

DOCUMENT INFORMATION PAGE

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Notes:	USE COR-SNDAACTION-05 for sNDA CMC APPROVALS if supplement contains labeling changes. For approvals with COL: CC the OGD Labeling Review Branch within DARRTS at CDEROGDDLRLB@fda.hhs.gov

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END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204640/S-002

APPROVAL LETTER

Par Sterile Products, LLC
One Upper Pond Road
Building D, 3rd Floor
Parsippany, NJ 07054

Attention: Carla English
Manager, Regulatory Affairs

Dear Ms. English:

Please refer to your Supplemental New Drug Application (sNDA) dated March 31, 2015, received March 31, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Adrenalin® (epinephrine injection, USP) 1 mg/mL, 30 mL vial.

We acknowledge receipt of your amendment dated September 3, 2015, which constituted a complete response to our July 31, 2015, action letter.

This prior approval supplemental new drug application proposes a change in formulation for the Adrenalin 30 mL vial presentation.

We have completed our review of this supplemental new drug application, as amended. This supplement is approved for use as recommended in the enclosed, agreed-upon labeling text.

We note that your December 10, 2015, submission includes final printed labeling (FPL) for your package insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate-container labels submitted on September 3, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 204640/S-002.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REPORTING REQUIREMENTS

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Colette Jackson, Senior Regulatory Health Project Manager, at (301) 796-1230.

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Sincerely,

{See appended electronic signature page}

Lydia Gilbert-McClain, M.D.
Deputy Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Approved package insert, immediate container, and carton labeling.

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 (1:1000)
1mL vial: for intramuscular, subcutaneous, and intraocular 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 1), including anaphylaxis (Adrenalin® 1 mL and 30 mL vials) (1.1)
- Induction and maintenance of mydriasis during intraocular surgery (Adrenalin® 1 mL vial only) (1.2)

DOSAGE AND ADMINISTRATION

- **Anaphylaxis** (Adrenalin® 1 mL and 30 mL vials):
 - *Adults and Children 30 kg (66 lbs) or more:* 0.3 to 0.5 mg (0.3 to 0.5 mL) intramuscularly or subcutaneously into anterolateral aspect of the thigh every 5 to 10 minutes as necessary (2.1)
 - *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 (2.1)
- **Intraocular surgery** (Adrenalin® 1 mL vial only): Dilute 1 mL with 100 to 1000 mL of an ophthalmic irrigation fluid, for ophthalmic irrigation or intracameral injection (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: 1 mg/mL (1:1000), 1 mL single-use vials and 30 mL multiple-dose vials (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Do not use 30 mL vial for ophthalmic indication (5.1)
- Undiluted ophthalmic administration: associated with corneal endothelial damage (5.2)

- Do not inject into buttocks, digits, hands, or feet (5.3)
- May aggravate angina pectoris or produce ventricular arrhythmias, particularly in patients with underlying heart disease, administer with caution when used intramuscularly or subcutaneously (5.4)
- Patients with hyperthyroidism, Parkinson's disease, diabetes, and pheochromocytoma are at greater risk of having adverse reactions when used intramuscularly or subcutaneously (5.4)
- Presence of sulfite in this product should not deter use for anaphylaxis (5.5)

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. Arrhythmias, including fatal ventricular fibrillation, rapid rises in blood pressure producing cerebral hemorrhage, and angina have occurred (6.1)

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

DRUG INTERACTIONS

- Sympathomimetic agents: possible additive effects (7)
- Cardiac glycosides, halogenated hydrocarbon anesthetics, or diuretics: observe for development of cardiac arrhythmias (7)
- Tricyclic antidepressants, MAO inhibitors, levothyroxine sodium, and certain antihistamines: potentiate effects of epinephrine (7)
- Beta-adrenergic blocking drugs: antagonize the cardiostimulating and bronchodilating effects of epinephrine (7)
- Alpha-adrenergic blocking drugs: antagonize the vasoconstricting and hypertensive effects of epinephrine (7)
- Ergot alkaloids may reverse the pressor response to epinephrine (7)

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)

See 17 for PATIENT COUNSELING INFORMATION

Revised: December 2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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- 1.1 Anaphylaxis (Adrenalin® 1 mL single-use and 30 mL multiple-dose vials)
- 1.2 Induction and Maintenance of Mydriasis during Intraocular Surgery (Adrenalin® 1 mL single-use vial only)

