfite has been associated with several cases of local tissue damage when used in the eye at undiluted concentrations (1 mg/mL) [see Dosage and Administration (2.2)].

5.3 Incorrect Locations of Injection

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 the buttocksor near smaller muscles, such as in the deltoid, is not recommended due to possible differences in absorption associated with this site.

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

Cleansing with alcohol does not kill bacterial spores, and therefore, does not lower this risk.

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 has been associated with tissue necrosis.

5.4 Disease Interactions

Some patients may be at greater risk for developing adverse reactions after systemic epinephrine administration. Due to these concerns, the use of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation.

Patients with Heart Disease

Epinephrine should be administered with caution in patients who have heart disease, including patients with cardiac arrhythmias, coronary artery or organic heart disease, or hypertension. In such patients, or in patients who are on drugs that may sensitize the heart to arrhythmias, epinephrine may precipitate or aggravate arrhythmias as well as produce ventricular arrhythmias. [see Drug Interactions (7) and Adverse Reactions (6.3)]

Other Patients and Diseases

Epinephrine should be administered with caution to patients with hypothyroidism, Parkinson's disease, diabetes mellitus, pheochromocytoma, elderly individuals, tend—in disorder of n

5.5 Allergic Reactions Associated with Sulfite

Adrenalin® contains sodium bisulfite which may cause mild to severe allergic reactions in susceptible individuals.

Due to the lack of randomized, controlled clinical trials of epinephrine for the treatment of anaphylaxis, 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 listed below by body system:

Cardiovascular: Angina, arrhythmias, hypertension, palpitations, tachycardia, tachycardia, xanthomata, ventricular ectopy.

Anxiety, apprehension, restlessness.

Gastrointestinal: Nausea, vomiting.

Respiratory: respiratory difficulties.

Neurological: dizziness, disorientation, excitability, headache, impaired memory, nervousness, panic, psychomotor agitation, sleepiness, tingling, tremor, and weakness.

Psychiatric: anxiety, apprehensiveness, restlessness.

Rapid rises in blood pressure associated with epinephrine use have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease. [see Warnings and Precautions (5.6)].

Respiratory: respiratory difficulties.

Neurological: dizziness, disorientation, excitability, headache, impaired memory, nervousness, panic, psychomotor agitation, sleepiness, tingling, tremor, and weakness.

Psychiatric: anxiety, apprehensiveness, restlessness.

Gastrointestinal: Nausea, vomiting.

Other:

Patients with Parkinson's disease may experience psychomotor agitation or a temporary worsening of Parkinson's disease. [see Warnings and Precautions (5.3)].

Diabetic patients may experience transient increases in blood sugar [see Warnings and Precautions (5.4)].

Accidental injection into the digits, hands, or feet may result in loss of blood flow to the affected area and has been associated with tissue necrosis. [see Warnings and Precautions (5.3)].

Adverse events resulting from injection into these areas include increased heart rate, local reactions including injection site paresthesia, coldness, hypotension, and tissue loss, or injury at the injection site resulting in bruising, bleeding, discoloration, erythema, and skeletal injury.

Injection into the buttock has resulted in cases of gangrene [see Warnings and Precautions (5.3)].

Risk: sweating.
6.2 Adverse Reactions Associated with Intracocular Use (for Mydriasis)

Epinephrine containing sodium bisulfite has been associated with corneal endothelial damage when used in the eye at undiluted concentrations (1 mg/mL).

To report SUSPECTED ADVERSE REACTIONS, contact JHP Pharmaceuticals at 1-866-903-2547 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

7 DRUG INTERACTIONS

Epinephrine should be administered cautiously to patients taking other sympathomimetic agents because of the possibility of additive effects.

Patients who are concomitantly receiving cardiac glycosides, digitals, diuretics, quinidine, and other antiarrhythmics should be observed carefully for the development of cardiac arrhythmias (see Warnings and Precautions (5.4) and Adverse Reactions (6.7)).

Administer epinephrine cautiously to patients receiving halogenated hydrocarbon general anesthetics, such as halothane, as coadministration may result in arrhythmias.

The effects of epinephrine may be potentiated by tricyclic antidepressants such as imipramine, monamines oxidase inhibitors (MAOIs), levodopa, sodium, and certain antihistamines, notably diphenhydramine, tripelennamine, and dexchlorpheniramine.

The cardiostimulating and bronchodilating effects of epinephrine are antagonized by beta-adrenergic blocking drugs, such as propranolol.

Vasoconstricting and hypertensive effects of epinephrine are antagonized by alpha-adrenergic blocking drugs, such as phentolamine.

Ergot alkaloids may reverse the pressor effects of epinephrine.

Epinephrine should not be used to counteract circulatory collapse or hypotension caused by phenothiazines, as a reversal of the pressor effects of epinephrine may result in further lowering of blood pressure.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (fetal anoxia, spontaneous abortion, or both). Epinephrine is teratogenic in rabbits, mice and hamsters dosed during organogenesis.

Epinephrine has been shown to have teratogenic effects (including gastrulation and embryonic lethality) when administered subcutaneously to rabbits at approximately 15 times the maximum recommended intramuscular or subcutaneous dose (on a mg/m² basis at a maternal subcutaneous dose of 1.2 mg/kg/day for two to three days).

In mice, teratogenic effects (including embryonic lethality) were observed at approximately 3 times the maximum recommended intramuscular or subcutaneous dose (on a mg/m² basis at a 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 hamsters, teratogenic effects were observed at approximately 2 times the maximum recommended intramuscular or subcutaneous dose (on a mg/m² basis at a maternal subcutaneous dose of 0.5 mg/kg/day for 4 days).

8.2 Labor and Delivery

Use with caution during labor and delivery.

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

8.3 Nursing Mothers

It is not known whether epinephrine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when epinephrine is administered to a nursing woman.

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.

The safety and effectiveness of epinephrine (at a dilution of 1:100,000 to 1:400,000) for induction and maintenance of mydriasis during intracocular surgery have been established in pediatric patients. Use of Adrenalin® for induction and maintenance of mydriasis during intracocular surgery in pediatric patients is supported by adequate and well controlled studies in adults and uncontrolled studies in pediatric patients.

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.

For induction and maintenance of mydriasis during intracocular surgery, no overall differences have been observed between elderly and other patients.

10 OVERDOSE

Overdosage of epinephrine may produce extremely elevated arterial pressures, 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. Treatment consists of rapidly acting a-adrenergic blocking drug and respiratory support.

Epinephrine is rapidly inactivated in the body and treatment following overdose with epinephrine is primarily supportive. If necessary, pressor effects may be counteracted by rapidly acting vasodilators or a-adrenergic blocking drugs. If prolonged hypotension follows such measures, it may be necessary to administer another pressor drug.

Epinephrine overdose 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).

16 HOW SUPPLIED/STORAGE AND HANDLING

Adrenalin® 1 mL Single-Use Vials: Each vial contains 25 single-use vials containing 1 mL Adrenalin® (epinephrine injection, USP) solution 1 mg/mL (1:1000) in a 3 mL clear glass vial.

NDC 42023-159-29 1 mL vial

Adrenalin® 30 mL Multi-Dose Vials: Each vial contains either 1 multiple-dose vial or 10 multiple-dose vials containing 30 mL Adrenalin® (epinephrine injection, USP) solution 1 mg/mL (1:1000) in a 3 mL amber glass vial.

NDC 42023-168-01 30 mL vial, pack of 1

NDC 42023-168-10 30 mL vial, pack of 10

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, swelling, nausea and vomiting, difficulty breathing, palp, 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.