

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

201739Orig1s004

Trade Name: (FDCA) for Auvi-Q Auto-Injector, 0.3 mg and 0.15 mg.

Generic or Proper Name: epinephrine

Sponsor: Kaleo, Inc

Approval Date: May 18, 2016

Indication: This supplemental new drug application provides for revisions to the labeling for Auvi-Q

CENTER FOR DRUG EVALUATION AND RESEARCH

201739Orig1s004

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201739Orig1s004

APPROVAL LETTER



NDA 201739/S-004

SUPPLEMENT APPROVAL

Kaléo, Inc.
111 Virginia Street
Suite 300
Richmond, VA 23219

Attention: Glen Kelley
Director of Regulatory Affairs

Dear Mr. Kelley:

Please refer to your Supplemental New Drug Application (sNDA) dated March 4, 2016, received March 4, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Auvi-Q (epinephrine injection, USP) Auto-Injector, 0.3 mg and 0.15 mg.

We also refer to our letter dated February 5, 2016, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Auvi-Q (epinephrine injection, USP) Auto-Injector. This information pertains to reports of lacerations and embedded needles after epinephrine injection and post-marketing adverse event reports of serious infection (e.g. *Clostridium perfringens*) at the injection site following epinephrine injection for anaphylaxis.

This supplemental new drug application provides for revisions to the labeling for Auvi-Q consistent with our February 5, 2016, letter and the changes agreed upon in our March 24, and 31, and April 15, 2016, correspondences, and changes to the carton and container labeling to incorporate the change in ownership.

APPROVAL & LABELING

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, text for the patient instructions for use, and text for the trainer instructions for use, with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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

The SPL will be accessible from publicly available labeling repositories.

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

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 201739/S-004.**” Approval of this submission by FDA is not required before the labeling is used.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

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 for Safety, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):

Content of Labeling
Carton and Container Labeling

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

/s/

SALLY M SEYMOUR
05/18/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201739Orig1s004

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AUVI-Q® safely and effectively. See full prescribing information for AUVI-Q.

AUVI-Q® (epinephrine injection, USP) 0.3 mg, 0.15 mg

Auto-Injector, for intramuscular or subcutaneous use

Initial U.S. Approval: 1939

-----**RECENT MAJOR CHANGES**-----

- Dosage and Administration (2) 05/2016
- Warnings and Precautions (5.2, 5.3) 05/2016

-----**INDICATIONS AND USAGE**-----

Auvi-Q contains 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): Auvi-Q 0.3 mg (2)
 - Patients 15 to 30 kg (33 lbs – 66 lbs): Auvi-Q 0.15 mg (2)
- Inject Auvi-Q 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**-----

- Injection, 0.3 mg: 0.3 mg/0.3 mL epinephrine injection, USP, pre-filled auto-injector (3)
- Injection, 0.15 mg: 0.15 mg/0.15 mL epinephrine injection, 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)
- To minimize the risk of injection-related injury, instruct caregivers to hold the child’s leg firmly in place and limit movement prior to and during injection when administering to young children. (5.2)
- Rare cases of serious skin and soft tissue infections have been reported following epinephrine injection. Advise patients to seek medical care if they develop signs or symptoms of infection at the epinephrine injection site. (5.3)
- The presence of a sulfite in this product should not deter use. (5.4)
- Administer with caution in patients with heart disease; may aggravate angina pectoris or produce ventricular arrhythmias. (5.5)

-----**ADVERSE REACTIONS**-----

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

To report SUSPECTED ADVERSE REACTIONS, contact kaleo, Inc. at 1-844/828-8742 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. (5.5, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: May 2016

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Emergency Treatment

5.2 Injection-related Complications

5.3 Serious Infections at the Injection Site

5.4 Allergic Reactions Associated with Sulfite

5.5 Disease Interactions

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Auvi-Q® is 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.

Auvi-Q is 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.

Auvi-Q is intended for immediate self-administration as emergency supportive therapy only and is not a substitute for immediate medical care.

2 DOSAGE AND ADMINISTRATION

Selection of the appropriate dosage strength (Auvi-Q 0.3 mg or Auvi-Q 0.15 mg) is determined according to patient body weight.

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

Inject Auvi-Q intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. Instruct caregivers of young children who are prescribed Auvi-Q and who may be uncooperative and kick or move during an injection to hold the child's leg firmly in place and limit movement prior to and during an injection [*see WARNINGS AND PRECAUTIONS (5.2)*].

Each Auvi-Q contains a single dose of epinephrine for single-use injection. Since the doses of epinephrine delivered from Auvi-Q 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 Auvi-Q 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 viewing window of Auvi-Q should be inspected visually for particulate matter and discoloration. Epinephrine is light sensitive and should be stored in the outer case provided to protect it from light [*see STORAGE AND HANDLING (16.2)*].

3 DOSAGE FORMS AND STRENGTHS

- Injection, 0.3 mg/0.3 mL epinephrine injection, USP, pre-filled auto-injector
- Injection, 0.15 mg/0.15 mL epinephrine injection, USP, pre-filled auto-injector

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 EMERGENCY TREATMENT

Auvi-Q is 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 (17.1)*].

5.2 INJECTION-RELATED COMPLICATIONS

Auvi-Q should **ONLY** be injected into the anterolateral aspect of the thigh [*see DOSAGE AND ADMINISTRATION (2) and PATIENT COUNSELING INFORMATION (17.1)*].

- **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 Clostridial infections (gas gangrene). Cleansing with alcohol does not kill bacterial spores, and therefore, does not lower this risk.
- **Do not inject into digits, hands or feet.** 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)*].

- **Hold leg firmly during injection.** To minimize the risk of injection-related injury when administering Auvi-Q to young children, instruct caregivers to hold the child's leg firmly in place and limit movement prior to and during injection.

5.3 SERIOUS INFECTIONS AT THE INJECTION SITE

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported at the injection site following epinephrine injection for anaphylaxis. *Clostridium* spores can be present on the skin and introduced into the deep tissue with subcutaneous or intramuscular injection. While cleansing with alcohol may reduce the presence of bacteria on the skin, alcohol cleansing does not kill *Clostridium* spores. To decrease the potential risk of a rare, but serious *Clostridium* infection, do not inject Auvi-Q into the buttock [*see WARNINGS AND PRECAUTIONS (5.2)*]. Advise patients to seek medical care if they develop signs or symptoms of infection, such as persistent redness, warmth, swelling, or tenderness, at the epinephrine injection site.

5.4 ALLERGIC REACTIONS ASSOCIATED WITH SULFITE

Epinephrine is the preferred treatment for serious allergic reactions or other emergency situations even though this product contains sodium bisulfite, 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 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.

The alternatives to using epinephrine in a life-threatening situation may not be satisfactory.

5.5 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 Auvi-Q 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 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 (5.5)*].

Arrhythmias, including fatal ventricular fibrillation, have been reported, particularly in patients with underlying cardiac disease or those receiving certain drugs [*see WARNINGS AND PRECAUTIONS (5.5) and DRUG INTERACTIONS (7)*].

Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease [*see WARNINGS AND PRECAUTIONS (5.5)*].

Angina may occur in patients with coronary artery disease [*see WARNINGS AND PRECAUTIONS (5.5)*].

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 of epinephrine into the buttock has resulted in cases of gas gangrene [*see WARNINGS AND PRECAUTIONS (5.2)*].

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

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 (5.5)*].

The effects of epinephrine may be potentiated by tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines, notably chlorpheniramine, tripeleminamine, 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/m^2 basis at a maternal dose of 1.2 $\text{mg}/\text{kg}/\text{day}$ for two to three days), in mice at approximately 7 times the maximum daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a maternal subcutaneous dose of 1 $\text{mg}/\text{kg}/\text{day}$ for 10 days), and in hamsters at approximately 5 times the maximum recommended daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a maternal subcutaneous dose of 0.5 $\text{mg}/\text{kg}/\text{day}$ 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/m^2 basis at a subcutaneous maternal dose of 0.5 $\text{mg}/\text{kg}/\text{day}$ 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 Auvi-Q is administered to a nursing woman.

