

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### ***APPLICATION NUMBER:***

**204640Orig1s008**

***Trade Name:*** ADRENALIN

***Generic or Proper Name:*** epinephrine

***Sponsor:*** Par Pharmaceutical

***Approval Date:*** August 9, 2017

***Indication:*** Adrenalin is a non-selective alpha and beta adrenergic agonist indicated for:  
Emergency treatment of allergic reactions (Type 1),  
including anaphylaxis

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 204640Orig1s008

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**204640Orig1s008**

**APPROVAL LETTER**



NDA 204200/S-007  
NDA 204640/S-008

**SUPPLEMENT APPROVAL**

PAR Sterile Products, LLC  
Six Ram Ridge Road  
Chestnut Ridge, NY 10977

Attention: Carla English  
Senior Regulatory Affairs

Dear Ms. English:

Please refer to your Supplemental New Drug Applications (sNDAs) dated July 13, 2017, 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.

We also refer to our letter dated June 28, 2017, notifying you, under Section 505(0)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Adrenalin (epinephrine injection, USP) 1 mg/mL. This information pertains to the serious risk of confusion between the previous Adrenalin product that was indicated for mydriasis (ophthalmic route of administration) and the reformulated Adrenalin product that is not indicated for mydriasis.

These supplemental new drug applications provide for revisions to the labeling for Adrenalin (epinephrine injection, USP) 1 mg/mL consistent with our June 28, 2017, correspondence and with our July 20, 2017, revisions to the package insert, including the addition of stress cardiomyopathy in the Adverse Reactions section of the package insert.

**APPROVAL & LABELING**

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**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 include 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, 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 titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 204200/S-007 and NDA 204640/S-008.**” Approval of this submission by FDA is not required before the labeling is used.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

NDA 204200/S-007

NDA 204640/S-008

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### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Carol F. Hill, Senior Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

*{See appended electronic signature page}*

Sally Seymour, MD  
Deputy Director for Safety  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

#### ENCLOSURES:

Content of Labeling  
Carton and Container Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LYDIA I GILBERT MCCLAIN  
08/09/2017

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204640Orig1s008**

**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, for intramuscular and subcutaneous use**

Initial U.S. Approval: 1939

### RECENT MAJOR CHANGES

Indications and Usage, Mydriasis (1)	Removed 09/2016
Dosage and Administration (2)	05/2016, 09/2016
Warnings and Precautions (5, 5.1, 5.2)	05/2016, 09/2016

### 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)

### DOSAGE AND ADMINISTRATION

- **Anaphylaxis:**
  - *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)
  - *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)

### DOSAGE FORMS AND STRENGTHS

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

### CONTRAINDICATIONS

None (4)

### WARNINGS AND PRECAUTIONS

- Do not inject into buttocks, digits, hands, or feet (5.1)
- Rare cases of serious skin and soft tissue infections have been reported following epinephrine injection. Advise patients to seek medical care if they develop signs or symptoms of infection. (5.2)

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

### 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)

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](http://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: 08/2017

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

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

Adrenalin<sup>®</sup> is available as a single-use 1 mL vial and a multiple-use 30 mL vial for intramuscular and subcutaneous use.

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.

### 2 DOSAGE AND ADMINISTRATION

Inject Adrenalin<sup>®</sup> 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 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<sup>®</sup> 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<sup>®</sup> 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.

### 3 DOSAGE FORMS AND STRENGTHS

Adrenalin<sup>®</sup> 1 mg/mL 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 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 Clostridial infections (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.

### 5.2 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. *Clostridium* spores can be present on the skin and introduced into the deep tissue with subcutaneous or intramuscular injection. While cleansing with alcohol may reduce presence of bacteria on the skin, alcohol cleansing does not kill *Clostridium* spores. To decrease the risk of *Clostridium* infection, do not inject Adrenalin<sup>®</sup> into the buttock [see *Warnings and Precautions (5.1)*]. 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 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)*].

### 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.

### **5.4 Allergic Reactions Associated with Sulfite**

Adrenalin<sup>®</sup> 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 (5.3)*].

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, ventricular ectopy and stress cardiomyopathy.

Angina may occur in patients with coronary artery disease [*see Warnings and Precautions (5.3)*].

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 (5.3)*].

Rapid rises in blood pressure associated with epinephrine use have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease [*see Warnings and Precautions (5.3)*].

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 (5.3)*].

Diabetic patients may experience transient increases in blood sugar [*see Warnings and Precautions (5.3)*].

Accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area [*see Warnings and Precautions (5.1)*]. 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 (5.1)*].

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)*].

Skin: sweating.

**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](http://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 (5.3) and Adverse Reactions (6)*].

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, triprolidine, 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<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> 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.

### **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.

## 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  $\alpha$ -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  $\alpha$ -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.

