Approval Package for:

APPLICATION NUMBER:  
019430Orig1s059

Trade Name: EPIPEN

Generic or Proper Name: epinephrine

Sponsor: Mylan Specialty L.P.

Approval Date: April 30, 2014

Indication: EpiPen and EpiPen Jr contain epinephrine, a non-selective alpha and beta-adrenergic receptor agonist, indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis.
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019430Orig1s059

APPROVAL LETTER
NDA 019430/S-059

Mylan Specialty L.P.
781 Chestnut Ridge Rd.
Morgantown, WV 26504-4301

Attention: Dawn Watson, Ph.D.
   Vice President, Global Regulatory Affairs

Dear Dr. Watson:

Please refer to your Supplemental New Drug Application (sNDA) dated October 25, 2013, received, October 28, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EpiPen and EpiPen Jr (epinephrine injection) Auto-Injector, 0.3 mg and 0.15 mg.

We acknowledge receipt of your amendments dated November 8 and 15, 2013, and February 28, March 17, April 9, 22, 24, and 28, 2014.

This prior approval supplemental new drug application proposes to update the labeling to incorporate the format and content of the Physician Label Rule (PLR) in compliance with governing regulations 21 CFR 201.56 and 21 CFR 201.57.

We have completed our review of this supplemental application, as amended. It is 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, text for the patient information leaflet/instructions for use insert and trainer instructions for use 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

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).

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,

Lydia I. 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(S):
Content of Labeling

Reference ID: 3498053
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LYDIA I GILBERT MCCLAIN
04/30/2014
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EPIPEN® and EPIPEN Jr® safely and effectively. See full prescribing information for EPIPEN and EPIPEN Jr.

EPIPEN® (epinephrine injection), Auto-Injector 0.3 mg, EPIPEN Jr® (epinephrine injection) Auto-Injector 0.15 mg, for intramuscular or subcutaneous use
Initial U.S. Approval: 1939

--- INDICATIONS AND USAGE ---
EpiPen and EpiPen Jr contain epinephrine, a non-selective alpha and beta-adrenergic receptor agonist, indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis. (1)

--- DOSAGE AND ADMINISTRATION ---
- Patients greater than or equal to 30 kg (66 lbs): EpiPen 0.3 mg (2)
- Patients 15 to 30 kg (33 lbs to 66 lbs): EpiPen Jr 0.15 mg (2)
Inject EpiPen and EpiPen Jr intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. Each device is a single-use injection. (2)

--- DOSAGE FORMS AND STRENGTHS ---
- EpiPen: Injection, 0.3 mg: 0.3 mg/0.3 mL epinephrine, USP, pre-filled auto-injector (3)
- EpiPen Jr: Injection, 0.15 mg: 0.15 mg/0.3 mL epinephrine, USP, pre-filled auto-injector (3)

--- CONTRAINDICATIONS ---
None (4)

--- WARNINGS AND PRECAUTIONS ---
- In conjunction with use, seek immediate medical or hospital care. (5.1)
- Do not inject intravenously, into buttock, or into digits, hands, or feet. (5.2)
- The presence of a sulfite in this product should not deter use. (5.3)
- Administer with caution in patients with heart disease; may aggravate angina pectoris or produce ventricular arrhythmias. (5.4)

--- ADVERSE REACTIONS ---
Adverse reactions to epinephrine include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, and/or respiratory difficulties. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan Specialty, L.P. at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

--- DRUG INTERACTIONS ---
- Cardiac glycosides or diuretics: observe for development of cardiac arrhythmias. (7)
- Tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines: potentiate effects of epinephrine. (7)
- Beta-adrenergic blocking drugs: antagonize cardiostimulating and bronchodilating effects of epinephrine. (7)
- Alpha-adrenergic blocking drugs: antagonize vasoconstricting and hypertensive effects of epinephrine. (7)
- Ergot alkaloids: may reverse the pressor effects of epinephrine. (7)

--- USE IN SPECIFIC POPULATIONS ---
- Elderly patients may be at greater risk of developing adverse reactions. (5.4, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling

Revised: April 2014

Reference ID: 3498053
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
EpiPen and EpiPen Jr are indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.

EpiPen and EpiPen Jr are intended for immediate administration in patients who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions.

Anaphylactic reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritus, rashes, urticaria or angioedema.

EpiPen and EpiPen Jr are intended for immediate administration as emergency supportive therapy only and are not a substitute for immediate medical care.

2 DOSAGE AND ADMINISTRATION
Selection of the appropriate dosage strength (EpiPen 0.3 mg or EpiPen Jr 0.15 mg) is determined according to patient body weight.

- Patients greater than or equal to 30 kg (approximately 66 pounds or more): EpiPen 0.3 mg
- Patients 15 to 30 kg (33 pounds to 66 pounds): EpiPen Jr 0.15 mg

Inject EpiPen or EpiPen Jr intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary.

Each EpiPen or EpiPen Jr contains a single dose of epinephrine for single-use injection. Since the doses of epinephrine delivered from EpiPen or EpiPen Jr are fixed, consider using other forms of injectable epinephrine if doses lower than 0.15 mg are deemed necessary.

The prescriber should carefully assess each patient to determine the most appropriate dose of epinephrine, recognizing the life-threatening nature of the reactions for which this drug is indicated. With severe persistent anaphylaxis, repeat injections with an additional EpiPen or EpiPen Jr may be necessary. More than two sequential doses of epinephrine should only be administered under direct medical supervision [see Warnings and Precautions (5.1)].

The epinephrine solution in the clear window of the EpiPen Auto-Injector should be inspected visually for particulate matter and discoloration. Epinephrine is light sensitive and should be stored in the carrier tube provided to protect it from light [see How Supplied/Storage and Handling (16.2)].

3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
None

5 WARNINGS AND PRECAUTIONS
5.1 Emergency Treatment
EpiPen and EpiPen Jr are intended for immediate administration as emergency supportive therapy and are not intended as a substitute for immediate medical care. In conjunction with the administration of epinephrine, the patient should seek immediate medical or hospital care. More than two sequential doses of epinephrine should only be administered under direct medical supervision [see Indications and Usage (1), Dosage and Administration (2) and Patient Counseling Information (17)].

5.2 Incorrect Locations of Injection
EpiPen and EpiPen Jr should only be injected into the anterolateral aspect of the thigh [see Dosage and Administration (2) and Patient Counseling Information (17)].
- Do not inject intravenously. Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine if there is such inadvertent administration.
- Do not inject into buttocK. Injection into the buttock may not provide effective treatment of anaphylaxis. Advise the patient to go immediately to the nearest emergency room for further treatment of anaphylaxis. Additionally, injection into the buttock has been associated with 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. Since epinephrine is a strong vasoconstrictor, accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area. Advise the patient to go immediately to the nearest emergency room and to inform the healthcare provider in the emergency room of the location of the accidental injection. Treatment of such inadvertent administration should consist of vasodilation, in addition to further appropriate treatment of anaphylaxis [see Adverse Reactions (6)].

5.3 Allergic Reactions Associated With Sulfite
The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations even if the patient is sulfite-sensitive.

Epinephrine is the preferred treatment for serious allergic reactions or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may, in other products, cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons.
The alternatives to using epinephrine in a life-threatening situation may not be satisfactory.

5.4 Disease Interactions
Some patients may be at greater risk for developing adverse reactions after epinephrine administration. Despite these concerns, it should be recognized that the presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation. Therefore, patients with these conditions, and/or any other person who might be in a position to administer EpiPen or EpiPen Jr to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which epinephrine should be used.

- Patients with Heart Disease
Epinephrine should be administered with caution to patients who have heart disease, including patients with cardiac arrhythmias, coronary artery or organic heart disease, or hypertension. In such patients, or in patients who are on drugs that may sensitize the heart to arrhythmias, epinephrine may precipitate or aggravate 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, diabetes, elderly individuals, and pregnant women. Patients with Parkinson’s disease may notice a temporary worsening of symptoms.

6 ADVERSE REACTIONS
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.

Common adverse reactions to systemically administered epinephrine include anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; nausea and vomiting; headache; and/or respiratory difficulties. These symptoms occur in some persons receiving therapeutic doses of epinephrine, but are more likely to occur in patients with hypertension or hyperthyroidism [see Warnings and Precautions (5.4)].

Arrhythmias, including fatal ventricular fibrillation, have been reported, particularly in patients with underlying cardiac disease or those receiving certain drugs [see Warnings and Precautions (5.4) and Drug Interactions (7)].

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

Angina may occur in patients with coronary artery disease [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 (5.2)].
Adverse events experienced as a result of accidental injections may include increased heart rate, local reactions including injection site pallor, coldness and hypoesthesia or injury at the injection site resulting in bruising, bleeding, discoloration, erythema or skeletal injury.

Injection into the buttock has resulted in cases of gas gangrene [see Warnings and Precautions (5.4)].

7 DRUG INTERACTIONS
Patients who receive epinephrine while concomitantly taking cardiac glycosides, diuretics, or anti-arrhythmics should be observed carefully for the development of cardiac arrhythmias [see Warnings and Precautions (5.4)].

The effects of epinephrine may be potentiated by tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines, notably chlorpheniramine, tripelennamine, and diphenhydramine.

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 also reverse the pressor effects of epinephrine.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Teratogenic Effects: Pregnancy Category C.
There are no adequate and well controlled studies of the acute effect of epinephrine in pregnant women.

Epinephrine was teratogenic in rabbits, mice and hamsters. 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 has been shown to have teratogenic effects when administered subcutaneously in rabbits at approximately 30 times the maximum recommended daily subcutaneous or intramuscular dose (on a mg/m² basis at a maternal dose of 1.2 mg/kg/day for two to three days), in mice at approximately 7 times the maximum daily subcutaneous or intramuscular dose (on a mg/m² basis at a maternal subcutaneous dose of 1 mg/kg/day for 10 days), and in hamsters at approximately 5 times the maximum recommended daily subcutaneous or intramuscular dose (on a mg/m² basis at a maternal subcutaneous dose of 0.5 mg/kg/day for 4 days).

These effects were not seen in mice at approximately 3 times the maximum recommended daily subcutaneous or intramuscular dose (on a mg/m² basis at a subcutaneous maternal dose of 0.5
mg/kg/day for 10 days).

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 EpiPen is administered to a nursing woman.

8.4 Pediatric Use
EpiPen or EpiPen Jr may be administered to pediatric patients at a dosage appropriate to body weight [see Dosage and Administration (2)]. 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. Since the doses of epinephrine delivered from EpiPen and EpiPen Jr are fixed, consider using other forms of injectable epinephrine if doses lower than 0.15 mg are deemed necessary.

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, EpiPen should be administered with caution in elderly individuals, who may be at greater risk for developing adverse reactions after epinephrine administration [see Warnings and Precautions (5.4), Overdosage (10)].

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 rapidly acting vasodilators or alpha-adrenergic blocking drugs and/or respiratory support.

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, and kidney failure. Suitable corrective measures must be taken in such situations.

11 DESCRIPTION
EpiPen (epinephrine injection, USP) 0.3 mg and EpiPen Jr (epinephrine injection, USP) 0.15 mg are auto-injectors and combination products containing drug and device components.

Each EpiPen Auto-Injector, 0.3 mg delivers a single dose of 0.3 mg epinephrine from epinephrine injection, USP 1:1000 (0.3 mL) in a sterile solution.
Each EpiPen Jr Auto-Injector, 0.15 mg delivers a single dose of 0.15 mg epinephrine from epinephrine injection, USP 1:2000 (0.3 mL) in a sterile solution.

The EpiPen and EpiPen Jr each contain 2 mL epinephrine solution. Approximately 1.7 mL remains in the auto-injector after activation, but is not available for future use, and should be discarded.

Each 0.3 mL in the EpiPen Auto-Injector contains 0.3 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and Water for Injection. The pH range is 2.2–5.0.

Each 0.3 mL in the EpiPen Jr Auto-Injector contains 0.15 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and Water for Injection. The pH range is 2.2-5.0.

Epinephrine is a sympathomimetic catecholamine. Chemically, epinephrine is (-)-3,4-Dihydroxy-α-[(methylamino)methyl]benzyl alcohol with the following structure:

Epinephrine solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. Replace EpiPen and EpiPen Jr if the epinephrine solution appears discolored (pinkish or brown color), cloudy, or contains particles.

Epinephrine solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. Replace EpiPen and EpiPen Jr if the epinephrine solution appears discolored (pinkish or brown color), cloudy, or contains particles.