8.4 PEDIATRIC USE

Auvi-Q 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 Auvi-Q 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 of Auvi-Q did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Epinephrine 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 (5.5), 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

Auvi-Q (epinephrine injection, USP) 0.3 mg and 0.15 mg is an auto-injector and a combination product containing drug and device components.

Auvi-Q includes audible (electronic voice instructions, beeps) and visible (LED lights) cues for use. The needle automatically retracts after the injection is complete.

Each Auvi-Q 0.3 mg delivers a single dose of 0.3 mg epinephrine from epinephrine injection, USP (0.3 mL) in a sterile solution.

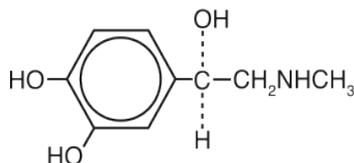
Each Auvi-Q 0.15 mg delivers a single dose of 0.15 mg epinephrine from epinephrine injection, USP (0.15 mL) in a sterile solution.

Auvi-Q 0.3 mg and Auvi-Q 0.15 mg each contain 0.76 mL epinephrine solution. 0.3 mL and 0.15 mL epinephrine solution is dispensed for Auvi-Q 0.3 mg and Auvi-Q 0.15 mg, respectively, when activated. The remaining solution is not available for future use and should be discarded.

Each 0.3 mL in Auvi-Q 0.3 mg contains 0.3 mg epinephrine, 2.3 mg sodium chloride, 0.5 mg sodium bisulfite, hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2–5.0.

Each 0.15 mL in Auvi-Q 0.15 mg contains 0.15 mg epinephrine, 1.2 mg sodium chloride, 0.2 mg sodium bisulfite, 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.

Auvi-Q is not made with natural rubber latex.

Auvi-Q instructional and safety systems should be thoroughly reviewed with patients and caregivers prior to use [*see PATIENT COUNSELING INFORMATION (17.1)*].

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

Carton containing two Auvi-Q (epinephrine injection, USP) 0.3 mg auto-injectors and a single Auvi-Q Trainer - NDC 60842-023-01

Carton containing two Auvi-Q (epinephrine injection, USP) 0.15 mg auto-injectors and a single Auvi-Q Trainer - NDC 60842-022-01

Rx only

16.2 STORAGE AND HANDLING

Epinephrine is light sensitive and should be stored in the outer case 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, 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 Auvi-Q, 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

Instruct patients and/or caregivers in the appropriate use of Auvi-Q. Auvi-Q 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 Auvi-Q.

Young children may be uncooperative and kick or move during and injection. Instruct caregivers to hold the leg of young children firmly in place and limit movement prior to and during injection. [*see WARNINGS AND PRECAUTIONS (5.2)*]

Complete patient information, including dosage, directions for proper administration and precautions can be found inside each Auvi-Q carton. Review Auvi-Q's instructional and safety systems with patients and/or caregivers. These systems include the printed label on the surface of Auvi-Q showing instructions for use and a diagram depicting the injection process, an automatic needle retraction system, visual prompts, electronic beeps, and voice instructions for use. Instruct patients and/or caregivers that the needle will not be visible after the injection.

Instruct patients and/or caregivers to use and practice with the Trainer to familiarize themselves with the use of Auvi-Q in an allergic emergency. The Trainer may be used multiple times.

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 symptoms and signs 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 (5.5)*].

Accidental Injection

Patients should be advised 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)*].

Serious Infections at the Injection Site

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported at the injection site

following epinephrine injection for anaphylaxis. Advise patients to seek medical care if they develop signs or symptoms of infection, such as persistent redness, warmth, swelling, or tenderness, at the epinephrine injection site [see WARNINGS AND PRECAUTIONS (5.3)].

Storage and Handling

Patients should be instructed to inspect the epinephrine solution visually through the viewing window periodically. Auvi-Q should be replaced if the epinephrine solution appears discolored (pinkish color or darker than slightly yellow), cloudy, or contains particles. Epinephrine is light sensitive and should be stored in the outer case provided to protect it from light. Instruct patients that Auvi-Q must be used or properly disposed once the red safety guard is removed [*see STORAGE AND HANDLING (16.2)*].

Complete patient information, including dosage, directions for proper administration and precautions can be found inside each Auvi-Q carton.

Manufactured for:

Kaleo, Inc.

Richmond, VA 23219 USA

This product may be covered by one or more U.S. patents or pending patent applications. See www.kaleopharma.com/pat for details.

***For California Only: This product uses batteries containing Perchlorate Material – special handling may apply. See www.dtsc.ca.gov/hazardouswaste/perchlorate**

PATIENT INFORMATION

Auvi-Q® (epinephrine injection)
Auto-Injector
For allergic emergencies (anaphylaxis)

Read this Patient Information Leaflet before you have to use Auvi-Q and each time you get a refill. There may be new information. You should know how to use Auvi-Q 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 Auvi-Q?

1. Always carry Auvi-Q with you because you may not know when a life-threatening allergic reaction (anaphylactic reaction) may happen. Talk to your doctor if you need additional units to keep at work, school, etc. An anaphylactic reaction is a life-threatening allergic reaction that can happen within minutes and can be caused by stinging and biting insects (bees, wasps, hornets, and mosquitoes), allergy shots, foods, medicines, exercise, or other unknown causes. Follow your healthcare provider's instructions on when to use Auvi-Q if you have the symptoms of an anaphylactic reaction, which may include the symptoms listed below:
 - 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
 - dizziness or fainting
2. Tell your family members and others where you keep Auvi-Q and how to use it before you need it. You may be unable to speak in an allergic emergency.
3. Get medical attention immediately after using Auvi-Q. If you have a serious allergic reaction, you may need more medicine.

What is Auvi-Q?

Auvi-Q is a prescription medicine used to treat life-threatening allergic reactions including anaphylaxis in people who are at risk for or have a history of serious allergic reactions.

Auvi-Q is for immediate self (or caregiver) administration and does not take the place of emergency medical care. You should get emergency medical help right away after using Auvi-Q.

It is not known if Auvi-Q is safe and effective in children who weigh less than 33 pounds (15 kg).

What should I tell my healthcare provider before using Auvi-Q?

Before you use Auvi-Q, tell your healthcare provider if you:

- have heart problems or high blood pressure
- have diabetes
- have thyroid problems
- have history of depression
- have Parkinson's disease
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if Auvi-Q will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Auvi-Q passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Auvi-Q and other medicines may affect each other, causing side effects. Auvi-Q may affect the way other medicines work, and other medicines may affect how Auvi-Q works.

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

How should I use Auvi-Q?

- Each Auvi-Q contains only 1 dose of medicine.
- Auvi-Q should only be injected into the muscle of your outer thigh. It can be injected through your clothing, if needed.
- Read the Instructions for Use at the end of this Patient Information Leaflet for information about the right way to use Auvi-Q.
- Use Auvi-Q exactly as your healthcare provider tells you to use it.
- An Auvi-Q Trainer with a separate Trainer Instructions for Use leaflet is included with Auvi-Q. Additional training resources are available at www.auvi-q.com.

- Practice with the Auvi-Q Trainer before an allergic emergency happens to make sure you are able to safely use the real Auvi-Q in an emergency.
- The Auvi-Q Trainer does not contain a needle or medicine and can be reused to practice your injection.

What are the possible side effects of Auvi-Q?

Auvi-Q may cause serious side effects.