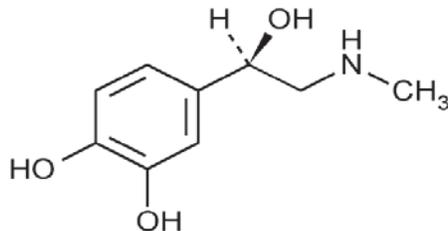
Myocardial ischemia, myocardial infarction and cardiomyopathy have been noted in the literature following overdose of epinephrine.

## 11 DESCRIPTION

Adrenalin<sup>®</sup> (epinephrine injection, USP) is a clear, colorless, sterile solution containing 1 mg/mL 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<sup>®</sup> solution contains 1 mg epinephrine, 7.3 mg sodium chloride, 0.457 mg sodium metabisulfite, 1 mg sodium hydroxide, 2.25 mg tartaric acid, 0.20 mg disodium edetate dihydrate, hydrochloric acid to adjust pH, and water for injection. In the 30 mL vial, each 1 mL of Adrenalin<sup>®</sup> 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- $\alpha$ -[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* (5.3)].

Epinephrine causes mydriasis when administered parenterally.

### 12.3 Pharmacokinetics

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

## 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<sup>®</sup> 1 mL Single-Use Vials:**

Each carton contains 25 single-use vials containing 1 mL Adrenalin<sup>®</sup> (epinephrine injection, USP) solution 1 mg/mL in a 3 mL clear glass vial.

NDC 42023-159-25      1 mL vial

### **Adrenalin<sup>®</sup> 30 mL Multi-Dose Vials:**

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

NDC 42023-168-01      30 mL 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)].

Distributed by:

**Par Pharmaceutical**

Chestnut Ridge, NY 10977

Adrenalin<sup>®</sup> is a registered trademark of Par Sterile Products, LLC (Chestnut Ridge, NY).  
Registered Trademark No. 53,934

R08/17  
3003592G

OS159J-01-90-07

USP Class MB is  
**Atenolol**  
 (see USP Class MB)  
 1 mg/ml  
 For oral use only  
 Mylan Pharmaceuticals  
 Fort Worth, TX 76104

In-Only  
 Keep out of reach  
 of children.  
 Do not use if  
 the seal is broken  
 or missing.

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(b) (4)

■ Non-varnished area (Does Not Print)    □ Non-printing Deline

- Iss./Rev. Date: R 07/17
- Software/Version: Adobe Illustrator CC
- Change notes: FDA Safety Changes

Reviewed by: \_\_\_\_\_ Approved by: \_\_\_\_\_  
 Date: \_\_\_\_\_ Date: \_\_\_\_\_

For Internal Use ONLY:  
 IA: 3  
 CVA: \_\_\_\_\_

1 mL x 25 Single-Dose Vials  
 NOT for Ophthalmic Use  
 For Intramuscular and Subcutaneous Use  
**Adrenalin®** (epinephrine injection, USP)  
**1 mg/mL**  
 Rx Only      NDC 42023-159-25

NDC 42023-159-25      Rx Only  
**Adrenalin®**  
 (epinephrine injection, USP)  
**1 mg/mL**  
 For Intramuscular and Subcutaneous Use  
 NOT for Ophthalmic Use

Each mL contains 1 mg Adrenalin (epinephrine) dissolved in Water for Injection, USP with sodium chloride, sodium hydroxide, tartaric acid, disodium edetate and not more than 0.05% sodium bisulfite as an antioxidant.  
 Do not use the solution if it is colored or cloudy, or if it contains particulate matter.  
 UC189 J-15-90-04      R07/17  
 Distributed by:  
 Par Pharmaceutical  
 Chestnut Ridge, NY 10977      **PAR**

**Adrenalin®**  
 (epinephrine injection, USP)  
 A sterile solution for intramuscular and subcutaneous use.  
 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.



NDC 42023-159-25      Rx Only  
**Adrenalin®**  
 (epinephrine injection, USP)  
**1 mg/mL**  
 For Intramuscular and Subcutaneous Use  
 NOT for Ophthalmic Use  
 1 mL x 25 Single-Dose Vials



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/s/  
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LYDIA I GILBERT MCCLAIN  
08/09/2017

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204640Orig1s008**

**MEDICAL REVIEW(S)**

**MEDICAL OFFICER REVIEW**

**Division Of Pulmonary, Allergy, and Rheumatology Products (HFD-570)**

Application: NDA 204200, S-007 Trade Name: Adrenalin, 1 mL vial  
NDA 204640, S-008 Adrenalin, 30 mL vial  
Applicant/Sponsor: Par Sterile Products USAN Name: Epinephrine injection, USP  
Medical Officer: Peter Starke, MD Category: Catecholamine: nonselective alpha and beta  
Deputy Dir. for Safety: Sally Seymour, MD adrenergic agonist  
Date: July 27, 2017 Route: *Anaphylaxis*: Intramuscular or subcutaneous