2 DOSAGE AND ADMINISTRATION

- 2.1 Anaphylaxis (Adrenalin® 1 mL single-use and 30 mL multiple-dose vials)
- 2.2 Induction and Maintenance of Mydriasis during Intraocular Surgery (Adrenalin® 1 mL single-use vial only)

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Potential for Ophthalmic Injury from Adrenalin® 30 mL multiple-dose vial
- 5.2 Injury with Undiluted Intraocular Solution
- 5.3 Incorrect Locations of Injection
- 5.4 Disease Interactions
- 5.5 Allergic Reactions Associated with Sulfite

6 ADVERSE REACTIONS

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Adrenalin[®] is available as a single-use 1 mL vial and a multiple-use 30 mL vial. The 1 mL vial is for intramuscular, subcutaneous, and intraocular use. The 30 mL vial is for intramuscular and subcutaneous use only, and is NOT FOR OPHTHALMIC USE.

1.1 Anaphylaxis (Adrenalin[®] 1 mL single-use and 30 mL multiple-dose 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, thready or unobtainable pulse associated with hypotension, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, airway swelling, laryngospasm, bronchospasm, pruritus, urticaria or angioedema, swelling of the eyelids, lips, and tongue.

1.2 Induction and Maintenance of Mydriasis during Intraocular Surgery (Adrenalin[®] 1 mL single-use vial only)

Induction and maintenance of mydriasis during intraocular surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Anaphylaxis (Adrenalin[®] 1 mL single-use and 30 mL multiple-dose vials)

Inject Adrenalin[®] intramuscularly or subcutaneously into the anterolateral aspect of the thigh. 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 5/8 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, with repeat doses titrated to effect. Do not administer repeated injections at the same site, as the resulting vasoconstriction may cause tissue necrosis.

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

Adults and Children 30 kg (66 lbs) or more: 0.3 to 0.5 mg (0.3 mL 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.

2.2 Induction and Maintenance of Mydriasis during Intraocular Surgery (Adrenalin[®] 1 mL single-use vial only)

Adrenalin[®] must be diluted prior to intraocular use. Dilute 1 mL of Adrenalin[®] 1 mg/mL (1:1000) in 100 to 1000 mL of an ophthalmic irrigation fluid to create an epinephrine concentration of 1:100,000 to 1:1,000,000 (10 mcg/mL to 1 mcg/mL). Use the irrigating solution as needed for the surgical procedure.

After dilution in an ophthalmic irrigating fluid, Adrenalin[®] may also be injected intracamerally as a bolus dose of 0.1 mL at a dilution of 1:100,000 to 1:400,000 (10 mcg/mL to 2.5 mcg/mL).

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

Note: The Adrenalin[®] 30 mL multiple-dose vial is not for ophthalmic use. USE ONLY THE ADRENALIN 1 ML SINGLE-USE VIAL FOR OPHTHALMIC USE.

3 DOSAGE FORMS AND STRENGTHS

Adrenalin[®] 1 mg/mL (1:1000) epinephrine injection, 1 mL solution in a single-use clear glass vial and 30 mL solution in a multiple-dose amber glass vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Ophthalmic Injury from Adrenalin[®] 30 mL multiple-dose vial

The Adrenalin[®] 30 mL multiple-dose vial is not for ophthalmic use because it contains chlorobutanol which may be harmful to the corneal endothelium.

5.2 Injury with Undiluted Intraocular Solution

The Adrenalin[®] 1 mL single-use vial, while it does not contain chlorobutanol, **must** be diluted before intraocular use. Epinephrine containing sodium bisulfite has been associated with corneal endothelial 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 (or near) smaller muscles, such as in the deltoid, is not recommended due to possible differences in absorption associated with this use.

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 gas gangrene. 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. Despite these concerns, the presence 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, cerebrovascular 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 angina pectoris as well as produce ventricular arrhythmias. [*see Drug Interactions (7) and Adverse Reactions (6.1)*]

Other Patients and Diseases

Epinephrine should be administered with caution to patients with hyperthyroidism, Parkinson's disease, diabetes mellitus, pheochromocytoma, elderly individuals, and pregnant women. Patients with Parkinson's disease may experience psychomotor agitation or notice a temporary worsening of symptoms. Diabetic patients may experience transient increases in blood sugar.