- **Auvi-Q should only be injected into your outer thigh. Do not** inject Auvi-Q into your:

- veins
- buttocks
- fingers, toes, hands or feet

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

- Rarely, patients who use Auvi-Q may develop infections at the injection site within a few days of an injection. Some of these infections can be serious. Call your healthcare provider right away if you have any of the following at an injection site:
 - redness that does not go away
 - swelling
 - tenderness
 - the area feels warm to the touch
- If you inject a young child with Auvi-Q, hold their leg firmly in place before and during the injection to prevent injuries. Ask your healthcare provider to show you how to properly hold the leg of a young child during an injection.
- **If you have certain medical conditions, or take certain medicines, your condition may get worse or you may have more or longer lasting side effects when you use Auvi-Q. Talk to your healthcare provider about all your medical conditions.**

Common side effects of Auvi-Q include:

- fast, irregular, or 'pounding' heart beat
- sweating
- shakiness
- headache
- paleness
- feelings of over excitement, nervousness, or anxiety
- weakness
- dizziness
- nausea and vomiting
- breathing problems

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

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

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

How should I store Auvi-Q?

- Store Auvi-Q at 68° to 77°F (20° to 25°C).
- Do NOT expose to extreme heat or cold. For example, do NOT store in your vehicle's glove box. Do not store Auvi-Q in the refrigerator or freeze.
- Examine contents in the viewing window periodically. Solution should be clear. If the solution is discolored (pinkish color or darker than slightly yellow), cloudy or contains solid particles, replace the unit.
- Your Auvi-Q has an expiration date. Replace it before the expiration date.
- Keep Auvi-Q in the outer case it comes in to protect it from light.

Keep Auvi-Q and all medicines out of the reach of children.

General information about the safe and effective use of Auvi-Q:

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use Auvi-Q for a condition for which it was not prescribed. Do not give Auvi-Q to other people, even if they have an allergic reaction or the same symptoms that you have. It may harm them.

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

For more information and video instructions on the use of Auvi-Q, go to www.auvi-q.com or call 1-844-828-8472.

What are the ingredients in Auvi-Q?

Active ingredient: epinephrine.

Inactive Ingredients: sodium chloride, sodium bisulfite, hydrochloric acid, and water.

Auvi-Q does not contain latex.

Instructions for Use

Read these Instructions for Use carefully before you need to use your Auvi-Q. Before you use Auvi-Q, make sure your healthcare provider shows you the right way to use it. If you have any questions, ask your healthcare provider.

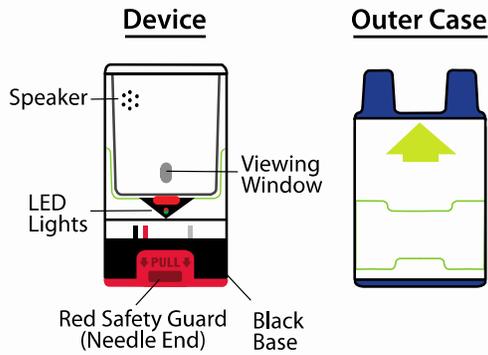
If you are administering Auvi-Q to a young child, hold the leg firmly in place and limit movement prior to and while administering an injection.

Automated Voice Instructions

Auvi-Q contains an electronic voice instruction system to help guide you through each step of your injection. If the voice instructions do not work for any reason, use Auvi-Q as instructed in these Instructions for Use. It will still work during an allergic reaction emergency.

How to use your Auvi-Q

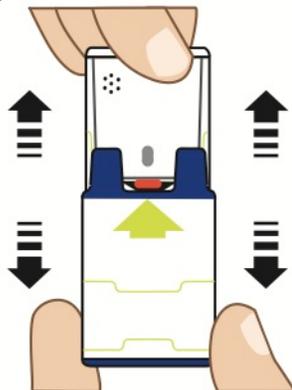
Figure A



1. Pull Auvi-Q from the outer case. See Figure B.

Do not go to step 2 until you are ready to use Auvi-Q. If you are not ready to use Auvi-Q, put it back in the outer case.

Figure B.

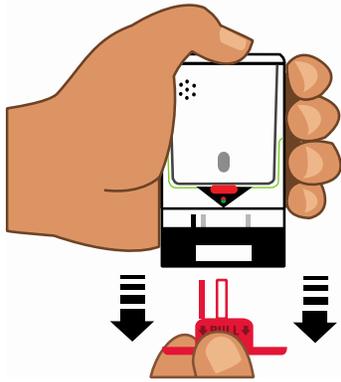


2. Pull off Red safety guard. See Figure C.

To reduce the chance of an accidental injection, do not touch the black base of the auto-injector, which is where the needle comes out. If an accidental injection happens, get medical help right away.

Note: The red safety guard is made to fit tight. **Pull firmly to remove.**

Figure C.



3. Place black end of Auvi-Q against the middle of the outer thigh (through clothing, if needed), then press firmly, and hold in place for 5 seconds. See Figure D.

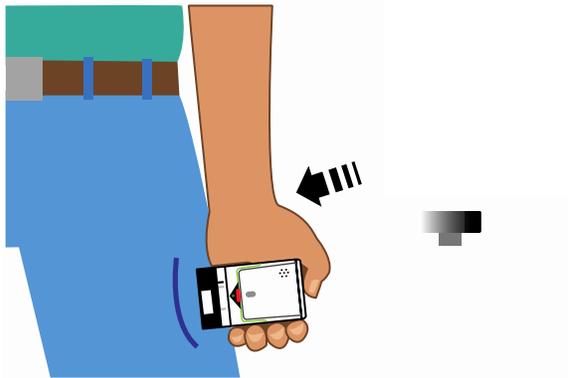
Only inject into the middle of the outer thigh. **Do not** inject into any other part of the body.

If you are administering Auvi-Q to a young child, hold the leg firmly in place while administering an injection.

Note: Auvi-Q makes a distinct sound (click and hiss) when you press it against your outer thigh. This is normal and indicates Auvi-Q is working correctly. Do not pull Auvi-Q away from your leg when you hear the click and hiss sound.

The needle automatically retracts after the injection is complete, so the needle will not be visible after the injection. Auvi-Q includes a 5-second countdown after it is activated, then the voice instruction will indicate the injection is complete, Auvi-Q will beep, and the lights will blink red.

Figure D.



4. Get emergency medical help right away.

Replace the outer case and talk to your healthcare provider about the right way to throw away your Auvi-Q.

Ask your healthcare provider for an Auvi-Q prescription refill.

After the use of Auvi-Q:

- The black base will lock into place.
- The voice instruction system will say Auvi-Q has been used and the lights will blink red.
- The red safety guard cannot be replaced.
- The viewing window will no longer be clear.
- It is normal for some medicine to remain in your Auvi-Q after you have received your dose of medicine.
- Talk to your healthcare provider about the right way to throw away your Auvi-Q.
- Auvi-Q is a single-use injectable device. Once Auvi-Q has been used, any medicine that remains in the auto-injector cannot be reused.

Until you throw away your used Auvi-Q, the electronic voice instruction system will remind you that it has been used when the outer case is removed.

If you will be administering Auvi-Q to a young child, ask your healthcare provider to show you how to properly hold the leg in place while administering a dose.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Rev May 2016

Manufactured for:

Kaleo, Inc.

Richmond, VA 23219 USA

This product may be covered by one or more U.S. patents or pending patent applications. See www.kaleopharma.com/pat for details.

***For California Only: This product uses batteries containing Perchlorate Material – special handling may apply. See www.dtsc.ca.gov/hazardouswaste/perchlorate**

Auvi-Q® TRAINER

Trainer Instructions for Use

Important:

The Auvi-Q Trainer Does Not contain a needle or medicine.

In case of an allergic emergency, use the real Auvi-Q and not the gray Trainer.

Always carry your real Auvi-Q with you in case of an allergic emergency.

Important Information about the Auvi-Q Trainer:

Inside your Auvi-Q Trainer are:

- batteries
- a speaker that will make a beeping sound and that produces electronic voice instructions
- red and green blinking lights

The Auvi-Q Trainer batteries are made to last long enough for you to practice 1 time each day for 2 years. If your Auvi-Q Trainer does not work properly call your healthcare provider for a new Trainer.

What is the Auvi-Q Trainer?