Thoroughly review the patient instructions and operation of EpiPen or EpiPen Jr with patients and caregivers prior to use. [see Patient Counseling Information (17)].

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.

When given subcutaneously or intramuscularly, 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 and to be an oxidative mutagen in a WP2 bacterial reverse mutation assay.

Epinephrine was positive in the DNA Repair test with B. subtilis (REC) assay, but was not mutagenic in the Salmonella bacterial reverse mutation assay.

The potential for epinephrine to impair fertility has not been evaluated.

This should not prevent the use of epinephrine under the conditions noted under Indications and Usage (1).

16  HOW SUPPLIED/STORAGE AND HANDLING
16.1  How Supplied
EpiPen Auto-Injectors (epinephrine injections, USP, 1:1000, 0.3 mL) are available as EpiPen 2-Pak®, NDC 49502-500-02, a pack that contains two EpiPen Auto-Injectors (epinephrine injections, USP, 1:1000, 0.3 mL) and one EpiPen Auto-Injector trainer device.

EpiPen Jr Auto-Injectors (epinephrine injections, USP, 1:2000, 0.3 mL) are available as EpiPen Jr 2-Pak®, NDC 49502-501-02, a pack that contains two EpiPen Jr Auto-Injectors (epinephrine injections, USP, 1:2000, 0.3 mL) and one EpiPen Auto-Injector trainer device.

EpiPen 2-Pak® and EpiPen Jr 2-Pak® also includes an S-clip to clip two carrier tubes together. Rx only

16.2  Storage and Handling
Protect from light. Epinephrine is light sensitive and should be stored in the carrier tube provided to protect it from light. Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) (See USP Controlled Room Temperature). Do not refrigerate. Before using, check to make sure the solution in the auto-injector is clear and colorless. Replace the auto-injector if the solution is discolored (pinkish or brown color), cloudy, or contains particles.

17  PATIENT COUNSELING INFORMATION
[see FDA-Approved Patient Labeling (Patient Information and Instructions for Use)]
A healthcare provider should review the patient instructions and operation of EpiPen and EpiPen Jr in detail, with the patient or caregiver.

Epinephrine is essential for the treatment of anaphylaxis. Patients who are at risk of or with a history of severe allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs, and other
allergens, as well as idiopathic and exercise-induced anaphylaxis, should be carefully instructed about the circumstances under which epinephrine should be used.

Administration and Training
Patients and/or caregivers should be instructed in the appropriate use of EpiPen and EpiPen Jr. EpiPen should be injected into the middle of the outer thigh (through clothing, if necessary). Each device is a single-use injection. Advise patients to seek immediate medical care in conjunction with administration of EpiPen.

Complete patient information, including dosage, directions for proper administration and precautions can be found inside each EpiPen or EpiPen Jr carton. A printed label on the surface of EpiPen shows instructions for use and a diagram depicting the injection process.

Patients and/or caregivers should be instructed to use the Trainer to familiarize themselves with the use of EpiPen in an allergic emergency. The Trainer may be used multiple times. A Trainer device is provided in 2-Pak cartons.

Adverse Reactions
Epinephrine may produce symptoms and signs that include 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 signs and symptoms usually subside rapidly, especially with rest, quiet and recumbency. Patients with hypertension or hyperthyroidism may develop more severe or persistent effects, and patients with coronary artery disease could experience angina. Patients with diabetes may develop increased blood glucose levels following epinephrine administration. Patients with Parkinson’s disease may notice a temporary worsening of symptoms [see Warnings and Precautions (5.4)].

Accidental Injection
Advise patients to seek immediate medical care in the case of accidental injection. Since epinephrine is a strong vasoconstrictor when injected into the digits, hands, or feet, treatment should be directed at vasodilatation if there is such an accidental injection to these areas [see Warnings and Precautions (5.2)].

Storage and Handling
Instruct patients to inspect the epinephrine solution visually through the clear window of the auto-injector periodically. EpiPen and EpiPen Jr should be replaced if the epinephrine solution appears discolored (pinkish or brown color), cloudy, or contains particles. Epinephrine is light sensitive and should be stored in the carrier tube provided to protect it from light. The carrier tube is not waterproof. Patients should be instructed that EpiPen and EpiPen Jr must be used or properly disposed once the blue safety release is removed or after use [see Storage and Handling (16.2)].

Complete patient information, including dosage, directions for proper administration and precautions can be found inside each EpiPen Auto-Injector carton.
PATIENT INFORMATION and INSTRUCTIONS FOR USE

EpiPen®
(epinephrine) Auto-Injector 0.3 mg
EpiPen® = one dose of 0.3 mg epinephrine (USP, t:1000, 0.3 mL)

EpiPen Jr®
(epinephrine) Auto-Injector 0.15 mg
EpiPen Jr® = one dose of 0.15 mg epinephrine (USP, t:2000, 0.3 mL)

For allergic emergencies (anaphylaxis)

Patient Information

Read this Patient Information Leaflet carefully before using the EpiPen® or EpiPen Jr® Auto-Injector and each time you get a refill. There may be new information. You, your parent, caregiver, or others who may be in a position to administer EpiPen or EpiPen Jr Auto-Injector, should know how to use it before you have an allergic emergency.

This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about the EpiPen and EpiPen Jr?

1. EpiPen and EpiPen Jr contain, a medicine used to treat allergic emergencies (anaphylaxis). Anaphylaxis can be life threatening, can happen with minutes, and can be caused by stinging and biting insects, allergy injections, foods, medicines, exercise, or unknown causes.

Symptoms of anaphylaxis may include:
- trouble breathing
- wheezing
- hoarseness (changes in the way your voice sounds)
- hives (raised reddened rash that may itch)
- severe itching
- swelling of your face, lips, mouth, or tongue
- skin rash, redness, or swelling
- fast heartbeat
- weak pulse
- feeling very anxious
- confusion
- stomach pain
- losing control of urine or bowel movements (incontinence)
- diarrhea or stomach cramps
• dizziness, fainting, or “passing out” (unconsciousness)

2. **Always carry your EpiPen or EpiPen Jr with you because you may not know when anaphylaxis may happen.**
Talk to your healthcare provider if you need additional units to keep at work, school, or other locations. Tell your family members, caregivers, and others where you keep your EpiPen or EpiPen Jr and how to use it before you need it. You may be unable to speak in an allergic emergency.

3. **When you have an allergic emergency (anaphylaxis)**
   - **Use EpiPen or EpiPen Jr right away.**
   - **Get emergency medical help right away.** You may need further medical attention. You may need to use a second EpiPen or EpiPen Jr if symptoms continue or recur. Only a healthcare provider should give additional doses of epinephrine if you need more than 2 injections for a single anaphylaxis episode.

**What are EpiPen and EpiPen Jr?**
- EpiPen and EpiPen Jr are disposable, prefilled automatic injection devices (auto-injectors) used to treat life-threatening, allergic emergencies including anaphylaxis in people who are at risk for or have a history of serious allergic emergencies. Each device contains a single dose of epinephrine.
- EpiPen and EpiPen Jr are for immediate self (or caregiver) administration and do not take the place of emergency medical care. You should get emergency help right away after using EpiPen and EpiPen Jr.
- EpiPen and EpiPen Jr are for people who have been prescribed this medicine by their healthcare provider.
- The EpiPen Auto-Injector (0.3 mg) is for patients who weigh 66 pounds or more (30 kilograms or more).
- The EpiPen Jr Auto-Injector (0.15 mg) is for patients who weigh about 33 to 66 pounds (15 to 30 kilograms).
- It is not known if EpiPen and EpiPen Jr are safe and effective in children who weigh less than 33 pounds (15 kilograms).

**What should I tell my healthcare provider before using the EpiPen or EpiPen Jr?**

**Before you use EpiPen or EpiPen Jr, tell your healthcare provider about all your medical conditions, but especially if you:**
- have heart problems or high blood pressure
- have diabetes
- have thyroid problems
- have asthma
- have a history of depression
- have Parkinson’s disease
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if epinephrine will harm your unborn baby.
are breastfeeding or plan to breastfeed. It is not known if epinephrine
passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including
prescription and over-the-counter medicines, vitamins, and herbal supplements. Tell your healthcare provider of all known allergies.

Especially tell your healthcare provider if you take certain asthma medicines.

EpiPen or EpiPen Jr and other medicines may affect each other, causing side
effects. EpiPen or EpiPen Jr may affect the way other medicines work, and other
medicines may affect how EpiPen or EpiPen Jr works.

Know the medicines you take. Keep a list of them to show your healthcare
provider and pharmacist when you get a new medicine.

Use your EpiPen or EpiPen Jr for treatment of anaphylaxis as prescribed by your
healthcare provider, regardless of your medical conditions or the medicines you
take.

How should I use EpiPen and EpiPen Jr?

- Each EpiPen or EpiPen Jr Auto-Injector contains only 1 dose of medicine.
- EpiPen or EpiPen Jr should be injected into the middle of your outer thigh
  (upper leg). It can be injected through your clothing if needed.
- Read the Instructions for Use at the end of this Patient Information Leaflet
  about the right way to use EpiPen and EpiPen Jr.
- Your healthcare provider will show you how to safely use the EpiPen or EpiPen
  Jr Auto-Injector.
- Use your EpiPen or EpiPen Jr exactly as your healthcare provider tells you to
  use it. You may need to use a second EpiPen or EpiPen Jr if symptoms
  continue or recur. Only a healthcare provider should give additional doses of
  epinephrine if you need more than 2 injections for a single anaphylaxis
  episode.
- Caution: Never put your thumb, fingers, or hand over the orange tip.
  Never press or push the orange tip with your thumb, fingers, or hand.
The needle comes out of the orange tip. Accidental injection into finger, hands
or feet may cause a loss of blood flow to these areas. If this happens, go
immediately to the nearest emergency room. Tell the healthcare provider
where on your body you received the accidental injection.
- Your EpiPen and EpiPen Jr Auto-Injector may come packaged with an EpiPen
  Trainer and separate Trainer Instructions for Use. The EpiPen Trainer has a
grey color. The grey EpiPen Trainer contains no medicine and no
needle. Periodically practice with your EpiPen Trainer before an allergic
emergency happens to make sure you are able to safely use the real EpiPen
and EpiPen Jr Auto-Injector in an emergency. Always carry your real EpiPen
or EpiPen Jr Auto-Injector with you in case of an allergic emergency.
Additional training resources are available at www.epipen.com.
- Do not drop the carrier tube or auto-injector. If the carrier tube or auto-
injector is dropped, check for damage and leakage. Dispose of the auto-injector and carrier tube, and replace if damage or leakage is noticed or suspected.

What are the possible side effects of the EpiPen and EpiPen Jr?

EpiPen and EpiPen Jr may cause serious side effects.

- The EpiPen or EpiPen Jr should only be injected into the middle of your outer thigh (upper leg). Do not inject the EpiPen or EpiPen Jr into your:
  - veins
  - buttocks
  - fingers, toes, hands, or feet

If you accidentally inject EpiPen or EpiPen Jr into any other part of your body, go to the nearest emergency room right away. Tell the healthcare provider where on your body you received the accidental injection.

- If you have certain medical conditions, or take certain medicines, your condition may get worse or you may have longer lasting side effects when you use your EpiPen or EpiPen Jr. Talk to your healthcare provider about all your medical conditions.

Common side effects of EpiPen and EpiPen Jr include:
- fast, irregular or “pounding” heartbeat
- sweating
- headache
- weakness
- shakiness
- paleness
- feelings of over excitement, nervousness or anxiety
- dizziness
- nausea or vomiting
- breathing problems

These side effects may go away with rest. **Tell your healthcare provider if you have any side effect that bothers you or that does not go away.**

These are not all the possible side effects of the EpiPen or EpiPen Jr. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store EpiPen and EpiPen Jr?

- Store EpiPen and EpiPen Jr at room temperature between 68° to 77° F (20° to 25° C).
- Protect from light.
Do not expose to extreme cold or heat. For example, do not store in your vehicle’s glove box and do not store in the refrigerator or freezer.

Examine the contents in the clear window of your auto-injector periodically. The solution should be clear. If the solution is discolored (pinkish or brown color) or contains solid particles, replace the unit.

Always keep your EpiPen or EpiPen Jr Auto-Injector in the carrier tube to protect it from damage; however, the carrier tube is not waterproof.

The blue safety release helps to prevent accidental injection. Keep the blue safety release on until you need to use EpiPen or EpiPen Jr.