5.5 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

6.1 Adverse Reactions Associated with Intramuscular/Subcutaneous Use (for Anaphylaxis)

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 (5.4)*].

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 are listed below by body system:

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

Angina may occur in patients with coronary artery disease [*see Warnings and Precautions (5.4)*].

Arrhythmias, including fatal ventricular fibrillation, have occurred, particularly in patients with underlying organic heart disease or patients receiving drugs that sensitize the heart to arrhythmias [*see Warnings and Precautions (5.4)*].

Rapid rises in blood pressure associated with epinephrine use have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease [*see Warnings and Precautions (5.4)*].

Respiratory: respiratory difficulties.

Neurological: dizziness, disorientation, excitability, headache, impaired memory, lightheadedness, 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 symptoms [*see Warnings and Precautions (5.4)*].

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 [*see Warnings and Precautions (5.3)*]. Adverse events experienced as a result of an injection into these areas include increased heart rate, local reactions including injection site pallor, coldness, hypoesthesia, 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 gas gangrene [*see Warnings and Precautions (5.3)*].

Skin: sweating.

6.2 Adverse Reactions Associated with Intraocular 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 Par Pharmaceutical, Inc. at 1-800-828-9393 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, digitalis, diuretics, quinidine, and other antiarrhythmics should be observed carefully for the development of cardiac arrhythmias [see *Warnings and Precautions (5.4) and Adverse Reactions (6.1)*].

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, monoamine oxidase inhibitors (MAOI), levothyroxine sodium, and certain antihistamines, notably diphenhydramine, tripelannamine, and dexchlorpheniramine.

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

The 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 gastroschisis and embryonic lethality) when administered subcutaneous in rabbits at approximately 15 times the maximum recommended intramuscular or subcutaneous dose (on a mg/m^2 basis at a maternal subcutaneous dose of 1.2 $\text{mg}/\text{kg}/\text{day}$ 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/m^2 basis at maternal subcutaneous dose of 1 $\text{mg}/\text{kg}/\text{day}$ 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/m^2 basis at a subcutaneous maternal dose of 0.5 $\text{mg}/\text{kg}/\text{day}$ for 10 days).

In hamsters, teratogenic effects were observed at approximately 2 times the maximum recommended intramuscular or subcutaneous dose (on a mg/m^2 basis at a maternal subcutaneous dose of 0.5 $\text{mg}/\text{kg}/\text{day}$ 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 intraocular surgery have been established in pediatric patients. Use of Adrenalin[®] for induction and maintenance of mydriasis during intraocular 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 intraocular surgery, no overall differences have been observed between elderly and other patients.

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. Treatment consists of a rapidly acting α -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 α -adrenergic blocking drugs. If prolonged hypotension follows such measures, it may be necessary to administer another pressor drug.

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. Treatment of arrhythmias consists of administration of a beta-adrenergic blocking drug such as propranolol.

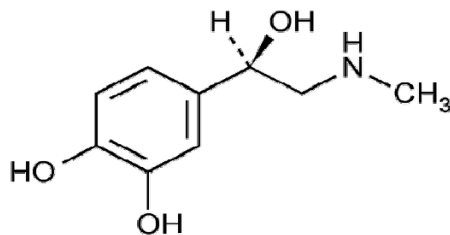
Overdosage sometimes results in extreme pallor and coldness of the skin, metabolic acidosis due to elevated blood lactic acid levels, and kidney failure. Suitable corrective measures must be taken in such situations.

11 DESCRIPTION

Adrenalin[®] (epinephrine injection, USP) is a clear, colorless, sterile solution containing 1 mg/mL (1:1000) epinephrine, packaged as 1 mL of solution in a single-use clear glass vial or 30 mL of solution in a multiple-dose amber glass vial. In the 1 mL vial, each 1 mL of Adrenalin[®] solution contains 1 mg epinephrine, 9.0 mg sodium chloride, 1.0 mg sodium metabisulfite, hydrochloric acid to adjust pH, and water for injection. 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:



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.

12.2 Pharmacodynamics

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.

