Prescribing Information

ANAPEN®

Sterile epinephrine injection Mfr. Std.
Unidose 0.3 mg epinephrine auto-injector

ANAPEN® JUNIOR

Sterile epinephrine injection Mfr. Std.
Unidose 0.15 mg epinephrine auto-injector

Catecholamine / Sympatomimetic

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ANAPEN®
Sterile epinephrine injection. Mfr. Std.

ANAPEN® JUNIOR
Sterile epinephrine injection. Mfr. Std.

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non medicinal Ingredients
Intramuscular Injection injected into anterolateral aspect of the thigh. Do not inject into the buttock.	ANAPEN® Solution, Unidose 0.3 mg epinephrine auto-injector; 0.3 mg in 0.3 mL ANAPEN JUNIOR® Solution, Unidose 0.15 mg epinephrine auto-injector; 0.15 mg in 0.3 mL	Hydrochloric acid, sodium chloride, sodium metabisulfite and water for injection.

INDICATIONS AND CLINICAL USE

ANAPEN® (0.3 mg Epinephrine Injection, 0.3 mg/0.3 mL) and ANAPEN® JUNIOR (0.15 mg Epinephrine Injection, 0.15 mg/0.3 mL) are indicated for the emergency treatment of anaphylactic reactions in patients who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions. Selection of the appropriate dosage strength is determined according to patient body weight (see DOSAGE AND ADMINISTRATION section).

ANAPEN® and ANAPEN® JUNIOR are intended for immediate self-administration for the emergency treatment of severe allergic reactions (Type I), including anaphylaxis associated with:

- foods (e.g., peanuts, tree nuts, shellfish, fish, milk, eggs, and wheat)
- stinging insects (e.g., Order Hymenoptera, including bees, wasps, hornets, yellow jackets, and fire ants) and biting insects (e.g., mosquitoes and black flies)
- medications
- latex
- idiopathic anaphylaxis
- exercise-induced anaphylaxis
- other allergens

Epinephrine (adrenaline) is the drug of choice for the emergency treatment of severe allergic reactions. The strong vasoconstrictor action of epinephrine, through its effect on alpha adrenergic receptors, quickly

counteracts vasodilation and increased vascular permeability which can lead toloss of intravascular fluid volume and hypotension during anaphylactic reactions.

ANAPEN® and ANAPEN® JUNIOR are designed as emergency supportive therapy only and not as a replacement or substitute for subsequent medical or hospital care, nor are they intended tosupplant insect venom hyposensitization.

Clinical Signs and Symptoms of Anaphylaxis

Anaphylaxis is a serious, acute, allergic reaction that may cause death[1]. It has a sudden onset and generally lasts less than 24 hours. Because anaphylaxis is a generalized reaction, a wide variety of clinical signs and symptoms may be observed.

One to 2% of the general population are estimated to be at risk for anaphylaxis from food allergies and insect stings, with a lower reported prevalence for drugs and latex. People with asthma are at particular risk.

Symptoms of anaphylaxis may include:

Oral: pruritus of lips, tongue, and palate, edema of lips and tongue; metallic taste in the mouth.

Cutaneous: flushing, pruritus, urticaria, angioedema, morbilliform rash, and pilor erecti.

Gastrointestinal: nausea, abdominal pain, vomiting, and diarrhea.

Respiratory:
Laryngeal: pruritus and "tightness" in the throat, dysphagia, dysphonia, hoarseness, wheezing, and cough:
Nasal: nasal pruritus, congestion, rhinorrhea, sneezing, and sensation of itching in the external auditory canals.

Cardiovascular: feeling of faintness, syncope, chest pain, dysrhythmia, hypotension. **Note:**Hypotension is a sign of anaphylaxis. Patients should be treated in the early stages of anaphylaxis to prevent hypotension from developing.

Other: periorbital pruritus, erythema and edema, conjunctival erythema, and tearing; lower back pain and uterine contractions in women; aura of "doom."

The severity of previous anaphylactic reactions does not determine the severity of future reactions, and subsequent reactions could be the same, better, or worse. The severity may dependon the degree of sensitivity, the dose of allergen, and other factors.

Research shows that fatalities from anaphylaxis are often associated with failure to use epinephrine or a delay in the use of epinephrine treatment.

Epinephrine should be administered as early as possible after the onset of symptoms of a severe allergic response. Patients requiring epinephrine will not always have predictable reactions.
Adequate warning signs are not always present before serious reactions occur.

It is recommended that epinephrine be given at the start of any reaction associated with a known or suspected allergen contact. In patients with a history of severe cardiovascular collapse on exposure to an allergen, the physician may advise that epinephrine be administered immediately after exposure to that

allergen, and before any reaction has begun.