**SUBMISSIONS REVIEWED IN THIS DOCUMENT / OTHER RELEVANT DOCUMENTS**

<u>Document Date</u>	<u>Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
February 1, 2017			<i>IR to update labeling per USP39-NF 34 chapter &lt;7&gt;</i>
June 28, 2017			<i>FDAAA Safety Labeling Change Notification</i>
July 13, 2017	July 13, 2017	S-007, SD-188	Adrenalin 1 mL labeling supplement
July 13, 2017	July 13, 2017	S-008, SD-84	Adrenalin 30 mL labeling supplement
July 20, 2017			<i>IR requesting to modify the RMC section of the HL section of the PI to show that the mydriasis indication was removed on 9/2016 (1 mL vial), and to include stress cardiomyopathy as an Adverse Reaction</i>
July 24, 2017	July 24, 2017	N204200, SD-189 N204640, SD-85	Response to labeling IR of July 20, 2017

**REVIEW SUMMARY:**

This is a review of two labeling supplements submitted by Par Sterile Products, one each to NDA 240200 and 240640, for Adrenalin (epinephrine injection) 1 mL and 30 mL vials, respectively. The supplements were submitted in response to a June 28, 2017, FDAAA, Safety Labeling Change Notification letter for the safety issue of confusion between the previous Adrenalin 1mL product, which included an indication for mydriasis (ophthalmic route of administration), and the reformulated Adrenalin 1 mL product for which Par requested that the indication be removed because there was insufficient support for all of the inactive ingredients with respect to intraocular use during eye surgery. The letter requested changes to the carton and container labeling of both the 1 mL and 30 mL vials to add the statement ‘NOT for Ophthalmic Use’ along with other labeling changes, to issue a Dear Healthcare Provider Letter to ambulatory surgical centers and ophthalmologists and post it on their website, and to provide a communication plan to address potential confusion regarding the inappropriate route of administration. The Agency also asked Par to change the Recent Major Changes (RMC) section in the Highlights (HL) of the Prescribing Information (PI) to indicate that the mydriasis indication was removed in September 2016, and to add ‘stress cardiomyopathy’<sup>1</sup> to the Adverse Reactions section (note that the two products share one PI). Par is also taking the opportunity to remove the ratio expression of 1:1000 as a methodology to express the concentration of epinephrine in the labeling, per USP39-NF 34 chapter <7> and a communication from the Agency dated February 1, 2017.

**OUTSTANDING ISSUES:**

None. The carton/container labeling submitted by Par on July 13 and the PI submitted on July 24 (attached) were reviewed and are acceptable.

**RECOMMENDED REGULATORY ACTION**

NDA/Supplements:  X  Approval  \_\_\_\_\_  Complete Response  
Other Action:  \_\_\_\_\_

<sup>1</sup> Nazir S, Lohani S, et al. Takotsubo cardiomyopathy associated with epinephrine use: A systematic review and meta-analysis. Int J Cardiol. 2017 Feb 15; 229:67-70.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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PETER R STARKE  
07/27/2017

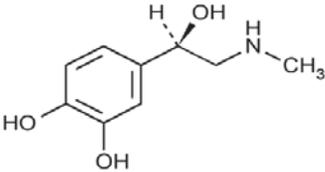
SALLY M SEYMOUR  
07/27/2017

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204640Orig1s008**

**CHEMISTRY REVIEW(S)**

CHEMIST'S REVIEW <i>Review #1</i>	1. ORGANIZATION Branch 1/PMAD1/OLDP/OPQ	2. NDA NUMBERS 204-640
3. NAME AND ADDRESS OF APPLICANT Par Sterile Products, LLC Six Ram Ridge Road Chestnut Ridge, NY 10977  Ms Carla English Senior Manager Regulatory Affairs Tel:845-573-5728, Fax: 845-573-5795 e-mail: regulatory.psp@parpharm.com		4. AF NUMBER
		5. SUPPLEMENT(S) NUMBER(S) & DATES(S) <b>S-008; PAS; SDN 84</b> Letter Date: 7/13/17 Stamp Date: 7/13/17 <b>[BL]; SDN 85</b> Letter Date: 7/13/17 Stamp Date: 7/13/17 <b>Due Date: 1/13/18</b>
6. NAME OF DRUG Adrenalin®	7. NONPROPRIETARY NAME epinephrine injection, USP	
8. SUPPLEMENT PROVIDES FOR: Safety labeling changes under 505(o)(4) - Prior Approval Supplement		
9. PHARMACOLOGICAL CATEGORY Emergency treatment of allergic reactions (Type 1), including anaphylaxis.	10. HOW DISPENSED RX <u>x</u> OTC ___	11. RELATED IND/NDA/DMF
12. DOSAGE FORM(S) Injection	13. POTENCY 1 mg/mL (1:1000)	
14. CHEMICAL NAME AND STRUCTURE 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (-)-3,4-Dihydroxy- $\alpha$ -[2-(methylamino)ethyl]benzyl alcohol   Molecular Formula: C <sub>9</sub> H <sub>13</sub> NO <sub>3</sub> Molecular Weight: 183.2		15. RECORDS AND REPORTS CURRENT YES_NO REVIEWED YES_NO
16. COMMENTS: Container label, carton label, and package insert are reviewed.		
17. CONCLUSION AND RECOMMENDATION The labeling changes are acceptable from CMC standpoint.		
18. REVIEWER NAME Chong-Ho Kim, Ph.D.	SIGNATURE	DATE COMPLETED August 2, 2017