Epinephrine increases glycogenolysis, reduces glucose up take by tissues, and inhibits insulin release in the pancreas, resulting in hyperglycemia and increased blood lactic acid [*see Warnings and Precautions (5.4)*].

Epinephrine causes mydriasis when administered intraocularly or parenterally.

12.3 Pharmacokinetics

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

The extent of human systemic exposure at the labeled intraocular dose has not been evaluated, however, significant systemic concentrations or plasma exposure of epinephrine are not expected when administered intraocularly.

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.

14 CLINICAL STUDIES

14.1 Induction and Maintenance of Mydriasis during Intraocular Surgery

In randomized, controlled studies, patients undergoing routine cataract extraction were evaluated after receiving intraocular irrigation with or without epinephrine diluted up to 1:1,666,666 (0.6 mcg/mL). Patients have also been evaluated after receiving bolus intracameral injections of epinephrine diluted between 1:25,000 (40 mcg/mL) and 1:400,000 (2.5 mcg/mL).

In patients with similar pupil diameters at baseline, with or without the use of preoperative mydriatic agents, mydriasis was maintained better in the eyes receiving epinephrine by an average of one to two millimeters in pupil diameter. Pupil constriction to 5mm or less occurred more often in the patients not receiving epinephrine.

Mean pulse rate and blood pressure showed no significant difference between patients receiving epinephrine and controls and there was no increased incidence of ventricular dysrhythmias in patients receiving epinephrine.

16 HOW SUPPLIED/STORAGE AND HANDLING

Adrenalin[®] 1 mL Single-Use Vials:

Each carton 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 42023-159-25 1 mL vial

Adrenalin[®] 30 mL Multi-Dose Vials:

Each carton 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 36 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, 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.

Distributed by:
Par Pharmaceutical Companies, Inc.
Chestnut Ridge, NY 10977

Adrenalin[®] is a registered trademark of Par Sterile Products, LLC (Chestnut Ridge, NY).
Registered Trademark No 53,934

R12/15
3003592B

OS159J-01-90-02

This label may not be the latest approved by FDA.
For the most current labeling information, please visit <https://www.fda.gov/>

NDC 42023-168-01

Adrenalin[®]
(epinephrine
injection, USP)

1 mg/mL
(30 mg/30 mL)
1:1000

For Intramuscular or
Subcutaneous Use

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.

Dosage:

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 _____

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Par Pharmaceutical Cos., Inc.
Chestnut Ridge, NY 10977

107/15

L A168J-52-90-01



(01)00342023168016

3 0 0 3 5 9 1

LOT

EXP

This label may not be the latest approved by FDA.
For the most current labeling information, please visit <https://www.fda.gov/>

NDC 42023-168-10

Adrenalin[®]
(epinephrine
injection, USP)

1 mg/mL
(30 mg/30 mL)
1:1000

For Intramuscular or
Subcutaneous Use

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.

Dosage:

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 _____

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Par Pharmaceutical Cos., Inc.
Chestnut Ridge, NY 10977

107/15

LA168J-10-90-01



101X00342023168108

3003589

LOT

EXP

This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugsatfda>

30 mL Multiple Dose Vial
Not for Ophthalmic Use
For Intramuscular or
Subcutaneous Use
1:1000
1 mg/mL
(30 mg/30 mL)
Adrenalin®
(epinephrine injection, USP)
Rx Only
NDC 42023-168-01

3003593A
136

NDC 42023-168-01 Rx Only

R

Adrenalin®
(epinephrine injection, USP)

1 mg/mL
(30 mg/30 mL)
1:1000

**For Intramuscular or
Subcutaneous Use**

Not for Ophthalmic Use

Discard 30 days after initial use:
Discard on _____

UC168J-52-90-02 R07/15

Distributed by:
Par Pharmaceutical Companies, Inc.
Chestnut Ridge, NY 10977



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

Note - Do not use the solution if it is colored or cloudy, or if it contains particulate matter.

Dosage: See full prescribing information.

A sterile solution for intramuscular or subcutaneous use.

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

See bottom of carton for lot number and expiration date.