Your EpiPen or EpiPen Jr has an expiration date. Replace it before the expiration date.

Keep EpiPen and EpiPen Jr and all medicines out of the reach of children.

General information about the safe and effective use of EpiPen and EpiPen Jr:
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use the EpiPen or EpiPen Jr for a condition for which it was not prescribed. Do not give your EpiPen or EpiPen Jr to other people.

This Patient Information Leaflet summarizes the most important information about EpiPen and EpiPen Jr. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about EpiPen and EpiPen Jr that is written for health professionals.

For more information and video instructions on the use of EpiPen and EpiPen Jr, go to www.epipen.com or call 1-800-395-3376.

What are the ingredients in EpiPen and EpiPen Jr?
Active Ingredients: Epinephrine
Inactive Ingredients: sodium chloride, sodium metabisulfite, hydrochloric acid, and water.

Important Information
- The EpiPen Auto-Injector has a yellow colored label.
- The EpiPen Jr Auto-Injector has a green colored label.
- The EpiPen Trainer has a grey color and contains no medicine and no needle.
- Your auto-injector is designed to work through clothing.
- The blue safety release on the EpiPen and EpiPen Jr Auto-Injector helps to prevent accidental injection of the device. Do not remove the blue safety release until you are ready to use it.
- Only inject into the middle of the outer thigh (upper leg). Never inject into any other part of the body.
- Never put your thumb, fingers, or your hand over the orange tip. The needle comes out of the orange tip.
- If an accidental injection happens, get medical help right away.
- Do not place patient information or any other foreign objects in the
carrier tube with the Auto-Injector, as this may prevent you from removing the Auto-Injector for use.
Instructions for Use

EpiPen®
(epinephrine) Auto-Injector 0.3 mg
EpiPen® = one dose of 0.30 mg epinephrine (USP, 1:1000, 0.3 mL)

EpiPen Jr®
(epinephrine) Auto-Injector 0.15 mg
EpiPen Jr® = one dose of 0.15 mg epinephrine (USP, 1:2000, 0.3 mL)

For allergic emergencies (anaphylaxis)

Read these Instructions for Use carefully before you use EpiPen or EpiPen Jr. Before you need to use your EpiPen or EpiPen Jr, make sure your healthcare provider shows you the right way to use it. Parents, caregivers, and others who may be in a position to administer EpiPen or EpiPen Jr Auto-Injector should also understand how to use it as well. If you have any questions, ask your healthcare provider.

Your EpiPen and EpiPen Jr Auto-Injector

A dose of EpiPen or EpiPen Jr® requires 3 simple steps: Prepare,
Administer and Get emergency medical help

Step 1. Prepare EpiPen or EpiPen Jr for injection

Remove the EpiPen or EpiPen Jr from the clear carrier tube.

Flip open the yellow cap of your EpiPen or the green cap of your EpiPen Jr carrier tube.

Tip and slide the auto-injector out of the carrier tube.

Grasp the auto-injector in your fist with the orange tip pointing downward.
With your other hand, remove the blue safety release by pulling straight up without bending or twisting it.

Note:
- The needle comes out of the orange tip.
- To avoid an accidental injection, never put your thumb, fingers or hand over the orange tip. If an accidental injection happens, get medical help right away.

Step 2. Administer EpiPen or EpiPen Jr

Hold the auto-injector with orange tip near the middle of the outer thigh (upper leg).
Swing and firmly push the orange tip against the middle of the outer thigh until it ‘clicks’.
Keep the auto-injector firmly pushed against the thigh at a 90° angle (perpendicular) to the thigh.
Hold firmly against the thigh for approximately 10 seconds to deliver the medicine. The injection is now complete.

Remove the auto-injector from the thigh. The orange tip will extend to cover the needle.

Massage the injection area for 10 seconds.

Step 3. Get emergency medical help now. You may need further medical attention. You may need to use a second EpiPen or EpiPen Jr Auto-Injector if symptoms continue or recur.
- Take your used auto-injector with you when you go to see a healthcare provider.
- Tell the healthcare provider that you have received an injection of epinephrine. Show the healthcare provider where you received the injection.
- Give your used EpiPen or EpiPen Jr Auto-Injector to the healthcare provider for inspection and proper disposal.
- Ask for a refill, if needed.

Note:
- The used auto-injector with extended needle cover will not fit in the carrier tube.
- EpiPen and EpiPen Jr are single-use injectable devices that deliver a fixed dose of epinephrine. The auto-injector cannot be reused. It is normal for most of the medicine to remain in the auto-injector after the dose is injected. The correct dose has been administered if the orange needle tip is extended and the window is blocked.
- Your EpiPen and EpiPen Jr Auto-Injector may come packaged with an EpiPen Trainer and separate Trainer Instructions for Use. The EpiPen Trainer has a grey color. The grey EpiPen Trainer contains no medicine and no needle. Practice with your EpiPen Trainer, but always carry your real EpiPen or EpiPen Jr Auto-Injector in case of an allergic emergency.
- Do not try to take the EpiPen or EpiPen Jr Auto-Injector apart.

This Patient Information and Instructions for Use has been approved by the U.S.
Register your EpiPen or EpiPen Jr Auto-Injector at MyEpiPen.com and find out more about:

- Free EpiPen Auto-Injector Refill Reminder Program. It is important to keep your auto-injector up-to-date.

Register up to 6 EpiPen or EpiPen Jr Auto-Injectors and receive automatic Refill Reminder Alerts.
- Receive periodic information related to allergies and allergens.
- Instructional Video

For more information about EpiPen or EpiPen Jr Auto-Injectors and proper use of the product, call Mylan at 1-877-446-3679 or visit www.epipen.com.
EpiPen® Trainer
Instructions For Use

EpiPen Trainer Instructions for Use

In an emergency: Do not use the grey Trainer. Use your real yellow EpiPen® or green EpiPen Jr® Auto-Injector.

Important Information

- The Trainer label has a grey color.
- The Trainer contains no medicine and no needle.
- Periodically practice with the grey colored Trainer before an allergic emergency (anaphylaxis) happens to make sure you are able to safely use the real yellow EpiPen or green EpiPen Jr Auto-Injector in case of an emergency.
- Always carry your real yellow EpiPen or green EpiPen Jr Auto-Injector in case of an allergic emergency.

Familiarize yourself with this grey Trainer. Practice until you are comfortable using it.

Your grey colored Trainer:

- Never put your thumb, other fingers, or hand over the Orange Tip.
- The Orange Tip is where the needle comes out of your EpiPen or EpiPen Jr Auto-Injector.
Practice Instructions

1 Prepare the Trainer for Simulated Injection
   - Grasp the grey Trainer in your fist with the orange tip pointing downward.
   - With your other hand, remove blue safety release by pulling straight up without bending or twisting it.
   - Removing the blue safety release unlocks the Trainer.

2 Administer the Trainer Simulation
   - Hold the Trainer with the orange tip near the middle of the outer thigh (upper leg).
   - Swing and firmly push the orange tip against the middle of the outer thigh until it ‘clicks.’ Keep the Trainer firmly pushed against the thigh at a 90º angle (perpendicular) to the thigh.
   - Hold firmly against the thigh for approximately 10 seconds.
   - Remove the Trainer from the thigh and massage the injection area for 10 seconds. The orange tip automatically extends out after use.
   
   Note:
   - In an actual emergency, you would need to seek medical help right away
   - The actual auto-injector is made to work through clothing
   - Do not inject into any other part of the body

3 To reset the Trainer
   - Put the blue safety release back on the Trainer
   - Place the orange tip on a hard surface
   - Squeeze the sides of the orange tip and push down on the Trainer with the other hand

Note: With the real yellow EpiPen or green EpiPen Jr Auto-Injector, the orange tip covers the needle after self-injection to help protect you from accidentally sticking yourself or others.
Practice Session Information

In case of an allergic emergency, use the real yellow EpiPen or green EpiPen Jr Auto-Injector and not the grey Trainer.

Follow instructions above. Repeat as often as needed until you are able to self-inject quickly and correctly.

Reread:
- These Trainer Instructions for Use
- The “Patient Information” that comes with your EpiPen or EpiPen Jr Auto-Injector

Train others who could help you in an emergency:
- Your parents, caregivers, and others who may be in a position to administer EpiPen or EpiPen Jr should know how to help you during an allergic emergency (anaphylaxis). Before an emergency occurs, have them:
  - Practice activating the Trainer
  - Read these Trainer Instructions and the “Patient Information”

For more information about the EpiPen and EpiPen Jr Auto-Injector and the proper use of the products, go to www.epipen.com.

Caution:

Important differences between the Trainer and your real yellow EpiPen or green EpiPen Jr Auto-Injector

<table>
<thead>
<tr>
<th></th>
<th>TRAINER (Grey)</th>
<th>EpiPen (Yellow)</th>
<th>EpiPen Jr (Green)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contains medication?</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Has needle?</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Comes in Carrier Tube?</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Color of Label</td>
<td>Grey</td>
<td>Yellow</td>
<td>Green</td>
</tr>
<tr>
<td>Has expiration date?</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Can be reused?</td>
<td>YES</td>
<td>NO (use only once)</td>
<td>NO (use only once)</td>
</tr>
<tr>
<td>Okay to remove and replace safety release?</td>
<td>YES</td>
<td>NO (remove just once before use)</td>
<td>NO (remove just once before use)</td>
</tr>
<tr>
<td>Pressure needed to hold against thigh?</td>
<td>Moderate</td>
<td>Strong</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Reference ID: 3498053
APPLICATION NUMBER:

019430Orig1s059

MEDICAL REVIEW(S)
This is a review of a prior approval supplement (S-059) submitted by Mylan Specialty L.P. (Mylan) for EpiPen® and EpiPen® Jr. Auto-Injectors to voluntarily convert the Prescribing Information (PI) into Physicians Labeling Rule (PLR) format. Mylan assumed ownership of Meridian Medical Technologies, Inc. on [REDACTED] Mylan stated that they have considered the implications of being an RLD for other epinephrine auto-injectors, including the recent approval of NDA 201739 for Auvi-Q, and decided to voluntarily submit PLR labeling that takes into account the language the Agency used for that PI. The supplement also contains minor proposed revisions to the PI, PIL (Patient Instruction Leaflet, which includes the Patient Package Insert [PPI] and Instructions for Use [IFU]), and TIFU (Trainer Instructions for Use). The supplement carries a 6 month clock, with a due date of April 28, 2014.

Labeling submitted with the supplement is electronic (both non-eCTD and eCTD), although for various reasons labeling was submitted multiple times, as outlined in the table above. The last approved PI, PPI-IFU, TIFU, and carton/container labeling was approved on August 20, 2012 (S-053). Concurrent with the review of this supplement, Mylan submitted a labeling supplement (S-058) that primarily focuses on changes to the carton labels. Minor changes to the PI and PPI-IFU proposed with S-058 were incorporated into this supplement, but an action on S-058 is delayed because of revisions to the proposed carton artwork.

A key element in the review of this supplement was the Division’s attempt to ensure that the labeling for EpiPen match as closely as possible with that of other epinephrine auto-injectors, with any differences primarily being in the description and Instructions for Use that are unique to each product. During the course of the review, consults were sent to the Division of Medication Error Prevention and Analysis (DMEPA), the Division of Medical Policy Programs (DMPP), and the Office of Prescription Drug Promotion (OPDP). Comments from all teams were consolidated and sent to Mylan on March 26, 2014, and the company responded on April 9, 2014. The near-final PI was sent to the SEALD labeling team for final review of the PLR format, labeling comments were sent to Mylan on April 16 and April 18. After several teleconferences to clarify minor issues, Mylan responded with final labeling that was submitted after COB on April 28, 2014. The revisions to the PI, PIL (PPI-IFU), and TIFU were reviewed and compared with previous versions and found to be acceptable.

OUTSTANDING ISSUES:
None. The final labeling, submitted [after COB] on April 28, 2014 is attached to this review.