**Background**

Par is submitting this Prior Approval supplement in response to the Agency’s June 28, 2017 Safety Labeling Change Notification advising of new safety information for the reformulated Adrenalin® product.

Further reference is made to Applicant’s June 30, 2017 General Correspondence which addressed the Agency’s request to outline our communication efforts to address potential confusion regarding inappropriate route of administration of Adrenalin.

In accordance with section 505(o)(4) of the FDCA, Par hereby submits a Prior Approval Supplement to propose labeling changes to their vial and carton labeling. Par believes that the addition of the “NOT for Ophthalmic Use” and increased prominence of the “For Intramuscular and Subcutaneous Use” statements on the container and carton labeling, in conjunction with the broadened communication plan to healthcare professionals including ambulatory surgical centers and ophthalmologists, adequately addresses the potential confusion regarding inappropriate route of administration and will help ensure the safe use of the drug product.

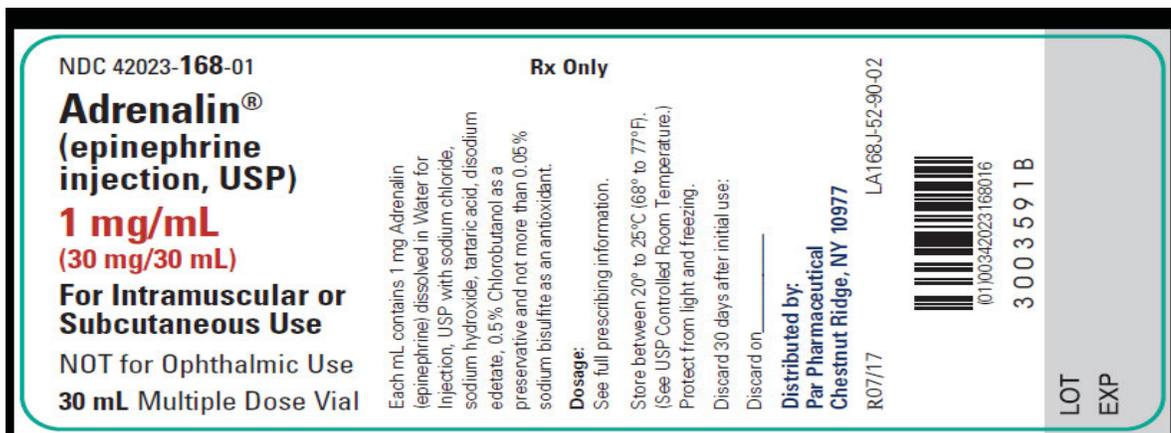
Additionally, Par has updated their labeling to remove the ratio expression of epinephrine in accordance with USP 39-NF 34 chapter <7>, as communicated to the Agency on March 30, 2017. Par intends to implement the removal of the ratio expression concurrent with the safety labeling changes proposed in this supplement. A copy of the revised 30 mL vial label and carton label are provided in Module 1.