- The Auvi-Q Trainer does not contain a needle or medicine and can be reused to practice your injection.
 - Practice with the Auvi-Q Trainer before an allergic emergency happens to make sure you are able to safely use the real Auvi-Q in an emergency.
-

Your Auvi-Q Trainer



Auvi-Q Trainer:

- is inside a **gray outer case**
- does not have a needle or medicine inside
- can be reused (the red safety guard can be placed back on the base of the Trainer after use)
- has no expiration date

Auvi-Q:

- is inside an **orange (0.3 mg)** or **blue (0.15 mg) outer case**
- contains a needle and epinephrine medicine
- **cannot be reused** (the red safety guard cannot be placed back on the base of Auvi-Q after use)
- has a medicine expiration date listed on the device

In case of an allergic emergency, use the real Auvi-Q and **not** the gray Trainer.

Who should practice using the Auvi-Q Trainer?

Anyone who may need to help you with Auvi-Q in case of an allergic emergency:

- You
- Caregivers
- Family
- Friends
- Co-workers
- Teachers
- Child Care or Day Care Workers

Have them practice using the Trainer and review the Patient Information Leaflet included in the packaging with each prescription of Auvi-Q.

For more information and video instructions on the use of Auvi-Q, go to www.auvi-q.com or call 1-844-828-8472.

Practicing with the Auvi-Q Trainer

Practice with the Auvi-Q Trainer before an allergic emergency happens to make sure you are able to safely use the real Auvi-Q in an emergency.

- You should practice daily for the first week after you receive your Auvi-Q Trainer to help you feel comfortable using Auvi-Q quickly and safely. Even when you are comfortable using the Trainer, continue to practice using it often.

How to Use the Trainer

How the Auvi-Q Trainer works

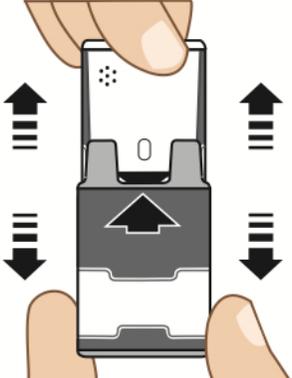
Although the Trainer does not have a needle and contains no medicine, it works the same way as the real Auvi-Q.

As with the real Auvi-Q, the Auvi-Q Trainer contains an electronic voice instruction system to help guide you through each step of your injection. If the voice instructions do not work for the Auvi-Q Trainer for any reason, you can still use the Auvi-Q Trainer as instructed in this leaflet to practice.

The Auvi-Q Trainer has the same blinking red and green lights as the real Auvi-Q.

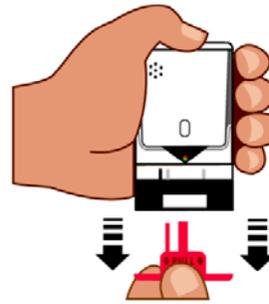
As with the real Auvi-Q, if practicing with a young child, hold the child's leg firmly in place while using the Auvi-Q Trainer.

Ask your healthcare provider to show you how to properly hold the leg to practice so that you will be prepared before an allergic emergency happens.

Follow These Steps	
<p>1. Pull the Auvi-Q Trainer from the outer case.</p>	

2. Pull off Red safety guard.

Note: The red safety guard is made to fit tight similar to the safety guard on the real Auvi-Q. **Pull firmly to remove.**



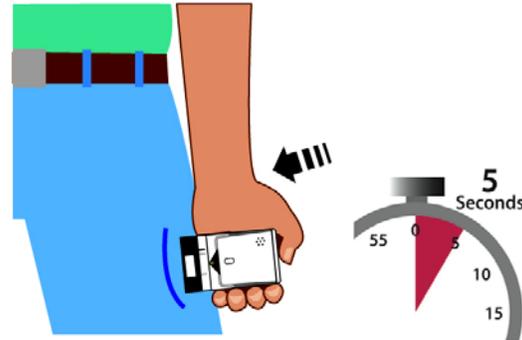
3. Place black end against the middle of the outer thigh (through clothing, if needed), then press firmly, and hold in place for 5 seconds.

Note: In an actual emergency, after the injection you would need to seek medical help right away.

Only practice using the middle of your outer thigh. The outer thigh is where you would inject with the real Auvi-Q.

As with the real Auvi-Q, if practicing with a young child, hold the child's leg firmly in place while using the Auvi-Q Trainer.

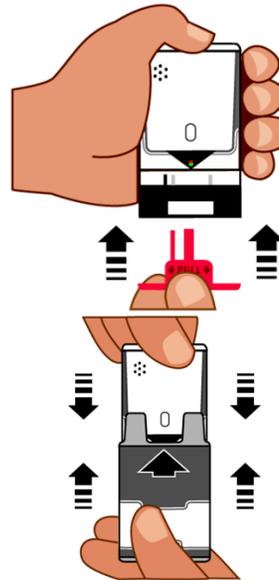
Note: The Auvi-Q Trainer makes a distinct sound (click and hiss) when you press it against your outer thigh. This is the same sound that is made with the real Auvi-Q. This is normal, and indicates Auvi-Q is working correctly. Do not pull Auvi-Q away from your leg when you hear the click and hiss sound.



4. After practicing, reset the Auvi-Q Trainer:

- a. Replace the Red safety guard**
- b. Slide the Auvi-Q Trainer all the way back into the gray outer case to reset the electronic voice system**

Note: Leave the Auvi-Q Trainer in its outer case for at least 5 seconds between each time you practice to allow the electronic voice system to reset.



Storage:

- Store the Auvi-Q Trainer at room temperature; the Auvi-Q Trainer should not be used at temperatures less than 50°F (10°C) or greater than 104°F (40°C).
- Store the Auvi-Q Trainer in its outer case.
- Keep the Auvi-Q Trainer away from dirt, chemicals, and water.

Disposal:

The Auvi-Q Trainer contains electronics and lithium coin cell batteries, and should be disposed of in the correct manner. Follow your State and local environmental regulations for disposal.

For California Only: This product uses batteries containing Perchlorate Material - special handling may apply. See www.dtsc.ca.gov/hazardouswaste/perchlorate

Manufactured for:

Kaleo, Inc.

Richmond, VA 23219 USA

This product may be covered by one or more U.S. patents or pending patent applications. See www.kaleopharma.com/pat for details.

Rev May 2016

SA6017-01-08

NDC 60842-023-01 Rx Only SA6017-01-08

Keep Auvi-Q in this case until you need to use it

Pull device from this case

Auvi-Q[®]
epinephrine injection, USP
0.3 mg auto-injector

For single-use injection. Refill prescription after use.

FOR ALLERGIC EMERGENCIES
in patients weighing over 66 lb

Instructions for use found inside on device

Manufactured for
kaléo[®]
www.auvi-q.com
Origin Germany IMO-MJL

- Do not refrigerate or freeze
- Protect from heat and light
- Store at room temperature 68° to 77°F (20° to 25°C); excursions permitted to 59° to 86°F (15° to 30°C)

Replace auto-injector if solution is discolored, cloudy, or contains particles

FRONT **BACK**

SA6017-02-08

Keep Auvi-Q in this case until you need to use it

NDC 60842-022-01 Rx Only SA6017-02-08

Pull device from this case

Auvi-Q[®]
epinephrine injection, USP
0.15 mg auto-injector

For single-use injection. Refill prescription after use.