RECOMMENDED REGULATORY ACTION
NDA/BLA SUPPLEMENTS: X APPROVAL _______ COMPLETE RESPONSE

Reference ID: 3497523
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PETER R STARKE
04/29/2014

JANET W MAYNARD
04/29/2014
APPLICATION NUMBER:

019430Orig1s059

CHEMISTRY REVIEW(S)
CHEMIST REVIEW OF SUPPLEMENT

1. ORGANIZATION: ONDQA – Division of Post-Marketing Evaluation
2. NDA Number: 19430
3. SUPPLEMENT NUMBERS/DATES:
   - Letter date: S059 (PA) October 25, 2013
   - Stamp date: October 28, 2013
4. AMENDMENTS/REPORTS/DATES:
   - Letter date: RS Amendment (SDN823) February 28, 2014
   - Stamp date: February 28, 2014
5. RECEIVED BY CHEMIST:

6. APPLICANT NAME & ADDRESS
Mylan Specialty L.P.
110 Allen Road
Basking Ridge, NJ 07920

7. NAME OF DRUG:
EpiPen® and EpiPen® Jr Auto-Injector

8. NONPROPRIETARY NAME:
epinephrine

9. CHEMICAL NAME/STRUCTURE:
(-)-3,4-Dihydroxy-α-[[(methylamino)methyl]-benzyl alcohol,
C₉H₁₃NO₃, Mol. Wt. 183.20

10. DOSAGE FORM(S):
Sterile Intramuscular Injectable Solution

11. POTENCY:
0.3 mg/0.3 mL (EpiPen), 0.15 mg/0.3 mL (EpiPen Jr)

12. PHARMACOLOGICAL CATEGORY:
Emergency treatment of severe allergic reactions (Type I) to allergens as well as anaphylaxis to unknown substances (idiopathic anaphylaxis) or exercise-induced anaphylaxis.

13. HOW DISPENSED:

14. RECORDS & REPORTS CURRENT:
REVIEW RECORDS & REPORTS CURRENT

15. RELATED IND/NDA/DMF:
None


17. COMMENTS: Mylan Specialty L.P. (Mylan) NDA 19430 for EpiPen and EpiPen Jr (epinephrine) Auto-Injector (EpiPen and EpiPen Jr) was first approved December 22, 1987. With reference to the subject NDA, Mylan assumed ownership from Meridian Medical Technologies, Inc (St. Louis, MO), with an effective date of

Mylan is proposing a PLR label format conversion of the EpiPen and EpiPen Jr Full Prescribing Information (FPI) and updating the EpiPen and EpiPen Jr Trainer Insert (TI) and Patient Information (PI). The PLR conversion and labeling updates were submitted on October 25, 2013. On November 13, 2013, The FDA acknowledged that Mylan’s proposed PLR Label Format Conversion would be reviewed as Prior Approval Supplement 19430/S059. This review evaluates the proposed changes with respect to CMC. The ONDQA Initial Quality Assessment (IQA) of 19430/S059 is provided in Attachment 1. PAS 19430/S059 is managed by

Reference ID: 3471277
the Division of Pulmonary, Allergy and Rheumatology Products (PARP) with a PDUFA due date of April 28, 2014.

The changes proposed in the October 25, 2013 PAS were submitted as three attachments that are described below:

**Attachment 1:** The *Prescribing Information, Trainer Insert and Patient Information* documents are presented in the current format, in track changes, to facilitate the Division’s review of changes being proposed to clarify the language in these three labeling documents. Regardless of the PLR format labeling change to the *Prescribing Information*, Mylan intends to continue to provide in the *EpiPen® Auto-Injectorカラム the Trainer Instructions* with the trainer auto-injector, and the *Patient Information* as separate documents. Therefore the Agency’s review of these two latter documents in Attachment 1 would result in updated versions of those documents. Accordingly, the *Trainer Instructions* and the *Patient Information* are also provided as clean documents.

**Attachment 2:** The PLR formatted *Full Prescribing Information* is presented in Attachment 2. In recognition of the Agency’s recent approval of NDA 201739, which referenced the *EpiPen® Auto-Injector* but provided the *Full Prescribing Information* in PLR format, we have based our PLR format conversion on the Agency’s prior efforts to convert the *EpiPen® label information into PLR format*. This DRAFT document also includes all the track changes proposed edits noted in Attachment 1 to the current *EpiPen® Auto-Injector* labeling.

**Attachment 3:** The PLR formatted DRAFT *Full Prescribing Information* is presented in Attachment 3. This DRAFT document is the same MS Word document as provided in Attachment 2 but without track changes.

On February 14, 2014, Ms. Carol Hill (Project Manager-PARP) requested Mylan clearly outline what changes are proposed for the EpiPen and EpiPen Jr FPI, TI and PI. On February 28, 2014, Mylan submitted a Re-Submission (RS) Amendment (SDN823) to 19430/S059 in order to address the FDA’s request. The RS Amendment contained the following documents:

- Copies of the current approved *Prescribing Information, Trainer Insert* and *Patient Information* documents (PDF)
- Copies of the current approved *Prescribing Information, Trainer Insert* and *Patient Information* (MS Word)
- Annotated (red-line track changes denoted) copies of the revised *Prescribing Information, Trainer Insert* and *Patient Information* (PDF and Clean versions)

In addition, Mylan stated in the cover letter to the RS Amendment that the primary purpose of 19430/S059 is as follows:

1) To support the use of *EpiPen® Auto-Injector* by individuals in addition to the patient (self-administering) and relative/caregiver by including text “others who may be in a position to administer emergency response to an anaphylactic event” in the *Indication and Usage* section and in the *Dosage and Administration* section. We further included in the *Dosage and Administration* section wording to support periodic review of how to dose with the EAI by using the Trainer device.

2) To comply with the Agency’s *Draft Guidance for Industry and Food and Drug Administration Staff - Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex*, March 11, 2013, by removing language referring to latex from the *Description* section of the proposed label.

3) To provide a company address change from Basking Ridge, NJ to Morgantown, WV

4) To voluntarily convert the label into PLR format
The CMC relevant changes in the EpiPen and EpiPen Jr PLR label format conversion of the FPI and updated TI and PI for EpiPen and EpiPen Jr are acceptable from a CMC standpoint. The CMC relevant Highlights section of the PLR conversion, namely **Dosage Forms and Strengths** accurately capture the data in **Section 3 DOSAGE FORMS AND STRENGTHS** of the FPI. The remaining changes, namely providing a company address change and removal of language referring to latex are minor changes that are acceptable from a CMC standpoint. The question of removing the claim that the EpiPen and EpiPen Jr device is free of latex was brought to the attention of senior ONDQA staff, and the consensus was that such a move was acceptable (Attachment 2) from a CMC standpoint.

Nanotechnology product evaluating questions are appended to this review (Attachment 3).

18. CONCLUSIONS & RECOMMENDATIONS: Recommend issue approval letter from a CMC perspective.

19. REVIEWER NAME SIGNATURE DATE COMPLETED
   Lorenzo A. Rocca Signed Electronically

20. BRANCH CHIEF NAME SIGNATURE DATE COMPLETED
   Ramesh Raghavachari Signed Electronically

cc:
   RRaghavachari
   LRocca
   YLiu
F/T by: LRocca, File: C:Data\LR\Supplement\n19430pm\S059(PAS)\S-059Review1.doc
From: Raghavachari, Ramesh
Sent: Friday, March 07, 2014 2:29 PM
To: Liu, Youbang; Gautam-Basak, Mamta
Cc: Rocca, Lorenzo A
Subject: RE: NDA 019430/059 - PI, PPI, TIFU Word/PDF/Track Changes - IQA

OK Thanks, I will assign this to Lorenzo.

From: Liu, Youbang
Sent: Friday, March 07, 2014 2:14 PM
To: Gautam-Basak, Mamta; Raghavachari, Ramesh
Subject: RE: NDA 019430/059 - PI, PPI, TIFU Word/PDF/Track Changes - IQA

Lorenzo Rocca was assigned to NDA 19430/S-058, Labeling.

From: Gautam-Basak, Mamta
Sent: Friday, March 07, 2014 2:12 PM
To: Raghavachari, Ramesh; Liu, Youbang
Subject: FW: NDA 019430/059 - PI, PPI, TIFU Word/PDF/Track Changes - IQA

Hi Ramesh,
This is a PLR conversion labeling supplement. NDA 19-430/S059 RS dated February 28, 2014: EpiPen and EpiPen Jr Autoinjector

This labeling supplement (paper copy) provides for label changes as per Agency request. The cover letter also makes a reference to S058 that is being reviewed for carton labels (IQA was completed on 11/14/2013). May be this supplement can be assigned to same reviewer as overlapping information are provided. The pdufa goal date for both supplements is indicated to be April 28, 2014.

Thanks,

- Mamta

From: Liu, Youbang
Sent: Friday, March 07, 2014 9:07 AM
To: Hill, Carol
Cc: Ramanadham, Mahesh; Gautam-Basak, Mamta
Subject: RE: NDA 0194/059 - PI, PPI, TIFU Word/PDF/Track Changes

Will let you know when assignment is made.
Youbang
Hello Peter and Craig,

I would like to remove any reference to “latex statements” being used in any of the approved epinephrine drug applications. I note it is part of the description of the Auvi-Q as well.

Prasad

---

From: Starke, Peter
Sent: Wednesday, March 05, 2014 3:09 PM
To: Bertha, Craig M; Peri, Prasad
Cc: Rocca, Lorenzo A
Subject: RE: Latex and Epinephrine injector labeling

Actually, EpiPen does not have that statement “XXX does not contain latex” in their label, and AdrenaClick does. I would like to remove the statement from AdrenaClick to ensure that there is no marketing advantage for one product over the other. From a clinical perspective, we feel it would be ok to do so, but want to be sure that there was no other reason for having it there before we tell them to remove it. I do not recall the history precisely, but I think it was there for reassurance only.

--peter

---

From: Bertha, Craig M
Sent: Wednesday, March 05, 2014 1:29 PM
To: Peri, Prasad
Cc: Rocca, Lorenzo A; Starke, Peter
Subject: Latex and Epinephrine injector labeling

Prasad, Peter asked me about one of the labels for the various epinephrine pen injectors where they want to remove the claim that the device is free of latex (the elastomeric sealing components I assume). He is OK from a clinical perspective with allowing this removal, to be more consistent with the other two injector products that do not mention this. But, he was wondering if you know anything about why this language was there in the first place. Any idea?

Craig
**Attachment 3**

**Attachment A:** Nanotechnology product evaluating questions:

<table>
<thead>
<tr>
<th>1. This review contains new information added to the table below: _____Yes; ___X__No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review date: ________________</td>
</tr>
</tbody>
</table>

| 2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) | Yes_____; No_____; Maybe (please specify)____________________ |

<table>
<thead>
<tr>
<th>3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>___________________________________________________________________________</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3 b) What is the source of the nanomaterial?</th>
</tr>
</thead>
<tbody>
<tr>
<td>___________________________________________________________________________</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4) Is the nanomaterial a reformulation of a previously approved product?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes ______ No ____________________</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5) What is the nanomaterial functionality?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier_________________; Excipient_____________; Packaging_____________; API_________________; Other___________________</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soluble_________________; Insoluble____________________</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7) Was particle size or size range of the nanomaterial included in the application?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes_______(Complete 8); No________ (go to 9).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8) What is the reported particle size?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean particle size_________; Size range distribution_________; Other________________</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9) Please indicate the reason(s) why the particle size or size range was not provided:</th>
</tr>
</thead>
<tbody>
<tr>
<td>___________________________________________________________________________</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10) What other properties of the nanoparticle were reported in the application (See Attachment E)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>___________________________________________________________________________</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>11) List all methods used to characterize the nanomaterial?__________________________________________</th>
</tr>
</thead>
</table>

Reference ID: 3471277
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LORENZO A ROCCA
03/14/2014

RAMESH RAGHAVACHARI
03/14/2014
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019430Orig1s059

PHARMACOLOGY REVIEW(S)
Division of Pulmonary, Allergy and Rheumatology Products
Pharm/Tox Review

NDA: 19430
Document: SD-757 (New/Supplement), SD-770 (Labeling/SPL Draft)
CDER received date: 10/24/13, 11/18/13
Sponsor: Mylan Specialty LP
Drug: EpiPen® and EpiPen® Jr. Auto-Injectors (Epinephrine injection USP)
Indication: Emergency treatment of allergic reactions (Type I) including anaphylaxis
Reviewer: Jane J. Sohn, Ph.D.
Supervisor/Team Leader: Timothy W. Robison, Ph.D., DABT

Recommendations
There are no recommended changes to the proposed label from the nonclinical perspective.