**Review**

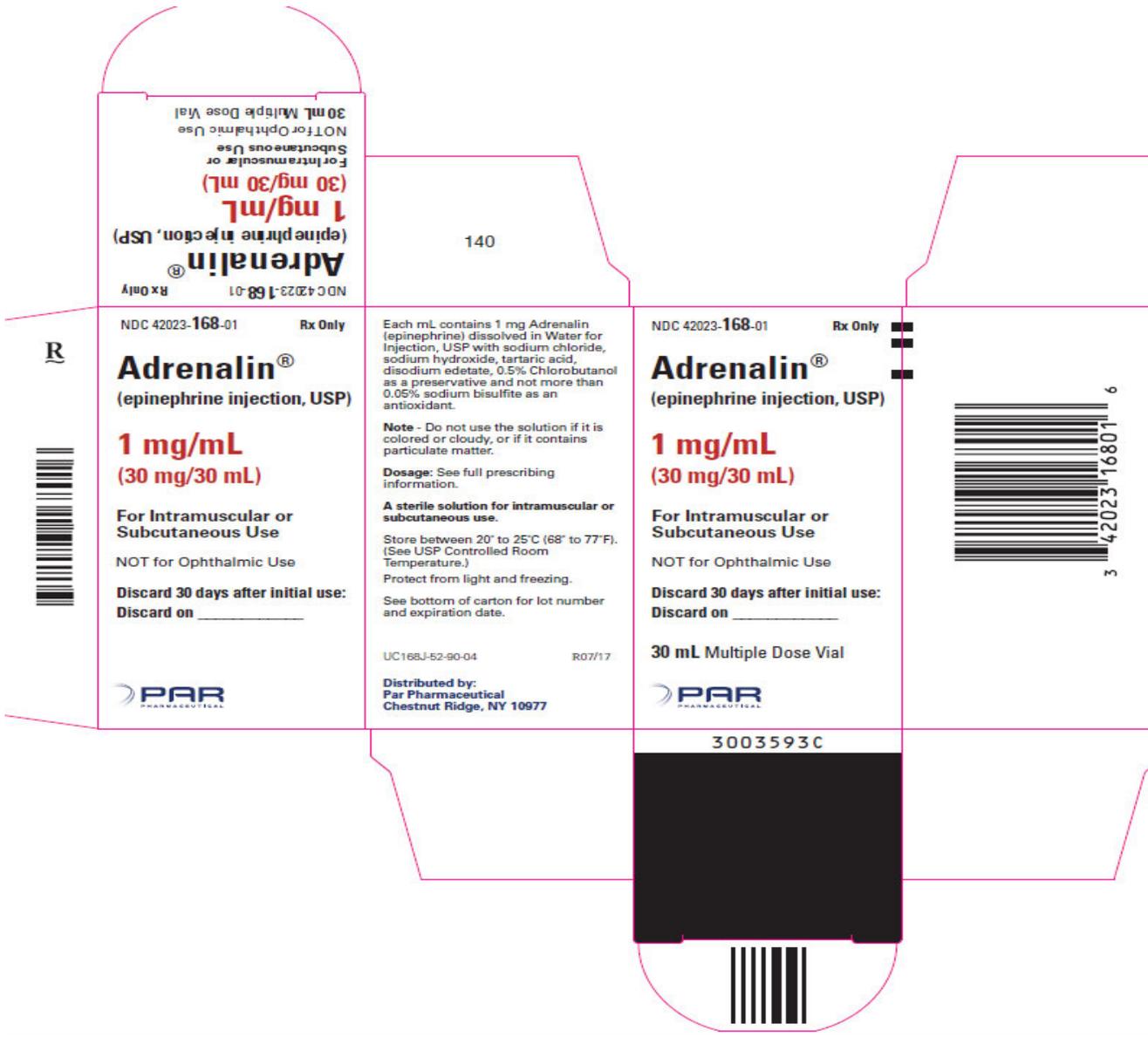
**1.14. Labeling**

1.14.1. Draft Labeling

1.14.1.1. Draft Carton and Container Labels



*Evaluation: Acceptable  
The container label is acceptable.*



Evaluation: Acceptable  
 The carton label is acceptable.

**Amendment (SDN 85) dated July 24, 2017**

This amendment is the applicant’s response to the Agency’s July 20, 2017 communication advising of additional recommendations to the package insert labeling.

The following documents are provided in Module 1:

- Package insert in Microsoft Word format (clean and marked-up)

- Side-By-Side Comparison – Current Insert vs Proposed Insert (highlighted and annotated)

Review:

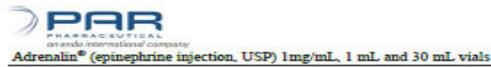
1.14. Labeling

1.14.1. Draft Labeling

1.14.1.2. Annotated Draft Labeling Text

Insert July 2017 – Side-By-Side

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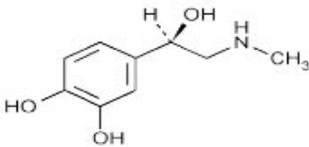
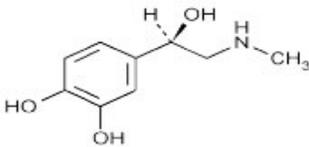