FOR ALLERGIC EMERGENCIES
in patients weighing 33 lb to 66 lb

Instructions for use found inside on device

Do not refrigerate or freeze
Protect from heat and light
Store at room temperature
68° to 77°F (20° to 25°C); excursions permitted to 59° to 86°F (15° to 30°C)

Replace auto-injector if solution is discolored, cloudy, or contains particles

Manufactured for
kaléo[®]
www.auvi-q.com
Origin: Germany IMO-MIL

FRONT **BACK**

Each 0.5 mL contains:
• 0.3 mg epinephrine
• 2.3 mg sodium chloride
• 0.5 mg sodium hydroxide
• Water for Injection

Auvi-Q[®]
epinephrine injection, USP
0.3 mg auto-injector

FOR ALLERGIC EMERGENCIES

1) Pull Off RED safety guard

2) Place BLACK end AGAINST OUTER THIGH, then PRESS FIRMLY and hold for 5 seconds

SEEK MEDICAL ATTENTION

SA6026-01-09

For single-use injection
Refill prescription after use

Replace the outer case and take your used Auvi-Q with you to a healthcare professional for proper disposal

Replace auto-injector if solution is discolored, cloudy, or contains particles

After use, some liquid may remain visible

IMO- P.H.L. Needle-End Needle-End

Manufactured for
kaleo, Inc.
Richmond, VA 23269 USA

Each 0.35 mL contains:

- 0.35 mg epinephrine
- 1.2 mg sodium chloride
- 0.2 mg sodium bisulfite
- Water for injection

Auvi-Q®
epinephrine injection, USP
0.35 mg auto-injector

FOR ALLERGIC EMERGENCIES

- 1) Pull Off **RED** safety guard
- 2) Place **BLACK** end **AGAINST OUTER THIGH**, then **PRESS FIRMLY** and hold for **5 seconds**

SEEK MEDICAL ATTENTION

Needle-End

Needle-End

Manufactured for
Kaleo, Inc.
Pōhōmōhū, HI 96729 USA

SA6026-02-09

For single-use injection
Refill prescription after use

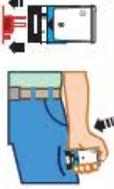
Replace the outer case and take your used Auvi-Q with you to a healthcare professional for proper disposal

Replace auto-injector if solution is discolored, cloudy, or contains particles

After use, some liquid may remain visible

IMO-MJL

kaleo

A diagram showing a hand holding the Auvi-Q auto-injector against the outer thigh. The device is shown in two states: first, with the red safety guard being pulled off, and second, with the black end pressed against the thigh. Arrows indicate the direction of the pull and the pressure applied.

SA6079-01-06



TRAINER FOR Auvi-Q®
CONTAINS NO ACTIVE DRUG OR NEEDLE

TRAINER
FOR **Auvi-Q®**
FOR PRACTICE ONLY – REUSABLE

1) Pull Off **RED** safety guard 
2) Place **BLACK** end **AGAINST OUTER THIGH**, then **PRESS FIRMLY** and hold for **5 seconds** 