Integrated Summary and Evaluation
Mylan Specialty LP (Mylan) has submitted a supplement providing conversion of the Package Insert (PI) to the PLR format. The PI is for Epipen and EpiPen Jr epinephrine auto-injectors (EAI), which each contain 2 mL epinephrine for intramuscular injection for the emergency treatment of allergic reactions (Type I) including anaphylaxis. Each EpiPen® auto-injector delivers a single dose of 0.3 mg epinephrine in 0.3 mL of sterile solution. Each EpiPen® Jr auto-injector delivers a single dose of 0.15 mg epinephrine in 0.3 mL of sterile solution.

Sections 8.1, 8.3, 12.1, and 13 were reviewed for compliance to PLR format. Section 10 was reviewed to ensure that it does not contain any nonclinical information. There are no recommended changes to sections 8.1, 8.3, 10, 12.1, and 13 from the nonclinical perspective. Medical Officer Dr. Peter Starke has recommended the following minor formatting change, indicated in red. Pharm/Tox concurs with the change:

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 and to be an oxidative mutagen in a WP2 bacterial reverse mutation assay.

Epinephrine was positive in the DNA Repair test with B. subtilis (REC) assay, but was not mutagenic in the Salmonella bacterial reverse mutation assay.

The potential for epinephrine to impair fertility has not been evaluated.

This should not prevent the use of epinephrine under the conditions noted under INDICATIONS AND USAGE (1).

There are no recommended changes to the proposed label from the nonclinical perspective.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANE J SOHN
04/08/2014

TIMOTHY W ROBISON
04/08/2014

I concur
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019430Orig1s059

OTHER REVIEW(S)
SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

<table>
<thead>
<tr>
<th>Product Title¹</th>
<th>EPIPEN (epinephrine injection) Auto-Injector 0.3 mg, EPIPEN Jr (epinephrine injection) Auto-Injector 0.15 mg For intramuscular or subcutaneous use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applicant</td>
<td>Mylan Specialty, L.P.</td>
</tr>
<tr>
<td>Application/Supplement Number</td>
<td>NDA 19430 S-59</td>
</tr>
<tr>
<td>Type of Application</td>
<td>PLR Conversion</td>
</tr>
<tr>
<td>Indication(s)</td>
<td>The emergency treatment of allergic reactions (Type I) including anaphylaxis.</td>
</tr>
<tr>
<td>Office/Division</td>
<td>ODEII/DPARP</td>
</tr>
<tr>
<td>Division Project Manager</td>
<td>Carol Hill</td>
</tr>
<tr>
<td>Date FDA Received Application</td>
<td>October 28, 2013</td>
</tr>
<tr>
<td>Goal Date</td>
<td>April 28, 2014</td>
</tr>
<tr>
<td>Date PI Received by SEALD</td>
<td>April 16, 2014</td>
</tr>
<tr>
<td>SEALD Review Date</td>
<td>April 18, 2014</td>
</tr>
<tr>
<td>SEALD Labeling Reviewer</td>
<td>Debra Beitzell</td>
</tr>
<tr>
<td>Acting SEALD Division Director</td>
<td>Sandra Kweder</td>
</tr>
</tbody>
</table>

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO**: The PI does not meet the requirement for this item (deficiency).
- **YES**: The PI meets the requirement for this item (not a deficiency).
- **N/A**: This item does not apply to the specific PI under review (not applicable).

Reference ID: 3491765
Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

   Comment: Correct margins on top of page, left edge, and in between columns to 1/2 inch.

2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

   Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

   ➢ For the Filing Period:
     • For efficacy supplements: If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
     • For NDAs/BLAs and PLR conversions: Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

   ➢ For the End-of-Cycle Period:
     • Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

   Comment: Highlights is one-half page after top of page margin is corrected to 1/2 inch.

3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

   Comment: Insert horizontal line separating TOC from FPI.

4. All headings in HL must be bolded and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

   Comment: Bold "Contraindications" heading and horizontal lines on either side.

5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

   Comment: Remove line of white space in between product titles and initial U.S. approval date.

6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Reference ID: 3491765
Selected Requirements of Prescribing Information

Comment:

YES 7. Section headings must be presented in the following order in HL:

<table>
<thead>
<tr>
<th>Section</th>
<th>Required/Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highlights Heading</td>
<td>Required</td>
</tr>
<tr>
<td>Highlights Limitation Statement</td>
<td>Required</td>
</tr>
<tr>
<td>Product Title</td>
<td>Required</td>
</tr>
<tr>
<td>Initial U.S. Approval</td>
<td>Required</td>
</tr>
<tr>
<td>Boxed Warning</td>
<td>Required if a BOXED WARNING is in the FPI</td>
</tr>
<tr>
<td>Recent Major Changes</td>
<td>Required for only certain changes to PI*</td>
</tr>
<tr>
<td>Indications and Usage</td>
<td>Required</td>
</tr>
<tr>
<td>Dosage and Administration</td>
<td>Required</td>
</tr>
<tr>
<td>Dosage Forms and Strengths</td>
<td>Required</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Required (if no contraindications must state “None.”)</td>
</tr>
<tr>
<td>Warnings and Precautions</td>
<td>Not required by regulation, but should be present</td>
</tr>
<tr>
<td>Adverse Reactions</td>
<td>Required</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Optional</td>
</tr>
<tr>
<td>Use in Specific Populations</td>
<td>Optional</td>
</tr>
<tr>
<td>Patient Counseling Information Statement</td>
<td>Required</td>
</tr>
<tr>
<td>Revision Date</td>
<td>Required</td>
</tr>
</tbody>
</table>

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be bolded and should appear in all UPPER CASE letters: “HIGHLIGHTS OF PRESCRIBING INFORMATION”.

Comment:

Highlights Limitation Statement

NO 9. The bolded HL Limitation Statement must include the following verbatim statement: “These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).” The name of drug product should appear in UPPER CASE letters.

Comment: Drug names should be presented in all upper case letters; correct "EPIPEN Jr" to "EPIPEX JR".

Product Title in Highlights

YES 10. Product title must be bolded.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be bolded, and include the verbatim statement “Initial U.S. Approval:” followed by the 4-digit year.

Comment:
Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be bolded.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word “WARNING” (even if more than one warning, the term, “WARNING” and not “WARNINGS” should be used) and other words to identify the subject of the warning (e.g., “WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement “See full prescribing information for complete boxed warning.” This statement should be centered immediately beneath the heading and appear in italics.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “See full prescribing information for complete boxed warning.”).

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.
Selected Requirements of Prescribing Information

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim bolded statement must be present: “To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch”.

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three bolded verbatim statements that is most applicable:
If a product does not have FDA-approved patient labeling:
  • “See 17 for PATIENT COUNSELING INFORMATION”
If a product has FDA-approved patient labeling:
  • “See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling”
  • “See 17 for PATIENT COUNSELING INFORMATION and Medication Guide”

Comment:

Revision Date in Highlights

NO 24. The revision date must be at the end of HL, and should be bolded and right justified (e.g., “Revised: 9/2013”).

Comment: Right justify revision date.
Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: “FULL PRESCRIBING INFORMATION: CONTENTS”. This heading should be in all UPPERCASE letters and bolded.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPERCASE letters and bolded.

Comment:

YES 28. In the TOC, all section headings must be bolded and should be in UPPERCASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”

Comment:
Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

NO 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<table>
<thead>
<tr>
<th>BOXED WARNING</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 INDICATIONS AND USAGE</td>
</tr>
<tr>
<td>2 DOSAGE AND ADMINISTRATION</td>
</tr>
<tr>
<td>3 DOSAGE FORMS AND STRENGTHS</td>
</tr>
<tr>
<td>4 CONTRAINDICATIONS</td>
</tr>
<tr>
<td>5 WARNINGS AND PRECAUTIONS</td>
</tr>
<tr>
<td>6 ADVERSE REACTIONS</td>
</tr>
<tr>
<td>7 DRUG INTERACTIONS</td>
</tr>
<tr>
<td>8 USE IN SPECIFIC POPULATIONS</td>
</tr>
<tr>
<td>8.1 Pregnancy</td>
</tr>
<tr>
<td>8.2 Labor and Delivery</td>
</tr>
<tr>
<td>8.3 Nursing Mothers</td>
</tr>
<tr>
<td>8.4 Pediatric Use</td>
</tr>
<tr>
<td>8.5 Geriatric Use</td>
</tr>
<tr>
<td>9 DRUG ABUSE AND DEPENDENCE</td>
</tr>
<tr>
<td>9.1 Controlled Substance</td>
</tr>
<tr>
<td>9.2 Abuse</td>
</tr>
<tr>
<td>9.3 Dependence</td>
</tr>
<tr>
<td>10 OVERDOSAGE</td>
</tr>
<tr>
<td>11 DESCRIPTION</td>
</tr>
<tr>
<td>12 CLINICAL PHARMACOLOGY</td>
</tr>
<tr>
<td>12.1 Mechanism of Action</td>
</tr>
<tr>
<td>12.2 Pharmacodynamics</td>
</tr>
<tr>
<td>12.3 Pharmacokinetics</td>
</tr>
<tr>
<td>12.4 Microbiology (by guidance)</td>
</tr>
<tr>
<td>12.5 Pharmacogenomics (by guidance)</td>
</tr>
<tr>
<td>13 NONCLINICAL TOXICOLOGY</td>
</tr>
<tr>
<td>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</td>
</tr>
<tr>
<td>13.2 Animal Toxicology and/or Pharmacology</td>
</tr>
<tr>
<td>14 CLINICAL STUDIES</td>
</tr>
<tr>
<td>15 REFERENCES</td>
</tr>
<tr>
<td>16 HOW SUPPLIED/STORAGE AND HANDLING</td>
</tr>
<tr>
<td>17 PATIENT COUNSELING INFORMATION</td>
</tr>
</tbody>
</table>

**Comment:** Throughout the FPI, correct all subsection headings to title case letters (subsection headings should remain bolded; see examples above).

NO 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “*[see Warnings and Precautions (5.2)]*” or “*[see Warnings and Precautions (5.2)]*”.

SRPI version 3: October 2013

Reference ID: 3491765
Selected Requirements of Prescribing Information

Comment: Throughout the FPI, correct all section headings within cross references to title case letters (see example above).

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be bolded and appear at the beginning of the FPI: “FULL PRESCRIBING INFORMATION”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be bolded.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word “WARNING” (even if more than one Warning, the term, “WARNING” and not “WARNINGS” should be used) and other words to identify the subject of the Warning (e.g., “WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”).

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment: Modified statement is included at the beginning of section 6.

YES 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: See comment under #39.

PATIENT COUNSELING INFORMATION Section in the FPI

YES
41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: Attach Patient Information and Instructions for Use to end of FPI.
Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME] (nonproprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- [text]
- [text]

RECENT MAJOR CHANGES
[section (X X)] [m/year]
[section (X X)] [m/year]

INDICATIONS AND USAGE
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

DOSAGE AND ADMINISTRATION
- [text]
- [text]

DOSAGE FORMS AND STRENGTHS
- [text]

CONTRAINDICATIONS
- [text]

WARNINGS AND PRECAUTIONS
- [text]

ADVERSE REACTIONS
Most common adverse reactions (incidence > 5%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

USE IN SPECIFIC POPULATIONS
See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling or and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS

WARNING: [SUBJECT OF WARNING]
1 INDICATIONS AND USAGE
1.1 [text]
1.2 [text]

2 DOSAGE AND ADMINISTRATION
2.1 [text]
2.2 [text]

3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 [text]
5.2 [text]

6 ADVERSE REACTIONS
6.1 [text]
6.2 [text]

7 DRUG INTERACTIONS
7.1 [text]
7.2 [text]

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES
14.1 [text]
14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEBRA C BEITZELL
04/18/2014

ERIC R BRODSKY
04/18/2014

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, Acting SEALD Director.
PATIENT LABELING REVIEW

Date: March 12, 2014

To: Badrul Chowdhury, M.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Matthew J. Falter, Pharm.D
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): EPIPEN and EPIPEN Jr (epinephrine)

Dosage Form and Route: Auto-Injector
Application
Type/Number: NDA 19430
Supplement Number: S-059

Applicant: Mylan Specialty L.P.
INTRODUCTION

On October 25, 2013, Mylan Specialties L.P. submitted for the Agency’s review a labeling supplement for conversion of the current label to the Physician’s Labeling Rule (PLR) Format for EPIPEN and EPIPEN Jr (epinephrine) Auto-Injectors which are indicated for the emergency treatment of allergic reactions including anaphylaxis.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on November 13, 2013, for DMPP and OPDP to review the Applicant’s proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for EPIPEN and EPIPEN Jr. (epinephrine) Auto-Injectors.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and DMEPA deferred to DMPP to provide IFU review comments.