FDA Approved Labeling September 12, 2016 (S-004)	Revised Labeling According to FDA General Advice Letter Dated February 1, 2017 and SLC Notification dated July 20, 2017
<p><b>HIGHLIGHTS OF PRESCRIBING INFORMATION</b> These highlights do not include all the information needed to use ADRENALIN safely and effectively. See full prescribing information for ADRENALIN.</p> <p><b>ADRENALIN (epinephrine injection) 1 mg/mL (1:1000),</b> for intramuscular and subcutaneous use Initial U.S. Approval: 1939</p> <p>-----<b>RECENT MAJOR CHANGES</b>-----                      Indications and Usage (1) 09/2016                      Dosage and Administration (2) 05/2016, 09/2016                      Warnings and Precautions (5, 5.1, 5.2) 05/2016, 09/2016</p> <p>-----<b>INDICATIONS AND USAGE</b>-----                      Adrenalin® is a non-selective alpha and beta adrenergic agonist indicated for:                      • Emergency treatment of allergic reactions (Type 1), including anaphylaxis (1)</p>	<p><b>HIGHLIGHTS OF PRESCRIBING INFORMATION</b> These highlights do not include all the information needed to use ADRENALIN safely and effectively. See full prescribing information for ADRENALIN.</p> <p><b>ADRENALIN (epinephrine injection) 1 mg/mL,</b> for intramuscular and subcutaneous use Initial U.S. Approval: 1939</p> <p>-----<b>RECENT MAJOR CHANGES</b>-----                      Indications and Usage, <b>Mydriasis (1) Removed</b> 09/2016                      Dosage and Administration (2) 05/2016, 09/2016                      Warnings and Precautions (5, 5.1, 5.2) 05/2016, 09/2016</p> <p>-----<b>INDICATIONS AND USAGE</b>-----                      Adrenalin® is a non-selective alpha and beta adrenergic agonist indicated for:                      • Emergency treatment of allergic reactions (Type 1), including anaphylaxis (1)</p>
<p>Deleted ratio expression 1:1000 per FDA General Advice letter dated February 1, 2017. Updated Recent Major Changes section per FDA Safety Labeling Change Notification dated July 20, 2017.</p>	

FDA Approved Labeling September 12, 2016 (S-004)	Revised Labeling According to FDA General Advice Letter Dated February 1, 2017 and SLC Notification dated July 20, 2017
<p>-----<b>DOSAGE AND ADMINISTRATION</b>-----</p> <p>• <b>Anaphylaxis:</b>                      ◦ <i>Adults and Children 30 kg (66 lbs) or more:</i> 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)                      ◦ <i>Children 30 kg (66 lbs) or less:</i> 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)</p> <p>-----<b>DOSAGE FORMS AND STRENGTHS</b>-----                      Injection: 1 mg/mL (1:1000), 1 mL single-use vials and 30 mL multiple-dose vials (3)</p> <p>-----<b>CONTRAINDICATIONS</b>-----                      None (4)</p>	<p>-----<b>DOSAGE AND ADMINISTRATION</b>-----</p> <p>• <b>Anaphylaxis:</b>                      ◦ <i>Adults and Children 30 kg (66 lbs) or more:</i> 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)                      ◦ <i>Children 30 kg (66 lbs) or less:</i> 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)</p> <p>-----<b>DOSAGE FORMS AND STRENGTHS</b>-----                      Injection: 1 mg/mL, 1 mL single-use vials and 30 mL multiple-dose vials (3)</p> <p>-----<b>CONTRAINDICATIONS</b>-----                      None (4)</p>
<p>Deleted ratio expression 1:1000 per FDA General Advice letter dated February 1, 2017.</p>	

Evaluation:     Acceptable

FDA Approved Labeling September 12, 2016 (S-004)	Revised Labeling According to FDA General Advice Letter Dated February 1, 2017 and SLC Notification dated July 20, 2017
<p><b>11 DESCRIPTION</b></p> <p>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, 7.3 mg sodium chloride, 0.457 mg sodium metabisulfite, 1 mg sodium hydroxide, 2.25 mg tartaric acid, 0.20 mg disodium edetate dihydrate, 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.</p>	<p><b>11 DESCRIPTION</b></p> <p>Adrenalin® (epinephrine injection, USP) is a clear, colorless, sterile solution containing 1 mg/mL 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, 7.3 mg sodium chloride, 0.457 mg sodium metabisulfite, 1 mg sodium hydroxide, 2.25 mg tartaric acid, 0.20 mg disodium edetate dihydrate, 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.</p>
<p>Deleted ratio expression 1:1000 per FDA General Advice letter dated February 1, 2017.</p>	

FDA Approved Labeling September 12, 2016 (S-004)	Revised Labeling According to FDA General Advice Letter Dated February 1, 2017 and SLC Notification dated July 20, 2017
<p>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.</p> <p>The chemical structure of epinephrine is:</p>  <p>The molecular weight of epinephrine is 183.2.</p> <p>Epinephrine solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin.</p>	<p>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.</p> <p>The chemical structure of epinephrine is:</p>  <p>The molecular weight of epinephrine is 183.2.</p> <p>Epinephrine solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin.</p>
<p>No change to this section.</p>	