NDC 42023-168-01 Rx Only

Adrenalin®
(epinephrine injection, USP)

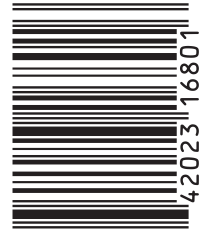
1 mg/mL
(30 mg/30 mL)
1:1000

**For Intramuscular or
Subcutaneous Use**

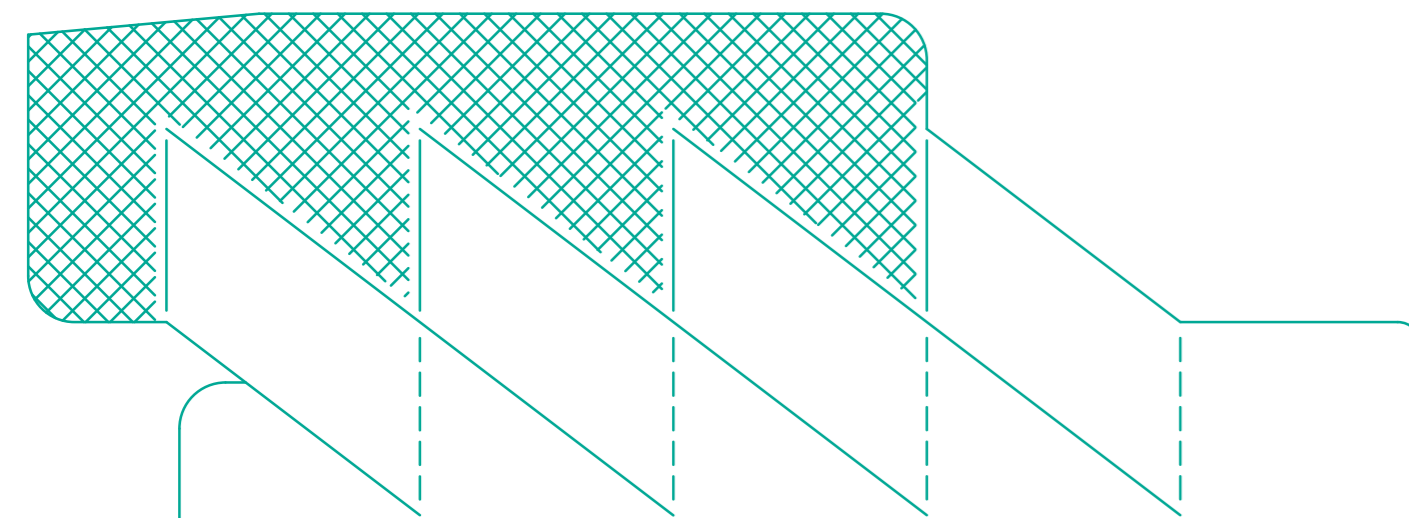
Not for Ophthalmic Use

Discard 30 days after initial use:
Discard on _____

30 mL Multiple Dose Vial



3 42023 16801 6



30 mL x 10 Multiple Dose Vials

Not for Ophthalmic Use
For Intramuscular or Subcutaneous Use

1 mg/mL
(30 mg/30 mL)
1:1000

Rx Only

NDC 42023-168-10

Rx Only

NDC 42023-168-10

Adrenalin[®]
(epinephrine injection, USP)