CONTAINS NO ACTIVE DRUG OR NEEDLE

TRAINER RESET INSTRUCTIONS

A Replace **RED** Safety Guard 

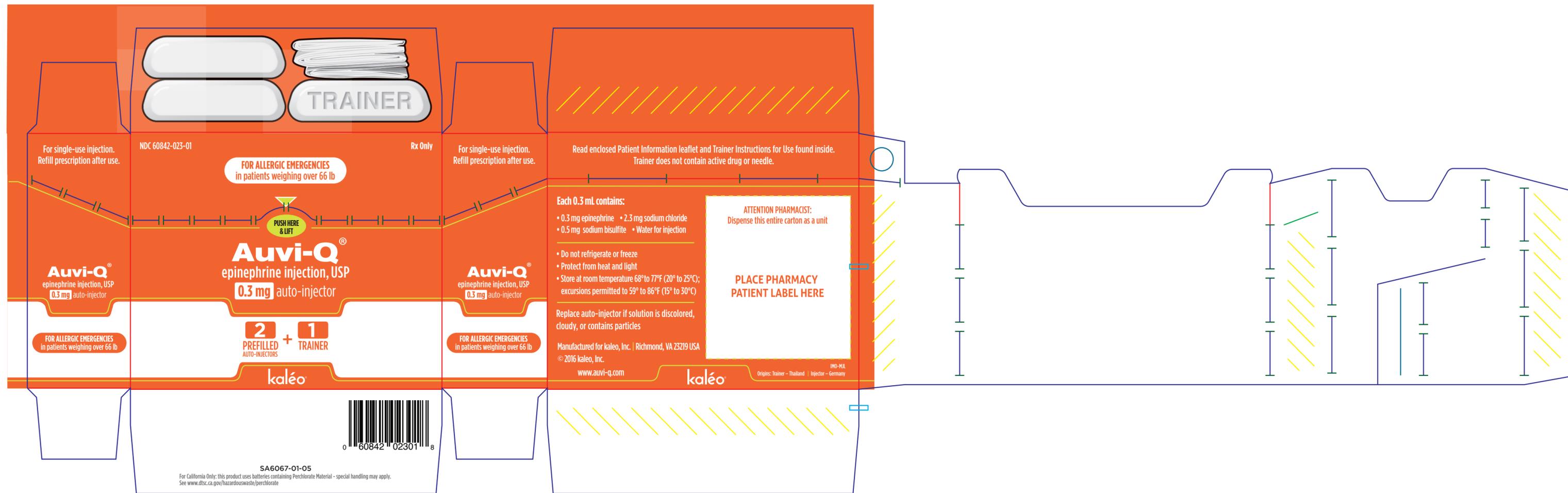
B Replace **GRAY** Outer Case 

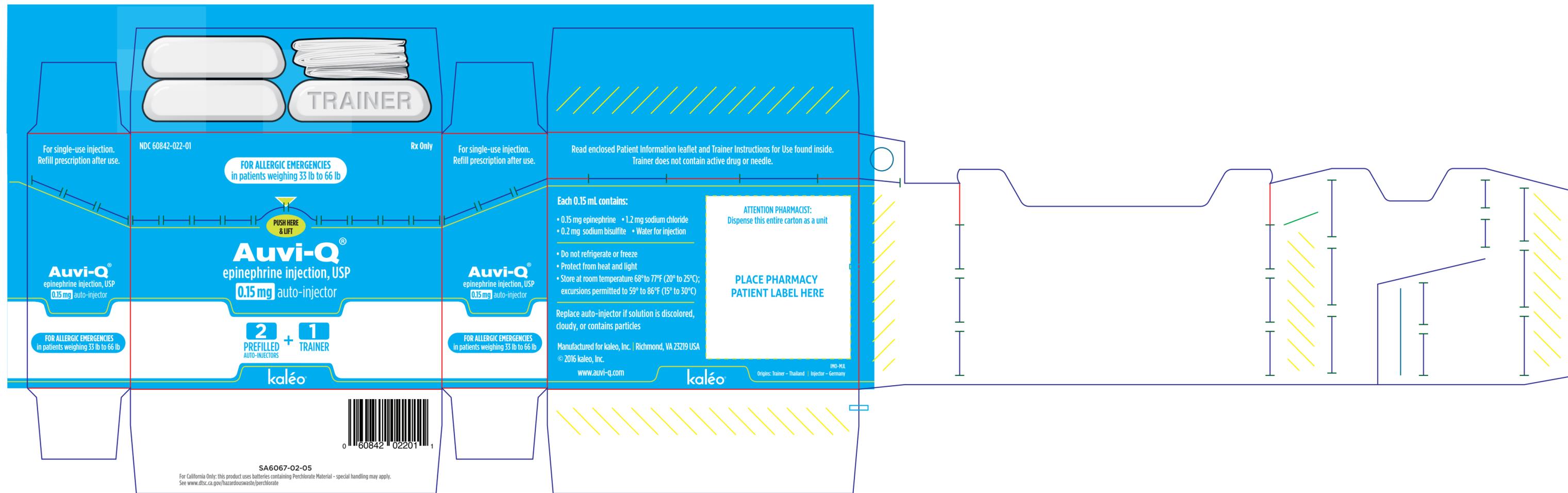
kaléo

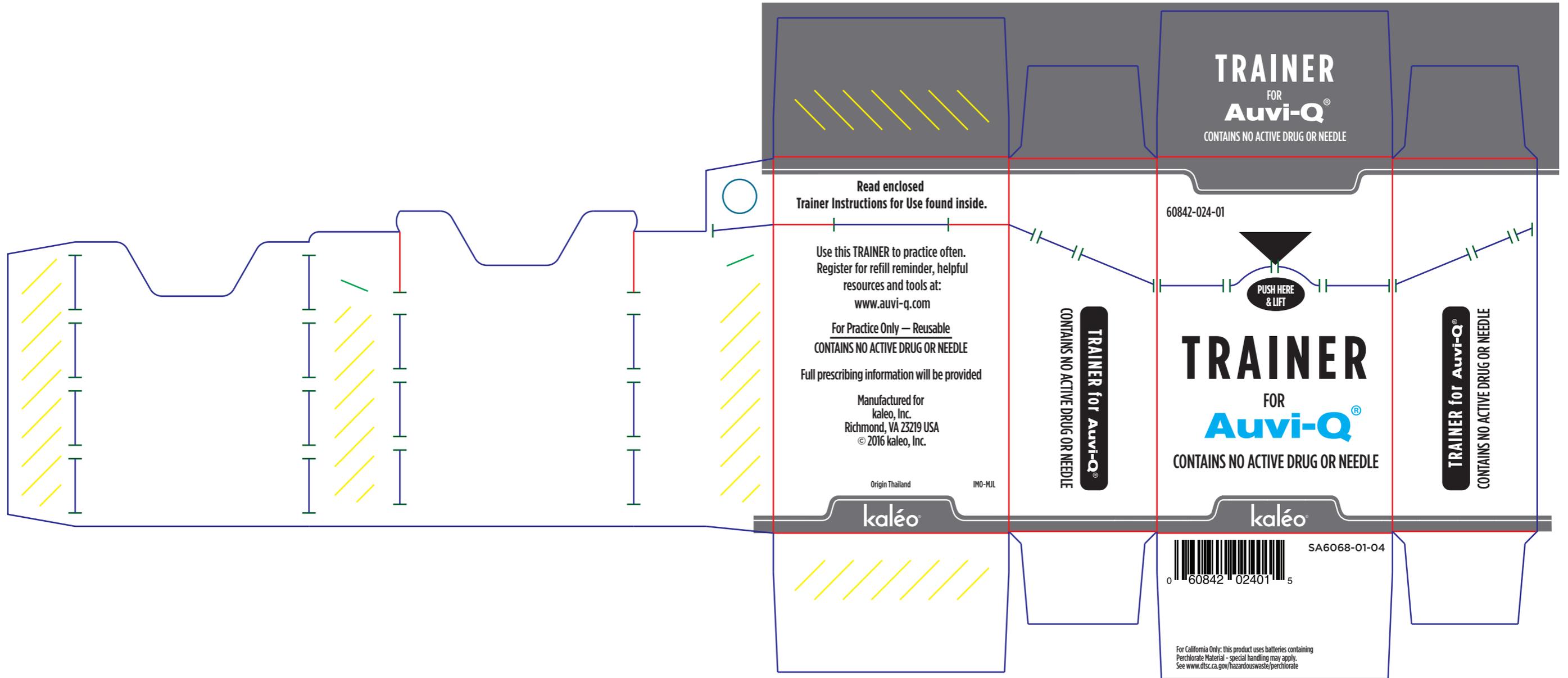
Manufactured for
kaléo, Inc.
Richmond, VA 23279 USA

SA6078-01-06

IMO-MJL







TRAINER

FOR
Auvi-Q®
CONTAINS NO ACTIVE DRUG OR NEEDLE

60842-024-01



TRAINER

FOR
Auvi-Q®
CONTAINS NO ACTIVE DRUG OR NEEDLE

TRAINER for Auvi-Q®
CONTAINS NO ACTIVE DRUG OR NEEDLE

TRAINER for Auvi-Q®
CONTAINS NO ACTIVE DRUG OR NEEDLE

Read enclosed
Trainer Instructions for Use found inside.

Use this TRAINER to practice often.
Register for refill reminder, helpful
resources and tools at:
www.auvi-q.com

For Practice Only — Reusable
CONTAINS NO ACTIVE DRUG OR NEEDLE

Full prescribing information will be provided

Manufactured for
kaleo, Inc.
Richmond, VA 23219 USA
© 2016 kaleo, Inc.

Origin Thailand IMO-MJL

kaleo

kaleo



SA6068-01-04

For California Only: this product uses batteries containing
Perchlorate Material - special handling may apply.
See www.dtsc.ca.gov/hazardouswaste/perchlorate

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

/s/

SALLY M SEYMOUR
05/18/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201739Orig1s004

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

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

APPLICATION: NDA# 201739, S-004 **TRADE NAME:** Auvi-Q® Auto-Injector
APPLICANT/SPONSOR: Kaleo, Inc. **USAN NAME:** Epinephrine injection, USP
MEDICAL OFFICER: Peter Starke, MD **CATEGORY:** Catecholamine: nonselective alpha and beta adrenergic agonist
DEPUTY DIRECTOR FOR SAFETY: Sally Seymour, MD
DATE: May 2, 2016 **ROUTE:** Intramuscular or subcutaneous

SUBMISSIONS REVIEWED IN THIS DOCUMENT / OTHER RELEVANT DOCUMENTS

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
October 30, 2015			Information request regarding lacerations after use of Auvi-Q
November 20, 2015		SD-577	Response to IR of October 30, 2015
February 5, 2016			FDAAA Safety Labeling Change (SLC) notification letter
March 4, 2016	March 4, 2016	SD-586	New supplement in response to February 5, 2016, FDAAA SLC
March 24, 2016			Labeling IR#1
April 4, 2016	April 4, 2016	SD-591	Response to Labeling IR of March 4, 2016
April 11, 2016	April 11, 2016	SD-594	Amended labeling with corrections to 4/4/16 submission
April 15, 2016			Labeling IR#2
April 22, 2016	April 22, 2016	SD-595	Response to Labeling IR of April 15, 2016
April 28, 2016			Labeling IR#3
April 29, 2016	April 29, 2016	SD-596	Response to Labeling IR of April 28, 2016

REVIEW SUMMARY:

This is a review of a labeling supplement from Kaleo for NDA 201739 for Auvi-Q® (epinephrine injection, USP) Auto-Injector. The supplement was submitted in response to a February 5, 2016, FDAA, Safety Labeling Changes Notification Letter for two safety issues of lacerations and embedded needles caused by epinephrine auto-injector use in children, and Clostridial infections at or near the injection site following injection of epinephrine for treatment of anaphylaxis. These safety issues were each the subject of a Tracked Safety Issue (TSI) involving each of the approved epinephrine products, TSI 1541 for lacerations, etc., and TSI 1555 for Clostridial infections.

Note that during the review of this supplement the ownership of this NDA was transferred from Sanofi Aventis to Kaleo Inc., effective March 23, 2016.

After labeling negotiations, the agreed upon labeling (attached), is recommended for approval.

OUTSTANDING ISSUES:

None.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS: APPROVAL COMPLETE RESPONSE

OTHER ACTION:

I. Introduction

This is a review of a labeling supplement (S-004) submitted to NDA 201739 for Auvi-Q® (epinephrine injection, USP) Auto-Injector. The supplement was submitted in response to two safety issues of lacerations and embedded needles caused by epinephrine auto-injector use in children, and Clostridial infections following injection of epinephrine for treatment of anaphylaxis. These safety issues were each the subject of a Tracked Safety Issue (TSI) involving each of the approved epinephrine products, TSI 1541 for lacerations, etc., and TSI 1555 for Clostridial infections. Note that during the review of this supplement the ownership of this NDA was transferred from Sanofi Aventis to Kaleo Inc., effective March 23, 2016.

II. Lacerations, bent needles and embedded needles

This safety issue (TSI 1541) is based upon a publication summarizing reports of lacerations and embedded needles after epinephrine injection from epinephrine auto-injectors for treatment of anaphylaxis [Brown JC, Tuuri RE, Akhter S, et al. Lacerations and Embedded Needles Caused by Epinephrine Autoinjector Use in Children. *Annals of Emergency Medicine* 2016;67:307-15.e8]. The authors assessed emergency medicine email discussion lists and social media allergy groups to identify epinephrine autoinjector injuries involving children. They identified 22 cases, including 17 children with lacerations and 5 other needle-related traumas associated with epinephrine auto-injector use (all EpiPen devices) in children. Some of the lacerations required sutures to close the wounds, and some left scars.