Evaluation:     Acceptable

FDA Approved Labeling September 12, 2016 (S-004)	Revised Labeling According to FDA General Advice Letter Dated February 1, 2017 and SLC Notification dated July 20, 2017
<p><b>16 HOW SUPPLIED/STORAGE AND HANDLING</b></p> <p><b>Adrenalin® 1 mL Single-Use Vials:</b>                      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</p> <p><b>Adrenalin® 30 mL Multi-Dose Vials:</b>                      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</p> <p>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.</p>	<p><b>16 HOW SUPPLIED/STORAGE AND HANDLING</b></p> <p><b>Adrenalin® 1 mL Single-Use Vials:</b>                      Each carton contains 25 single-use vials containing 1 mL Adrenalin® (epinephrine injection, USP) solution 1 mg/mL in a 3 mL clear glass vial.                      NDC 42023-159-25 1 mL vial</p> <p><b>Adrenalin® 30 mL Multi-Dose Vials:</b>                      Each carton contains 1 multiple-dose vial containing 30 mL Adrenalin® (epinephrine injection, USP) solution 1 mg/mL in a 36 mL amber glass vial.                      NDC 42023-168-01 30 mL vial, (b) (4)</p> <p>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.</p>
<p>Deleted ratio expression 1:1000 per FDA General Advice letter dated February 1, 2017. Removed 10 pack per Marketing as this presentation is not being commercially distributed.</p>	

Evaluation:     *Acceptable*

**CONCLUSION AND RECOMMENDATION**

Container label, carton label, and package insert are reviewed.

The labeling changes are acceptable from CMC standpoint.

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/s/  
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CHONG HO KIM  
08/02/2017

RAMESH RAGHAVACHARI  
08/03/2017

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204640Orig1s008**

**OTHER REVIEW(S)**

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

---

**Date of This Memorandum:** July 18, 2017

**Requesting Office or Division:** Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

**Application Type and Number:** NDA 204200/S-007 and NDA 204640/S-008

**Product Name and Strength:** Adrenalin (epinephrine) Injection, 1 mg/mL, 1 mL vial  
Adrenalin (epinephrine) Injection, 30 mL vial

**Applicant/Sponsor Name:** Par Pharmaceuticals

**Submission Date:** July 13, 2017

**OSE RCM #:** 2017-1407 and 2017-1409

**DMEPA Primary Reviewer:** Lissa C. Owens, PharmD

**DMEPA Team Leader:** Sarah K. Vee, PharmD

**DMEPA Associate Director:** Mishale Mistry, PharmD, MPH

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#### 1 PURPOSE OF MEMO

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the revised container label and carton labeling for Adrenalin (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous postmarket medication error review.<sup>a</sup>

#### 2 CONCLUSION

The revised container label and carton labeling for Adrenalin are acceptable from a medication error perspective. We have no further recommendations at this time.

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<sup>a</sup> Owens, L. Postmarket Medication Error Review for PRODUCT NAME (NDA 204200 and NDA 204640). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUN 21. RCM No.: 2017-547.

APPENDIX A. LABEL AND LABELING SUBMITTED ON JULY 13, 2017

Container labels

NDC 42023-159-25

**Adrenalin<sup>®</sup>**  
(epinephrine injection, USP)

**1 mg/mL**

**For Intramuscular and Subcutaneous Use**

NOT for Ophthalmic Use

1 mL Single-Dose Vial

**Rx Only**

**Dosage and Storage:**  
See full prescribing information.

**Distributed by:**  
**Par Pharmaceutical**  
Chestnut Ridge, NY 10977

R07/17 LA159J-52-90-03



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NDC 42023-168-01

**Adrenalin<sup>®</sup>**  
**(epinephrine injection, USP)**

**1 mg/mL**  
**(30 mg/30 mL)**

**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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Chestnut Ridge, NY 10977