MATERIAL REVIEWED

- Draft EPIPEN and EPIPEN Jr. (epinephrine) PPI and IFU received on February 28, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on March 5, 2014.
- Draft EPIPEN and EPIPEN Jr. (epinephrine) PPI and IFU received on February 28, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on March 5, 2014.
- Draft EPIPEN and EPIPEN Jr. (epinephrine) Prescribing Information (PI) received on October 25, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on February 12, 2014.
- Draft EPIPEN and EPIPEN Jr. Prescribing Information (PI) received on October 25, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on February 12, 2014.

REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
• ensured that the PPI and IFR are free of promotional language or suggested revisions to ensure that it is free of promotional language
• ensured that the PPI and IFU meet the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS
The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS
• Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
• Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHARON W WILLIAMS
03/12/2014

MATTHEW J FALTER
03/12/2014

MELISSA I HULETT
03/12/2014

LASHAWN M GRIFFITHS
03/12/2014
Memorandum

Date: February 26, 2014

To: Carol Hill, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Roberta Szydlo, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Kathleen Klemm, Team Leader
OPDP

Subject: NDA 019430/S-059
OPDP labeling comments for EpiPen® (epinephrine injection, USP) Auto-Injector 0.3 mg and EpiPen Jr® (epinephrine injection, USP) Auto-Injector 0.15 mg (EpiPen)

In response to DPARP’s consult request dated November 13, 2013, OPDP has reviewed the draft Package Insert (PI) for EpiPen associated with S-059. This supplement provides for conversion of the PI to PLR format.

Reference is made to the February 13, 2014, email exchange between DPARP (Carol Hill) and the Division of Medical Policy Programs (DMPP) (Sharon Williams) in which DPARP indicated that review of patient labeling should be deferred at this time. Therefore, this review is limited to the PI only.

OPDP’s comments on the PI are based on the proposed draft marked-up labeling titled “NDA 19430 S-059 PI PLR 2013-11-8 DPARP 2014-2-12.docx” that was sent via email from DPARP to OPDP on February 12, 2014. Our comments on the PI are provided directly in the attached copy below.

Thank you for your consult. If you have any questions please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHLEEN KLEMM on behalf of ROBERTA T SZYDLO
02/26/2014

Reference ID: 3461660
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<td>Office of Medication Error Prevention and Risk Management</td>
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**Label, Labeling and Packaging Review**

Date: February 20, 2014

Reviewer: Lissa C. Owens, PharmD
Division of Medication Error Prevention and Analysis

Associate Director: Lubna Merchant, M.S., PharmD
Division of Medication Error Prevention and Analysis

Drug Name(s) and Strength(s): EpiPen (Epinephrine) Auto-Injector 0.3 mg
EpiPen (Epinephrine) Auto-Injector 0.15 mg

Application Type/Number: NDA 019430/S-058 and S-059

Applicant/sponsor: Mylan Specialty, LP

OSE RCM #: 2013-2645 and 2013-2606

*** This document contains proprietary and confidential information that should not be released to the public.***
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1 INTRODUCTION

This review responds to a consult from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to evaluate the container labels and carton labeling for EpiPen and EpiPen Jr. (Epinephrine) NDA 019430/S-058 and the full prescribing information and patient instructions for use for EpiPen and EpiPen Jr. (Epinephrine) NDA 019430/S-059 for areas of vulnerability that could lead to medication errors.

In Supplement 058, the Applicant is proposing to update the carton labeling to facilitate and improve use of the product by patients and caregivers by providing a visual summary on the carton of the 3 steps (Prepare, Administer, and Finalize) used to administer Epinephrine.

In Supplement 059, the Applicant is proposing the conversion of the Prescribing Information (PI) and Patient Instructions for use (PIFU) to the Physician Labeling Rule (PLR) format.

1.1 PRODUCT INFORMATION

EpiPen and EpiPen Jr. (Epinephrine) were approved on December 22, 1987 (NDA 019430). The following product information is provided in the October 28, 2013 prior approval supplement.

- Active Ingredient: Epinephrine
- Indication of Use: emergency treatment of allergic reactions (Type 1) including anaphylaxis to stinging insects and biting insects, allergen immunotherapy, foods, drugs, diagnostic testing substances, and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis
- Route of Administration: Intramuscular
- Dosage Form: Injection
- Strength: EpiPen is 0.3 mg and EpiPen Jr. is 0.15 mg
- Dose: Single-dose administered
- How Supplied: A carton containing 2 EpiPen Auto-Injectors and 1 Trainer
- Storage: excursions permitted between 15°C and 30°C (59°F and 86°F). Protect from light
- Container and Closure systems: Auto-Injector that also includes a S-clip to clip two cases together.

2 METHODS AND MATERIALS REVIEWED

DMoPA searched the FDA Adverse Event Reporting System (FAERS) database for EpiPen and EpiPen Jr. medication error reports (See Appendix A for a description of the FAERS database). We also reviewed the EpiPen and EpiPen Jr. labels and labeling, full prescribing information, and patient instructions for use submitted by the Applicant.
2.1 Selection of Medication Error Cases

We searched the FAERS database using the strategy listed in Table 1. The search was limited to the date of our last search in our last labeling review (OSE RCM # 2011-4500 dated February 22, 2012).

<table>
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<th>Table 1: FAERS Search Strategy</th>
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<tr>
<td>(EpiPen Jr.)</td>
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<td>MedDRA Search Strategy</td>
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<td>Medication Errors (HLGT)</td>
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<td>Product Packaging Issues HLT</td>
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<td>Product Label Issues HLT</td>
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<tr>
<td>Product Quality Issues (NEC)</td>
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<td>HLT</td>
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</tbody>
</table>

The FAERS database search identified 135 cases. Each case was reviewed for relevancy and duplication. After individual review, 44 cases were not included in the final analysis for the following reasons:

- Foreign Cases unrelated to label and labeling
- No error occurred
- Labeled adverse reactions (headache, palpitations, increased blood pressure)
- Device malfunction (needle bent after injecting)

2.2 Labels and Labeling

Using the principles of human factors and Failure Mode and Effects Analysis, along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted October 24, 2013 (Appendix C)
- Carton Labeling submitted October 24, 2013 (Appendix D)
- Full Prescribing Information submitted October 28, 2013 (no image)
- Patient Instructions For Use submitted October 28, 2013 (no image)

2.3 Previously Completed Reviews

DMEPA had previously reviewed EpiPen and EpiPen Jr. (OSE RCM # 2011-4500 dated February 22, 2012) and made recommendations to the labels and labeling. We note that these recommendations have been implemented by the Applicant.

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the Applicant’s proposed changes as well as the associated label and labeling.

3.1 Medication Error Cases

Following exclusions as described in section 2.1, ninety-one EpiPen and EpiPen Jr. medication error cases remained for our detailed analysis. Appendix B provides listings of all case numbers for the cases summarized in this review.

- Accidental Exposure (n=88)
  - The majority (n=37) of these cases included patients or trainers intentionally using the live pen versus the trainer device during demonstration and/or practicing how to use the pen at home or confusion between the trainer and the live pen. Of the thirty-seven cases, four were nurses and two were physicians. Outcomes included pain, jitteriness, and increased heart rate. The root cause included lack of differentiation between the trainer device and the live device and intentional use.
  - Twenty-one (n=21) cases of patients disposing of expired pens and accidently injecting their thumb or arm. Outcomes included pain, jitteriness, and increased heart rate. The root cause was not reported.
  - Fourteen (n=14) cases of lay persons administering the pen incorrectly and injecting themselves. Outcomes included pain, jitteriness, and increased heart rate. In nine (n=9) of these cases the root cause was reported as the person was unfamiliar with how to use the pen.
  - Eight (n=8) cases of physicians and nurses holding the pen incorrectly and administering the pen into their thumbs. Outcomes included pain and jitteriness. The root cause was reported as “using an old design pen.”
  - Six (n=6) cases of children playing with the live pen and the pen was activated or injected into their thumbs or in one case a child’s ankle. The outcomes included pain and paleness of the thumb. The root cause was not reported.
  - One (n=1) case of a patient being told the pen was “not real” and they injecting themselves. The patient experienced pain and recovered.
  - One (n=1) case of a patient who had the device turned around and his hand over the needle end and injected himself in the hand versus the thigh. He experienced pain and numbness and recovered.

- Wrong route (n=1) In this case a patient injected the device in the gluteus maximus versus the thigh. The patient experienced pain and throbbing. The root cause was not reported in this case.
• Wrong strength (n=1) In this case a prescription was written for EpiPen Jr. however, EpiPen was entered into the computer and filled. The pen was dispensed but not administered. The root cause was not reported.

• Wrong Technique (n=1) In this case a physician administered the pen into a patients thigh but removed it immediately versus holding it in place for ten seconds. A second pen was administered correctly and the patient recovered. The root cause was not reported.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

In Supplement 058, the Applicant is proposing changes to update the carton labeling to facilitate and improve use of the product by patients and caregivers by providing a visual summary on the carton of the 3 steps (Prepare, Administer, and Finalize) used to administer Epinephrine.

In Supplement 059, the Applicant is proposing the conversion of the Full Prescribing Information (PI) and Patient Instructions for use (PIFU) to the Physician Labeling Rule (PLR) format.

DMEPA performed a risk assessment of the carton labeling, the proposed full prescribing information and the patient instructions for use to identify any deficiencies that may lead to medication errors and did not find any at this time.

We retrieved eighty-seven cases of accidental exposure. Of the eighty-seven, thirty-seven were confusion between the trainer and the live device. These cases were prior to the labeling changes in supplement 053 (approved on August 20, 2012) where changes were made to revise the trainer label to more explicitly differentiate the label on the trainer from those on the live EpiPen and EpiPen Jr. In addition, most of the other cases, retrieved are prior to the labeling changes. For cases retrieved after the labeling changes were approved, it is unclear if the pens involved in the error utilized the updated labeling.

We have sent an information request to the Applicant requesting any reports of confusion between the live EpiPen and the trainer device from September 2012 to the present. We will continue to monitor for additional cases.

4 CONCLUSIONS

DMEPA concludes that the proposed changes to the carton labeling and the proposed Prescribing Information and Patient Instructions for Use in PLR format are acceptable at this time. We defer to the Division of Medical Policy Programs (DMPP) for further comments and/or recommendations.

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.
APPENDICES

Appendix A: Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA’s postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

Appendix B: FAERS Reports discussed in this review:

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

LISSA C OWENS
02/20/2014

LUBNA A MERCHANT
02/20/2014
REGULATORY PROJECT MANAGER
PHYSICIAN’S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 19430/S059

Application Type: PLR Conversion Labeling Supplement

Name of Drug/Dosage Form: EpiPen and EpiPen Jr (epinephrine) Auto-Injector

Applicant: Mylan Specialty L.P.

Receipt Date: October 28, 2013

Goal Date: April 28, 2014

1. Regulatory History and Applicant’s Main Proposals
EpiPen Auto-Injector was first approved in 1987. Per the final rule Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products and the Guidance for Industry Labeling for Human Prescription Drug and Biological Products – Implementing the PLR content and Format Requirements, conformance to the Physician Labeling Rule (PLR) is voluntary for products approved before June 30, 2001. In response to the Agency’s initiative to encourage manufacturers exempt from the final rule to implement the PLR labeling format change, Mylan voluntarily submitted a supplement to conform the labeling to the PLR format.

2. Review of the Prescribing Information
This review is based on the applicant’s submitted Word format of the prescribing information (PI). The applicant’s proposed PI was reviewed in accordance with the labeling format requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” checklist (see the Appendix).

3. Conclusions/Recommendations
SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

1. Periods, which are not allowed, appear after the numbers for the section and subsection headings of the FPI. These periods should be removed.
2. A horizontal line should be placed between the TOC and the FPI to separate the TOC from the FPI.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in an advice correspondence. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format. The resubmitted PI will be used for further labeling review.
Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

   Comment: Applicant should format HL to have 1/2 inch margins on all sides and between columns.

2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

   Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:
   
   ➢ For the Filing Period:
     • For efficacy supplements: If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
     • For NDAs/BLAs and PLR conversions: Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

   ➢ For the End-of-Cycle Period:
     • Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

   Comment:

3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

   Comment:

4. All headings in HL must be bolded and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.
Selected Requirements of Prescribing Information

**Comment:** The horizontal line can be a solid or dashed line and should extend over the entire length of the column. The applicant should extend the horizontal line in the headings over the entire width of the column.