Information requests were sent to the three application holders the approved epinephrine auto-injector products on October 30, 2015, informing the sponsors of the information regarding lacerations and requesting a response regarding how each company proposed to deal with the safety issue. The Division also requested information on injection time. The following is a brief summary of the responses submitted by Sanofi Aventis on November 20, 2015.

- Sanofi Aventis (SA) reviewed its available safety data and determined that no cases of skin laceration were reported with Auvi-Q. They did identify one case of bent needle. As a result, SA concluded that there was no safety issue of lacerations/skin injuries with use of Auvi-Q. SA provided the following supportive information:
 - While the injection hold time for Auvi-Q is labeled as 5 seconds and the CMC specifications are for an injection time of no more than 2 seconds, which provides a margin of 3 seconds, the device testing reports [as reported in DMF (b)(4) for Auvi-Q] show that the mean dispensing time for the 0.3 mg product is 0.194 (SD = 0.176) seconds, and the mean dispensing time for the 0.15 mg product is 0.136 (SD = 0.012) seconds.
 - Auvi-Q has a retractable needle that fully retracts into the housing once the injection is complete. Therefore, while the product counts to 5 for a hold time of 5 seconds, the injection time, as well as the time that the needle is embedded in the thigh, are much shorter. As a result, the design of the product minimizes the likelihood of lacerations due to a caregiver trying to re-insert an exposed needle into the skin.
 - The Auvi-Q instructional systems include both a printed label with instructions on the side of the device, and electronic voice instructions and an LED that assist in guiding the user through correct administration. Thus, this device differs from the other marketed

epinephrine auto-injector devices, providing both audible and visual cues to guide the injection process.

Responses from all three companies were analyzed and the Division determined that labeling recommendations to immobilize a child's leg during administration may limit the lacerations with epinephrine injection.

Regarding the dose delivery time information that was submitted and/or referenced as part of Sanofi's response, the Division responded that the Agency would consider (b) (4) the instruction to hold for 5 seconds (b) (4)

On February 5, 2016, the Division requested FDAAA Safety Labeling Changes (SLC) to add information to the DOSAGE AND ADMINISTRATION section to immobilize a child's leg prior to and during epinephrine injection. Given that there are two additional epinephrine solution products that are approved for anaphylaxis and Epinephrine Injection, 1 mg/mL (1:1000), these products were also included in the FDAAA safety labeling change requests.

III. Clostridial infections

The safety issue of Clostridial infections at the site of injection post-epinephrine treatment (TSI 1555) was based upon the report of a case of Clostridial infection of the thigh of a teenage patient after injection of epinephrine via an epinephrine auto-injector at home for the treatment of an anaphylactic reaction.

A review of FAERS and the literature was also conducted to identify whether the safety issue extended beyond the one case report. The review identified sporadic case reports of *Clostridium perfringens* infection associated with epinephrine injection dating back to the 1960s. There were 5 FAERS reports and multiple literature reports. The risk of Clostridial infection is not a new safety issue with epinephrine injection for anaphylaxis. *Clostridium* can be a skin contaminant. Given that epinephrine injection for anaphylaxis is an emergency situation, the skin is not prepped prior to administration and regardless, alcohol prep would not kill *Clostridium* spores. Since epinephrine causes local vasoconstriction, the anaerobic environment could foster a Clostridial infection. Thus, scattered reports of *Clostridium* infection following epinephrine injection for anaphylaxis is not surprising. Many of the older cases were associated with injection into the buttocks; therefore all of the products include a Warning to not inject into the buttocks to minimize the risk of gas gangrene.

However, information about the rare risk of serious localized infection in the thigh following epinephrine administration is not currently in the epinephrine labels. In addition, a delay in diagnosis of gas gangrene was noted in the case reported to the FDA. Therefore, raising awareness about the risk of Clostridial infection was deemed appropriate as well as statements informing patients to seek care if signs or symptoms of infection develop.

Requests for FDAAA Safety Labeling Changes to add a new WARNING along with additional information in the HIGHLIGHTS, ADVERSE REACTIONS and PATIENT COUNSELING INFORMATION sections were sent to the application holders for all of the approved epinephrine products on February 5, 2016. In addition to the application holders of the three epinephrine auto-injectors listed above, a request was also sent to the application holder of Adrenalin and Epinephrine Injection, 1 mg/mL (1:1000), as both of these products are indicated for anaphylaxis.

IV. Labeling

The agreed upon labeling is attached. The agreed class labeling (Warnings and Precautions) for the above safety issues is summarized below. The agreed upon labeling is attached. The agreed class labeling (Warnings and Precautions) for the above safety issues is summarized below. Note that the Division decided that only the auto-injectors need to have the safety issue of injection related injuries added as a Warning and Precaution. The epinephrine injection products that are administered in a hospital/clinic setting only have additional class language regarding the need to hold the leg during the injection in the Dosage and Administration section. In addition to changes to the Warnings and Precautions, related changes were incorporated in the Dosage and Administration, Adverse Reactions, Patient Information, and Instructions for Use sections. Specifically, the new Instructions for Use include the class statement that “If you are administering [product name] to a young child, hold the leg firmly in place [REDACTED] (b) (4) [REDACTED] while administering an injection.” The agreed upon language is very similar to the original language in the February 9, 2016, FDAAA SLC Notification Letter.

New Warnings and Precautions

The following class labeling is being added to Section 5.2, Injection-Related Complications. Note that, because 1) there have been no reports of lacerations with the use of Auvi-Q, 2) the Auvi-Q needle automatically retracts, and 3) the product includes auditory and visual feedback during use, the actual Warning language for Auvi-Q differs slightly from the class language in the other auto-injector products by not including the first sentence (shown in **Red** font).

Hold the leg firmly during injection. Lacerations, bent needles, and embedded needles have been reported when [product name] has been injected into the thigh of young children who are uncooperative and kick or move during an injection. To minimize the risk of injection related injury when administering [product name] to young children, instruct caregivers to hold the child’s leg firmly in place and limit movement prior to and during injection.

The following class labeling is being added as a new section:

Serious Infections at the Injection Site. Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported at the injection site following epinephrine injection for anaphylaxis. Clostridium spores can be present on the skin and introduced into the deep tissue with subcutaneous or intramuscular injection. While cleansing with alcohol may reduce the presence of bacteria on the skin, alcohol cleansing does not kill Clostridium spores. To decrease the potential risk of a rare, but serious Clostridium infection, do not inject [product name] into the buttock [see *WARNINGS AND PRECAUTIONS (5.2)*]. Advise patients to seek medical care if they develop signs or symptoms of infection, such as persistent redness, warmth, swelling, or tenderness, at the epinephrine injection site.

Other Labeling Changes

Additional labeling changes were made for Auvi-Q to match the labeling with the other epinephrine auto-injector products, including changes to the Adverse Reactions and Use in Specific Populations, Pediatric Use sections.

Other labeling changes include the addition of audio-visual feedback information that had not been previously included in the Instructions for Use. The Instructions for Use now state that “Auvi-Q includes a 5-second countdown after it is activated, then the voice instruction will indicate the injection is complete, Auvi-Q will beep, and the lights will blink red.”

Because the ownership of this application changed during the review period, the new owner, Kaleo, took the opportunity to update this information throughout the labeling of the product.

V. Recommendations

The clinical recommendation is approval of this labeling supplement.