R07/17 LA168J-52-90-02



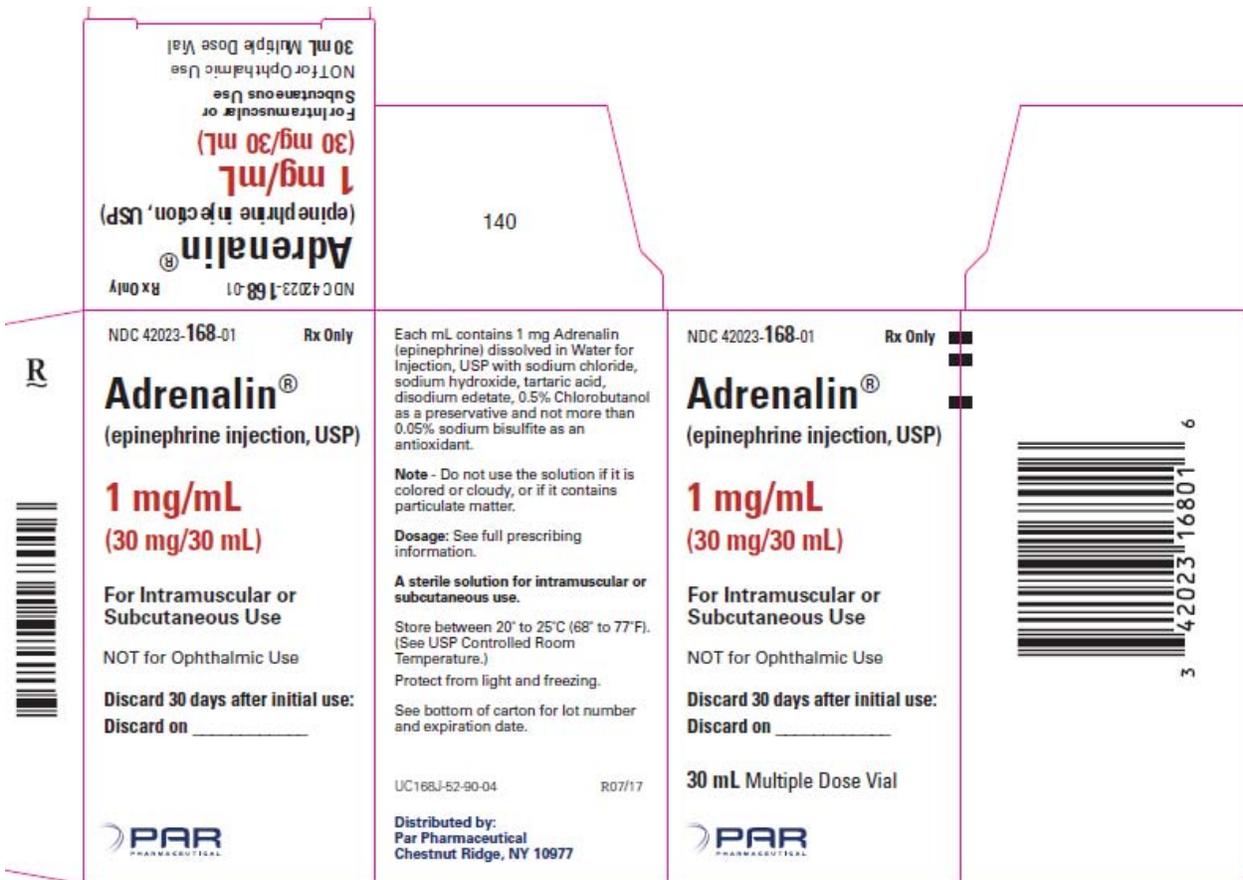
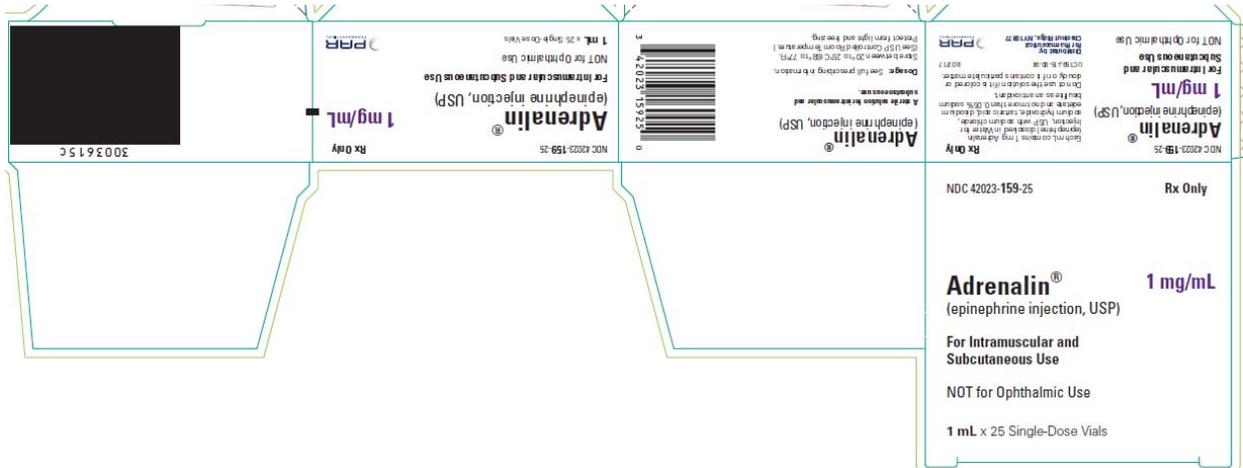
(01)00342023168016

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LOT

EXP

# Carton labeling



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/s/  
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LISSA C OWENS  
07/18/2017 11:57:54 AM

SARAH K VEE  
07/18/2017 01:12:26 PM

MISHALE P MISTRY  
07/19/2017 04:38:51 PM