1 mg/mL
(30 mg/30 mL)
1:1000

For Intramuscular or Subcutaneous Use
Not for Ophthalmic Use

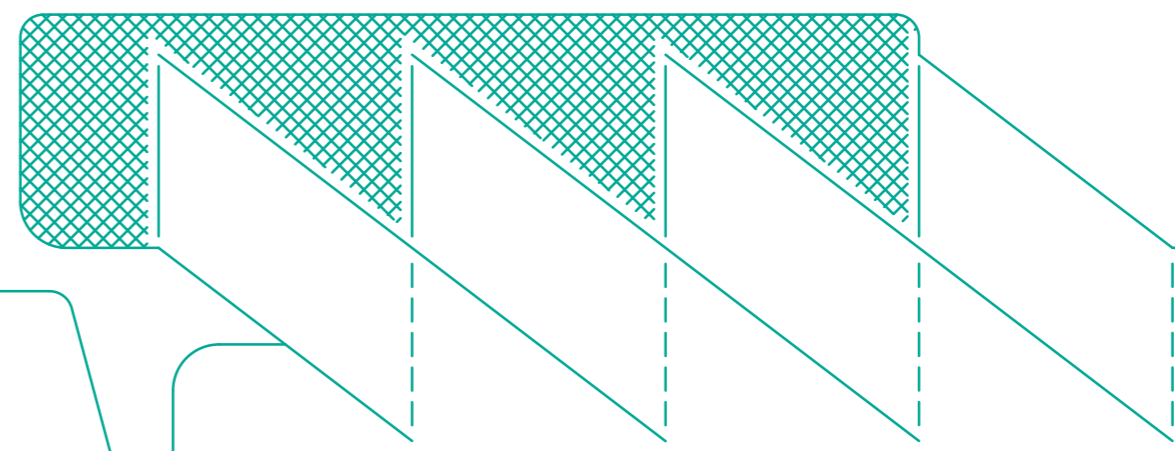
30 mL x 10 Multiple Dose Vials

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.

Note – Do not use the solution if it is colored or cloudy, or if it contains particulate matter.

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Chestnut Ridge, NY 10977

UC168J-62-90-01
10/7/15



3003590

NDC 42023-168-10

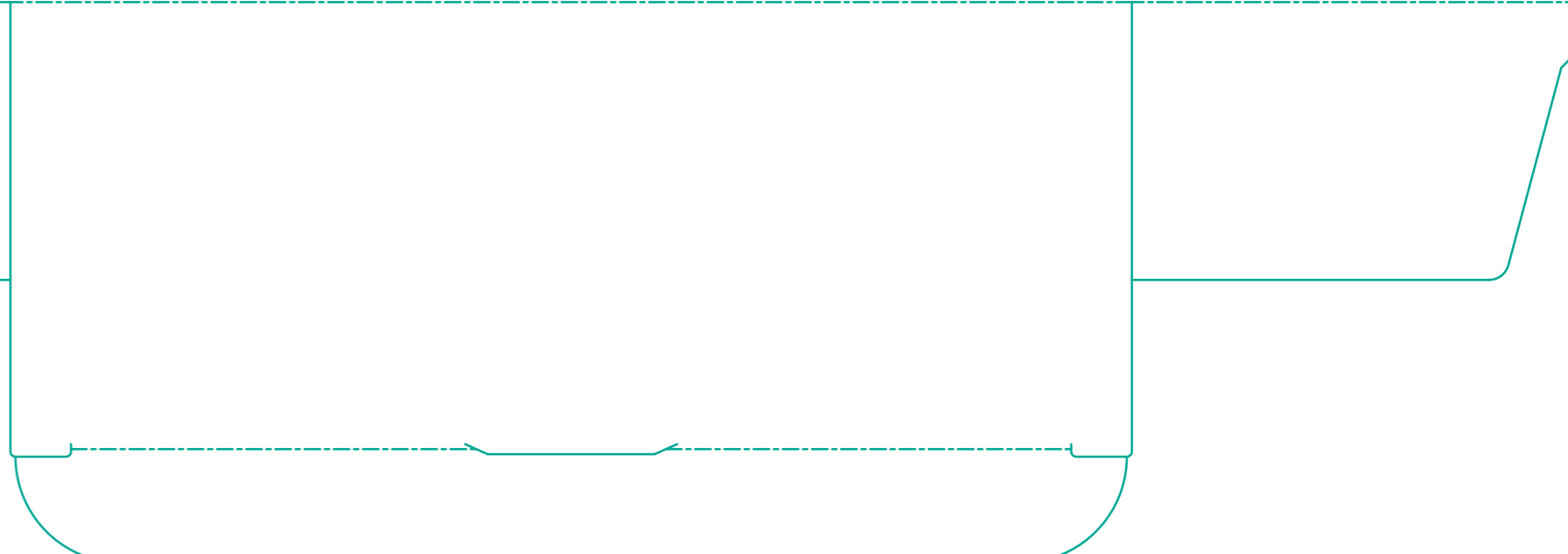
Rx Only

Adrenalin[®]
(epinephrine injection, USP)

For Intramuscular or Subcutaneous Use
Not for Ophthalmic Use

1 mg/mL
(30 mg/30 mL)
1:1000

30 mL x 10 Multiple Dose Vials



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/s/

LYDIA I GILBERT MCCLAIN
12/23/2015