**NO**
5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

**Comment:**
The applicant should remove the white space between the product title and Initial U.S. Approval.

**YES**
6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

**YES**
7. Section headings must be presented in the following order in HL:

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<tr>
<td>Highlights Limitation Statement</td>
<td>Required</td>
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<td>Product Title</td>
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<tr>
<td>Initial U.S. Approval</td>
<td>Required</td>
</tr>
<tr>
<td>Boxed Warning</td>
<td>Required if a BOXED WARNING is in the FPI</td>
</tr>
<tr>
<td>Recent Major Changes</td>
<td>Required for only certain changes to PI*</td>
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<tr>
<td>Dosage and Administration</td>
<td>Required</td>
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<tr>
<td>Dosage Forms and Strengths</td>
<td>Required</td>
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<tr>
<td>Contraindications</td>
<td>Required (if no contraindications must state &quot;None.&quot;)</td>
</tr>
<tr>
<td>Warnings and Precautions</td>
<td>Not required by regulation, but should be present</td>
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<tr>
<td>Adverse Reactions</td>
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<td>Drug Interactions</td>
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<td>Revision Date</td>
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</table>

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:**

**HIGHLIGHTS DETAILS**

**Highlights Heading**

**YES**
8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “HIGHLIGHTS OF PRESCRIBING INFORMATION”.

**Comment:**

**Highlights Limitation Statement**

**YES**
9. The **bolded** HL Limitation Statement must include the following verbatim statement: “These highlights do not include all the information needed to use (insert name of drug product)
Selected Requirements of Prescribing Information

safely and effectively. See full prescribing information for (insert name of drug product).” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be bolded.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be bolded, and include the verbatim statement “Initial U.S. Approval:" followed by the 4-digit year.

Comment: The initial U.S. Approval should be followed by the 4-digit year only. Remove the month that is listed before the 4-digit year.

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be bolded.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word “WARNING” (even if more than one warning, the term, “WARNING” and not “WARNINGS” should be used) and other words to identify the subject of the warning (e.g., “WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement “See full prescribing information for complete boxed warning.” This statement should be centered immediately beneath the heading and appear in italics.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “See full prescribing information for complete boxed warning.”).

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

N/A

Reference ID: 3456666
Selected Requirements of Prescribing Information

18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim bolded statement must be present: “To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch”.

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three bolded verbatim statements that is most applicable:

If a product does not have FDA-approved patient labeling:

• “See 17 for PATIENT COUNSELING INFORMATION”

If a product has FDA-approved patient labeling:

• “See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling”
• “See 17 for PATIENT COUNSELING INFORMATION and Medication Guide”

Comment:

Revision Date in Highlights

NO 24. The revision date must be at the end of HL, and should be bolded and right justified (e.g., “Revised: 9/2013”).

Reference ID: 3456666
Selected Requirements of Prescribing Information

Comment: The date of the most recent revision of the PI must be presented at the end of HL.
Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

25. The TOC should be in a two-column format.
   
   **Comment:** The TOC should be in a two-column format. The applicant should revised the TOC to a two-column format.

26. The following heading must appear at the beginning of the TOC: “FULL PRESCRIBING INFORMATION: CONTENTS”. This heading should be in all UPPER CASE letters and **bolded**.
   
   **Comment:**

27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
   
   **Comment:**

28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
   
   **Comment:**

29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in **title case** [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
   
   **Comment:**

30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
   
   **Comment:**

31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.*”
   
   **Comment:**
Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in **UPPER CASE** and **title case**, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<table>
<thead>
<tr>
<th>BOXED WARNING</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 INDICATIONS AND USAGE</td>
</tr>
<tr>
<td>2 DOSAGE AND ADMINISTRATION</td>
</tr>
<tr>
<td>3 DOSAGE FORMS AND STRENGTHS</td>
</tr>
<tr>
<td>4 CONTRAINDICATIONS</td>
</tr>
<tr>
<td>5 WARNINGS AND PRECAUTIONS</td>
</tr>
<tr>
<td>6 ADVERSE REACTIONS</td>
</tr>
<tr>
<td>7 DRUG INTERACTIONS</td>
</tr>
<tr>
<td>8 USE IN SPECIFIC POPULATIONS</td>
</tr>
<tr>
<td>8.1 Pregnancy</td>
</tr>
<tr>
<td>8.2 Labor and Delivery</td>
</tr>
<tr>
<td>8.3 Nursing Mothers</td>
</tr>
<tr>
<td>8.4 Pediatric Use</td>
</tr>
<tr>
<td>8.5 Geriatric Use</td>
</tr>
<tr>
<td>9 DRUG ABUSE AND DEPENDENCE</td>
</tr>
<tr>
<td>9.1 Controlled Substance</td>
</tr>
<tr>
<td>9.2 Abuse</td>
</tr>
<tr>
<td>9.3 Dependence</td>
</tr>
<tr>
<td>10 OVERDOSAGE</td>
</tr>
<tr>
<td>11 DESCRIPTION</td>
</tr>
<tr>
<td>12 CLINICAL PHARMACOLOGY</td>
</tr>
<tr>
<td>12.1 Mechanism of Action</td>
</tr>
<tr>
<td>12.2 Pharmacodynamics</td>
</tr>
<tr>
<td>12.3 Pharmacokinetics</td>
</tr>
<tr>
<td>12.4 Microbiology (by guidance)</td>
</tr>
<tr>
<td>12.5 Pharmacogenomics (by guidance)</td>
</tr>
<tr>
<td>13 NONCLINICAL TOXICOLOGY</td>
</tr>
<tr>
<td>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</td>
</tr>
<tr>
<td>13.2 Animal Toxicology and/or Pharmacology</td>
</tr>
<tr>
<td>14 CLINICAL STUDIES</td>
</tr>
<tr>
<td>15 REFERENCES</td>
</tr>
<tr>
<td>16 HOW SUPPLIED/STORAGE AND HANDLING</td>
</tr>
<tr>
<td>17 PATIENT COUNSELING INFORMATION</td>
</tr>
</tbody>
</table>

**Comment:**

33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see Warnings and Precautions (5.2)]” or “[see Warnings and Precautions (5.2)]”.

**Comment:**
34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be bolded and appear at the beginning of the FPI: “FULL PRESCRIBING INFORMATION”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be bolded.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word “WARNING” (even if more than one Warning, the term, “WARNING” and not “WARNINGS” should be used) and other words to identify the subject of the Warning (e.g., “WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”).

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

N/A 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and
Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:
Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME] (nonproprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: [year]

--- WARNING: [SUBJECT OF WARNING] ---
See full prescribing information for complete boxed warning.

--- RECENT MAJOR CHANGES ---
[section (X X)] [m/week]
[section (X X)] [m/week]

--- INDICATIONS AND USAGE ---
[DRUG NAME] is a [name of pharmacologic class] indicated for:

• [text]
• [text]

--- DOSAGE AND ADMINISTRATION ---
• [text]
• [text]

--- DOSAGE FORMS AND STRENGTHS ---
• [text]

--- CONTRAINDICATIONS ---
• [text]
• [text]

--- WARNINGS AND PRECAUTIONS ---
• [text]
• [text]

--- ADVERSE REACTIONS ---
Most common adverse reactions (incidence ≥ 5%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

--- DRUG INTERACTIONS ---
• [text]
• [text]

--- USE IN SPECIFIC POPULATIONS ---
• [text]
• [text]

See I for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling or and Medication Guide].

--- FULL PRESCRIBING INFORMATION: CONTENTS ---
FULL PRESCRIBING INFORMATION: CONTENTS

WARNING: [SUBJECT OF WARNING]
1 INDICATIONS AND USAGE
1.1 [text]
1.2 [text]
2 DOSAGE AND ADMINISTRATION
2.1 [text]
2.2 [text]
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 [text]
5.2 [text]
6 ADVERSE REACTIONS
6.1 [text]
6.2 [text]
7 DRUG INTERACTIONS
7.1 [text]
7.2 [text]
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
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9 DRUG ABUSE AND DEPENDENCE
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10 OVERDOSAGE
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12.1 Mechanism of Action
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12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 [text]
14.2 [text]
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

--- Reference ---
Reference ID: 3456666
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROL F HILL
02/19/2014

LADAN JAFARI
02/19/2014
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019430Orig1s059

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
NDA 19430

Mylan Specialty L.P.
781 Chestnut Ridge Road
P. O. Box 4310
Morgantown, WV 26504-4310

Attention: S. Wayne Talton
Head, Global Regulatory Science and Operations

Dear Mr. Talton:

We refer to your New Drug Application (NDA), 019430, for EpiPen and EpiPen Jr. (epinephrine injection) Auto-Injector, 0.3mg and 0.15 mg that was approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) on December 22, 1987, in which both single- and two-pack marketing configurations are listed in the How Supplied section of the Prescribing Information. We also refer to the labeling for EpiPen and EpiPen Jr. that was approved as part of Supplement S-059 on April 30, 2014, in which only a two-pack marketing configuration is listed.

We are reminding you that your NDA (019430) does not preclude marketing EpiPen as both single- and two-packs as you previously had in the U.S. market. Because current marketing of EpiPen is only as a two-pack, patients are unable to obtain a single dose even if their health care practitioner determines a single dose is appropriate or the patient needs to replace one used dose.

We acknowledge that the Dosing and Administration section of the EpiPen label states that some patients may require a second dose of epinephrine. However, the approved labeling does not recommend that patients be prescribed two doses. The number of patients reported to require more than one dose of epinephrine for treatment of anaphylaxis is generally quoted as approximately 12-36%, suggesting that the majority of patients will not need a second dose.


Reference ID: 4050351
dose of epinephrine after an anaphylactic episode. Whether a patient requires one or two doses is at the discretion of the prescriber and the patient or caregiver. Having EpiPen supplied as single- and two-packs would enable prescribers to write prescriptions for single-packs at their discretion and provide patients and caregivers greater options and in turn access to care when only a single dose is necessary.

Should you decide to resume marketing of the single-pack as well as the two-pack, you will need to update the “How Supplied” section of the labeling to reflect that both the single- and two-pack are marketed. This update can be described in an annual report (see FDA Guidance on Changes to an Approved NDA or ANDA, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm077097.pdf).

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

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
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/s/

LYDIA I GILBERT MCCLAIN
02/02/2017
DATE: April 18, 2014

<table>
<thead>
<tr>
<th>To:</th>
<th>Dawn Watson, Ph.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VP, Global Regulatory Affairs</td>
</tr>
<tr>
<td>From:</td>
<td>Carol Hill, M.S.</td>
</tr>
<tr>
<td></td>
<td>Sr. Regulatory Health Project Manager</td>
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<tr>
<td>Company:</td>
<td>Mylan Specialty and Dermal Products</td>
</tr>
<tr>
<td></td>
<td>Division of Pulmonary, Allergy, and Rheumatology Drug Products</td>
</tr>
<tr>
<td>E-Address:</td>
<td><a href="mailto:dawn.watson@mylan.com">dawn.watson@mylan.com</a></td>
</tr>
<tr>
<td>Fax number:</td>
<td>301-796-9728</td>
</tr>
<tr>
<td>Phone number:</td>
<td>304-554-6301</td>
</tr>
<tr>
<td></td>
<td>Phone number: 301-796-2300</td>
</tr>
</tbody>
</table>

Subject: NDA 19430/S059 – Labeling Revisions III

Total no. of pages including cover: 4

Comments: Please respond by COB on April 21, 2014

Document to be mailed: YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.
Dear Dr. Watson:

Your submission dated April 9, 2014, to NDA 19430, is currently under review. We have the following comments and requested revisions for the Prescribing Information. Be advised that these labeling changes are not necessarily the Agency’s final recommendations and that additional labeling comments may be forthcoming as we continue our review.

Highlights (HL)

1. The product title must contain the drug names, dosage form, route of administration and, if applicable, the controlled substance symbol (see 201.57(a)(2). The product titles for EpiPen and EpiPen Jr. contain additional descriptors that should not be included in the product title (i.e., “USP”, dosage strengths, and the delivery system). The proprietary name should be presented in all upper case letters. Revise the product titles to read:

   **EPIGEN (epinephrine injection), Auto-Injector 0.3 mg,**
   **EPIGEN JR. (epinephrine injection), Auto-Injector 0.15 mg,**
   **for intramuscular or subcutaneous use**

2. Highlights musts be in a minimum of 8-point font, two-column format with ½ inch margins on all sides and between columns. Correct the margins on the top of the page, the left edge, and in between columns to ½ inch.