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
05/02/2016

SALLY M SEYMOUR
05/02/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201739Orig1s004

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW <i>Review #1</i>	1. ORGANIZATION Branch 1/DPMA 1/OLDP/OPQ	2. NDA NUMBER 201739
3. NAME AND ADDRESS OF APPLICANT (<i>City and State</i>) kaleo, Inc. 111 Virginia Street, Suite 300 Richmond, VA 23219 Tel: 804-545-6368 Fax: 804-545-6219 glen.kelley@kaleopharma.com		4. AF NUMBER
		5. SUPPLEMENT (S) NUMBER(S) DATES(S) S-004; PAS; SDN 586 Letter Date: 03/04/2016 Received Date:03/04/2016 S-004[BL]; SDN 591* Letter Date: 04/04/2016 Received Date:04/04/2016 S-004[BL]; SDN 596* Letter Date: 04/29/2016 Received Date:04/29/2016 Due Date: 07/04/2016 * No formal assignment made! Subjects of current review.
6. NAME OF DRUG Auvi-Q (epinephrine) Auto-Injector	7. NONPROPRIETARY NAME Epinephrine Injection	
8. SUPPLEMENT PROVIDES FOR: Amendment of labeling based on FDA advice		
9. PHARMACOLOGICAL CATEGORY Indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis.	10. HOW DISPENSED RX <u>x</u> OTC ___	11. RELATED IND/NDA/DMF
12. DOSAGE FORM(S) sterile injectable solution	13. POTENCY 0.3 mg/0.3 mL and 0.15 mg/ (b) (4)	
14. CHEMICAL NAME AND STRUCTURE (-)-3,4- Dihydroxy- α -[(methylamino)methyl]benzyl alcohol See USAN Dictionary		15. RECORDS AND REPORTS CURRENT YES_NO_ REVIEWED YES_NO_
16. COMMENTS: 11. DESCRIPTION SECTION: <i>No changes are made.</i> 16.1 HOW SUPPLIED SECTION: <i>NDC numbers have been changed.</i> 16.2 STORAGE AND HANDLING: No changes are made.		
17. CONCLUSIONS AND RECOMMENDATIONS The labeling changes are acceptable from CMC standpoint.		
18. REVIEWER NAME Chong-Ho Kim, Ph.D.	SIGNATURE On file	DATE COMPLETED May 13, 2016

Background:

Reference is made to the FDA advice provided on April 28, 2016 in response to amended draft labeling submitted by kaleo, Inc. in serial #0102 on April 22, 2016.

This amendment is responsive to the FDA's request and amends s-004 to include an updated draft PI.

Review:

Pertinent sections of the draft labeling are reviewed:

Section 11 DESCRIPTION

No changes are made.

Section 16 HOW SUPPLIED /STORAGE AND HANDLING

16.1 HOW SUPPLIED

Carton containing two Auvi-Q (epinephrine injection, USP) 0.3 mg auto-injectors and a single Auvi-Q Trainer - NDC 60842-023-01

Carton containing two Auvi-Q (epinephrine injection, USP) 0.15 mg auto-injectors and a single Auvi-Q Trainer - NDC 60842-022-01

Rx only

Evaluation: *NDC numbers have been changed*

16.2 STORAGE AND HANDLING

No changes are made.

Evaluation: Acceptable

CONCLUSION AND RECOMMENDATION:

The labeling changes are acceptable from CMC standpoint.

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

/s/

CHONG HO KIM
05/13/2016

RAMESH RAGHAVACHARI
05/14/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201739Orig1s004

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: April 15, 2016

To: Glen Kelley Director, Regulatory Affairs	From: Carol Hill, M.S. Safety Regulatory Project Manager
Company: Kaléo, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
E-address: glen.kelley@kaleopharma.com	Fax number: 301-796-9728
Phone number: 804-545-6368	Phone number: 301-796-2300

Subject: NDA 201739/S-004 FDA Labeling Revisions II

**Total no. of pages including
cover:** 31

Comments:

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.

NDA 201739/S-004
Kaléo, Inc.
Auvi-Q

Dear Mr. Kelley:

Please refer to your supplement dated March 4, 2016, and the amendments to this supplement dated April 4 and 11, 2016. We are providing FDA recommendations and comments in the attached labeling for the proposed Package Insert (PI), Patient Information Leaflet (PIL), Instructions for Use (IFU), and Trainer Instructions for Use (TIFU). The FDA-proposed insertions are underlined and deletions are in strike-out. Be advised that these labeling revisions are not necessarily our final recommendations and that additional changes may be forthcoming.

If applicable, we request that you update the carton and container labeling to reflect any of the PI and IFU changes.

Submit draft labeling in tracked-changes and clean word versions by COB on April 22, 2016. If you have any questions, please contact Carol F. Hill, Safety Regulatory Project Manager, at 301-796-1226.

29 Page(s) of Draft Labeling 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
04/15/2016



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 31, 2016

To: Glen Kelley Director, Regulatory Affairs	From: Carol Hill, M.S. Safety Regulatory Project Manager
Company: Kaléco, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
E-address: glen.kelley@kaleopharma.com	Fax number: 301-796-9728
Phone number: 804-545-6368	Phone number: 301-796-2300
Subject: Extension of Time to Submit Response to Labeling Revisions Fax	

Total no. of pages including cover: 3

Comments:

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.

NDA 201739/S-004
Kaléco, Inc.
Auvi-Q

Dear Mr. Kelley:

We refer to the safety labeling changes, requested on March 24, 2016, with requested response by April 4, 2008. It has been requested that we allow for additional time for you to review our revised labeling and submit the requested response. We have re-considered the timeline for the request and will allow additional time to respond.

We are now requesting that you submit your response no later than close of business on April 8, 2016. If you have any questions, please contact Carol F. Hill, Safety Regulatory Project Manager, at 301-796-1226.

Drafted by: CHill/3-31-16
Clearance: SSeymour/3-31-16
Finalized: CHill/3-31-16

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
03/31/2016



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 24, 2016

To: Glen Kelley Director, Regulatory Affairs	From: Carol Hill, M.S. Safety Regulatory Project Manager
Company: Kaléo, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
E-address: glen.kelley@kaleopharma.com	Fax number: 301-796-9728
Phone number: 804-545-6368	Phone number: 301-796-2300
Subject: NDA 201739/S-004 – FDA Revised Labeling	

**Total no. of pages including
cover:** 23

Comments:

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.

NDA 201739/S-004
Kaléo, Inc.
Auvi-Q

Dear Mr. Kelley:

Your labeling submission dated March 4, 2016, is currently under review. We are providing our recommendations and comments in the attached labeling for the proposed Package Insert (PI), Patient Information Leaflet (PIL), Instructions for Use (IFU) and Trainer Instructions for Use (TIFU). The FDA-proposed insertions are underlined and deletions are in strike-out. Be advised that these labeling revisions are not necessarily our final recommendations and that additional changes may be forth coming.

We did not specifically address any carton and container labeling, if submitted. However, our recommendations and comments regarding changes to the other labeling would apply, i.e., changes to the IFU would apply to any instructions on the carton and container labels as well. Please submit revised carton and container labeling, if applicable.

We request that you submit draft labeling to incorporate these revisions by April 4, 2016. If you have any questions, please contact Carol F. Hill, Safety Regulatory Project Manager, at 301-796-1226.

23 Page(s) of Draft Labeling 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
03/24/2016



NDA 201739/S-004

LABELING DISCUSSION EXTENSION

Sanofi-Aventis US LLC
55 Corporate Drive
Bridgewater, NJ 08897

Attention: John Cook
Director, US Regulatory Affairs Marketed Products

Dear Mr. Cook:

Please refer to your March 4, 2016, supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Auvi-Q (epinephrine injection, USP) Auto-Injector, 0.3 mg and 0.15 mg.

On February 5, 2016, we sent a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of Auvi-Q to address the risk of lacerations and embedded needles after injection and serious infection (e.g. *Clostridium perfringens*) at the injection site, with the use of epinephrine, based on new safety information about these risks identified since the product was approved. You were directed to submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On March 4, 2016, we received your prior approval supplement containing your proposed safety related labeling changes. Section 505(o) requires FDA to promptly review the supplement and, if we disagree with the proposed changes, to initiate discussions with you. These discussions were to be completed within 30 days, unless FDA determined that an extension was warranted.

This letter is to inform you that we have determined that a 30-day extension of the discussion period is warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for this supplement ends on May 3, 2016.

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

SALLY M SEYMOUR
03/23/2016