3. Insert a bullet point prior to the third statement under the Dosage and Administration heading and indent the text to align with the first and second bulleted items. Remove white space in between second and third bulleted items.

4. Because each dosage strength of EpiPen is associated with a proprietary name, include the proprietary name before the dosage form and strength information in the Dosage Forms and Strengths section. For example:

   **EpiPen: Injection, 0.3 mg: 0.3 mg/0.3 mL epinephrine, USP, pre-filled auto-injector (3)**
   **EpiPen Jr: Injection, 0.15 mg: 0.15 mg/0.3 mL epinephrine, USP, pre-filled auto-injector (3)**

5. Remove the line of white space in between product titles and initial U.S. approval date.

6. Bold the Contraindications heading and the horizontal lines on either side.

7. Correct the revision date font to match the Highlights font and right justify.

8. Insert horizontal line separating Table of Content (TOC) from the Full Prescribing Information (FPI).
9. We recommend that you fix the margins of the FPI so that the Word document prints correctly.

10. Throughout the FPI, correct all subsection headings to title case letters (subsection headings should remain bolded).

11. Throughout the FPI, correct all section headings within cross references to title case letters (change from UPPER CASE to lower case letters).

12. Because each dosage strength of EpiPen is associated with a proprietary name, include the proprietary name before the dosage form and strength information (same as recommendation #4 above).

13. Attach the Patient Information and Instructions for Use to the end of FPI.

14. Revise section 17 as recommended below.

**Administration and Training**

*Patients, and/or caregivers,* [b] should be instructed in the appropriate use of EpiPen and EpiPen Jr. EpiPen should be injected into the middle of the outer thigh (through clothing, if necessary). Each device is a single-use injection. Advise patients to seek immediate medical care in conjunction with administration of EpiPen.

Complete patient information, including dosage, directions for proper administration and precautions can be found inside each EpiPen or EpiPen Jr carton. A printed label on the surface of EpiPen shows instructions for use and a diagram depicting the injection process.

*Patients, and/or caregivers,* [b] should be instructed to use the Trainer to familiarize themselves with the use of EpiPen in an allergic emergency. The Trainer may be used multiple times. A Trainer device is provided in 2-Pak cartons.

We request you to submit draft labeling incorporating the recommended changes by COB on April 21, 2014. If you have any questions, call Carol F. Hill, Senior Regulatory Health Project Manager at 301-796-1226.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROL F HILL

04/18/2014
DATE: April 16, 2014

To: Dawn Watson, Ph.D.  
   VP, Global Regulatory Affairs  
From: Carol Hill, M.S.  
   Sr. Regulatory Health Project Manager  

Company: Mylan Specialty and Dermal Products  
Fax number: 301-796-9728  

E-Address: dawn.watson@mylan.com  
Phone number: 304-554-6301  

Phone number: 301-796-2300  

Subject: NDA 19430/S059 – Labeling Revisions II  

Total no. of pages including cover: 24  
Comments: Please respond by COB on April 21, 2014

Document to be mailed: YES  

xNO

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Dear Dr. Watson:

Your submission dated April 9, 2014, to NDA 19430, is currently under review. We have the following revisions to the labeling. In the attached revised package insert, patient package insert/instructions for use and the trainer instructions for use, comments are embedded and insertions are underlined and deletions are strike-out. Be advised that these labeling changes are not necessarily the Agency’s final recommendations and that additional labeling comments may be forthcoming as we continue our review.

We request you to submit draft labeling incorporating the recommended changes by COB on April 21, 2014. If you have any questions, call Carol F. Hill, Senior Regulatory Health Project Manager at 301-796-1226.
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/s/

----------------------------------------------------
CAROL F HILL
04/16/2014
DATE: March 26, 2014

| **To:** | Dawn Watson, Ph.D.  
| VP, Global Regulatory Affairs | **From:** Carol Hill, M.S.  
|  | Sr. Regulatory Health Project Manager |
| **Company:** | Mylan Specialty and Dermal Products  
|  | Division of Pulmonary, Allergy, and Rheumatology Drug Products |
| **E-Address:** | dawn.watson@mylan.com  
|  | Fax number: 301-796-9728 |
| **Phone number:** | 304-554-6301  
|  | Phone number: 301-796-2300 |

**Subject:** NDA 19430/S059 – Labeling Revisions I

**Total no. of pages including cover:** 27

Comments: Please respond by COB on April 3, 2014

**Document to be mailed:** YES  

x NO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.
Dear Dr. Watson:

Your submission dated October 25, 2013, to NDA 19430, is currently under review. We have the following comments regarding the package insert below. In the attached revised package insert, patient package insert/instructions for use and the trainer instructions for use, insertions are underlined and deletions are strike-out. Be advised that these labeling changes are not necessarily the Agency’s final recommendations and that additional labeling comments may be forthcoming as we continue our review.

Highlights (HL)
1. HL must be a minimum of 8-point font in a two-column format, with ½ inch margins on all sides and between columns. Revise the HL to have a two-column format with ½ inch margins on all sides and between columns.
2. The date for the most recent revision of the physician insert (PI) must be presented at the end of the HL.

Table of Contents (TOC)
3. The TOC should be in a two-column format.

Full Prescribing Information (FPI)
4. Periods, which are not allowed, appear after the numbers for the section and subsection headings. Remove these periods.
5. A horizontal line must be placed between the TOC and the FPI to separate the Toc from the FPI.

Patient Information Leaflet (PIL, including the Patient Information (PPI) and Instructions for Use (IFU))
6. Reformat the PIL with margins greater than ½ that do not require special printing instructions.

We request you to submit draft labeling incorporating the recommended changes by COB on April 3, 2014. If you have any questions, call Carol F. Hill, Senior Regulatory Health Project Manager at 301-796-1226.
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/s/

CAROL F HILL
03/26/2014
REQUEST FOR CONSULTATION

TO (Division/Office): OSE
FROM: Carol Hill/RPM, ODEII/DPARP/301-796-1226
DATE: November 13, 2013
IND NO. 19430
NDA NO. 059
TYPE OF DOCUMENT: Labeling Supplement- PLR Conversion
DATE OF DOCUMENT: October 28, 2013
NAME OF DRUG: EpiPen/EpiPen Jr
PRIORITY CONSIDERATION: Standard
CLASSIFICATION OF DRUG
DESIGNED COMPLETION DATE: February 24, 2014
NAME OF FIRM: Mylan Specialty LP

REASON FOR REQUEST

I. GENERAL
☐ NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY
☐ PRE-NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ CONTROL SUPPLEMENT
☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☐ OTHER (SPECIFY BELOW):

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH
☐ TYPE A OR B NDA REVIEW
☐ END OF PHASE II MEETING
☐ CONTROLLED STUDIES
☐ PROTOCOL REVIEW
☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH
☐ CHEMISTRY REVIEW
☐ PHARMACOLOGY
☐ BIOPHARMACEUTICS
☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOAVAILABILITY STUDIES
☐ PHASE IV STUDIES
☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ REVIEW OF MARKETING EXPERIENCE; DRUG USE AND SAFETY
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL
☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This is a PLR conversion labeling supplement (PI, PIL, and TI) received October 28, 2013. This is a paper submission and we have requested the applicant to provide a word version of the label for review. Attached is the paper submission. We request that you provide comment regarding this conversion of the label to the PLR format. The PDUFA Date is April 28, 2014

Team Labeling Meeting: To be Arranged

SIGNATURE OF REQUESTER
Carol F. Hill

METHOD OF DELIVERY (Check all that apply)
☐ MAIL
☐ DARRTS
☐ HAND

SIGNATURE OF RECEIVER
SIGNATURE OF DELIVERER
Carol F. Hill

Reference ID: 3406416
Badrul Chowdhury, MD, PhD, Division Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltville, MD 20705-1266

Re: NDA 019430
EpiPen® and EpiPen Jr® (epinephrine) Auto-Injector
SLR - PLR Label Format Conversion

Dear Dr. Chowdhury:

Reference is made to the subject NDA, for which Mylan Specialty L.P. (Mylan) assumed ownership from Meridian Medical Technologies, Inc., with an effective date of [redacted]. Reference is further made to the final rule Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, as published in 71 FR 3922, January 24, 2006 and the supporting final Guidance for Industry Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements, February 2013, Labeling. As noted in this guidance, conformance to PLR labeling requirements is voluntary for products approved before June 30, 2001. Since only about 10% of exempt brand products have adopted the new label format, the Agency has recently made public its intention to launch an initiative to encourage manufacturers exempt from the final rule to implement the labeling format change anyway.

Mylan has considered the Agency’s public statements in this context, and although EpiPen® Auto-Injector was first approved in 1987, we appreciate both the Agency’s position regarding the value of the PLR formatted label and the fact that EpiPen® Auto-Injector is the reference listed drug (RLD) for other epinephrine auto-injectors (EAI). Accordingly, at this time, Mylan believes conversion to PLR format is an appropriate initiative for Mylan as the RLD NDA sponsor, and we are voluntarily submitting a PLR formatted label version of the EpiPen® and EpiPen Jr® Auto-Injector for the Division’s review. As part of this conversion, Mylan has made some small revisions to some language of the current Prescribing Information, Patient Information, and Trainer Insert. These changes are not intended to modify or add to the indication; there are no new data as these changes are only meant to improve the clarity and consistency across these three documents.

Lastly, reference is made to the Agency’s Draft Guidance for Industry and Food and Drug Administration Staff: Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex, March 11, 2013. Based on that guidance the Agency will see that the language referring to latex has been removed from the Description section of the proposed label.

This submission is being provided as several attachments, which the Sponsor respectfully requests the Agency consider in sequence:

Reference ID: 3406416
Attachment 1: The Prescribing Information, Trainer Insert and Patient Information documents are presented in the current format, in track changes, to facilitate the Division’s review of changes being proposed to clarify the language in these three labeling documents. Regardless of the PLR format labeling change to the Prescribing Information, Mylan intends to continue to provide in the EpiPen® Auto-Injector carton the EpiPen Trainer Instructions with the trainer auto-injector, and the Patient Information as separate documents. Therefore the Agency’s review of these two latter documents in Attachment 1 would result in updated versions of those documents. Accordingly, the Trainer Instructions and the Patient Information are also provided as clean documents.

Attachment 2: The PLR formatted Full Prescribing Information is presented in Attachment 2. In recognition of the Agency’s recent approval of NDA 201739, which referenced the EpiPen® Auto-Injector but provided the Full Prescribing Information in PLR format, we have based our PLR format conversion on the Agency’s prior efforts to convert the EpiPen® label information into PLR format. This DRAFT document also includes all the track changes proposed edits noted in Attachment 1 to the current EpiPen® Auto-Injector labeling.

Attachment 3: The PLR formatted DRAFT Full Prescribing Information is presented in Attachment 3. This DRAFT document is the same MS Word document as provided in Attachment 2 but without track changes.

Please note Mylan understands that once the Division has agreed to final wording for the PLR format label, SPL labeling would be required for all documents, and we intend to be fully compliant and submit the SPL labeling at that time.

If you have any questions regarding this submission, please contact me directly at 908-542-2677, or via e-mail at sandra.cottrell@mylan.com.

Sincerely,

Sandra Cottrell, MA, PhD
Vice President, Regulatory Affairs
Mylan Specialty L.P.

cc: Kay Loscuito, Manager, Regulatory Affairs, Meridian Medical Technologies, Inc. - A Pfizer Company

63 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROL F HILL
11/13/2013
ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Mylan Specialty L.P.
110 Allen Pond Road, 4th Floor
Basking Ridge, NJ  07920

Attention: Sandra Cottrell, M.A., Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Cottrell:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

**NDA NUMBER:** 19430

**SUPPLEMENT NUMBER:** S059

**PRODUCT NAME:** EpiPen and EpiPen Jr (epinephrine) Auto-Injector 0.3/0.15 mg

**DATE OF SUBMISSION:** October 25, 2013

**DATE OF RECEIPT:** October 28, 2013

This supplemental application proposes to implement the Physician Labeling Rule (PLR) to convert the current label to the PLR format and to incorporate minor revisions to the language in the Prescribing Information, Patient Information Leaflet (PIL) and the Trainer Insert (TI).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 27, 2013, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be April 28, 2014.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at [http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm](http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm). Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).
SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Carol F. Hill, M.S.
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROL F HILL
11/13/2013