Epinephrine may prove to be life saving when used as directed immediately following exposure to an allergen.

In most patients, epinephrine is effective after 1 injection. However, symptoms may recur and further injections may be required to control the reaction. Epinephrine can be re-injected every 5 to 15 minutes until there is resolution of the anaphylaxis or signs of adrenaline excess (such as palpitations, tremor, uncomfortable apprehension and anxiety).

All individuals receiving emergency epinephrine must be immediately transported to hospital, ideally by ambulance, for evaluation and observation. Repeat attacks have occurred hours later without additional exposure to the offending allergen.[2-4] Therefore, it is recommended that a patient suffering from an anaphylactic reaction be observed in an emergency facility for an appropriate period because of the possibility of either a "biphasic" reaction (a second reaction) or a prolonged reaction.[4] At least a four hour period of observation is advised, although this time may vary. The attending physician will take into consideration such factors as the severity of the reaction, the patient's response and history and the distance from the hospital to the patient's home.

Anaphylactic reactions typically follow a uniphasic course; however, 20% will be biphasic in nature. The second phase usually occurs after an asymptomatic period of 1 to 8 hours, but may occur up to 38 hours (mean 10 hours) after the initial reaction. About one third of the second- phase reactions are more severe, one third are as severe, and one third are less severe. The second-phase reactions can occur even following administration of corticosteroids.

Following treatment of anaphylaxis, the patient must stay within close proximity to a hospital or where he or she can call 911 for the next 48 hours.

Protracted anaphylaxis, which is frequently associated with profound hypotension and sometimes lasts longer than 24 hours, is minimally responsive to aggressive therapy, and has a poor prognosis.

CONTRAINDICATIONS

There are no absolute contraindications to the use of epinephrine in a life-threatening allergic situation.

WARNINGS AND PRECAUTIONS

Emergency Treatment

ANAPEN® and ANAPEN® JUNIOR 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.

General

All patients who are prescribed ANAPEN® and ANAPEN® JUNIOR should be thoroughly instructed to understand the indications for use and the correct method of administration. It is strongly advised also to educate the patient's immediate associates (e.g. parents, caregivers, teachers) for the correct usage of ANAPEN® and ANAPEN® JUNIOR in case support is needed in the emergency situation.

Patients with a history of anaphylaxis are at risk for subsequent episodes and even death. All patients who have had one or more episodes of anaphylaxis should have injectable epinephrine with them or with their parent or caregiver at all times, and should wear some form of medical identification bracelet or necklace.

Following the resolution of an anaphylactic episode and discharge from hospital, the patient should immediately obtain and fill a new ANAPEN® or ANAPEN® JUNIOR auto-injector prescription.

Epinephrine injection is not intended as a substitute for medical attention or hospital care. In conjunction with the administration of epinephrine, the patient should seek appropriate medical care.

The patient/carer should be informed about the possibility of biphasic anaphylaxis which is characterised by initial resolution followed by recurrence of symptoms some hours later.

In patients with a thick subcutaneous fat layer, there is risk for adrenaline not reaching the muscle tissue resulting in a suboptimal effect.

Antihistamines and asthma medications must not be used as first line treatment for an anaphylactic reaction[5].

Injection-Related Complications

Epinephrine should ONLY be injected into the anterolateral aspect of the thigh.

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: Patients should be advised that ANAPEN® and ANAPEN® JUNIOR is not intended for injection into the 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).

Do not inject into digits, hands or feet: Since epinephrine is a strong vasoconstrictor, accidental injection into the hands or feet may result in loss of blood flow to the affected areas and should be avoided. If there is an accidental injection into these areas, the patient must go immediately to the nearest emergency room for treatment.

Hold leg firmly during injection. Lacerations, bent needles, and embedded needles have been reported with epinephrine auto-injectors when epinephrine 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 ANAPEN® and ANAPEN® JUNIOR to young children, instruct caregivers to hold the child's leg firmly in place and limit movement prior to and during injection.

Serious Infections at the Injection Site

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported at the injection site following epinephrine injection for anaphylaxis. *Clostridium* spores can be present on the skin and introduced into the deep tissue with subcutaneous or intramuscular injection. While cleansing with alcohol may reduce presence of bacteria on the skin, alcohol cleansing does not kill *Clostridium* spores. To decrease the risk of *Clostridium* infection, do not inject ANAPEN® and ANAPEN® JUNIOR into the buttock. 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.

The presence of a condition listed below is not a contraindication to epinephrine administration in an acute, life-threatening situation. Therefore, patients with these conditions, or any other person who might be in a position to administer epinephrine to a patient with these conditions experiencing anaphylaxis, should be instructed about the circumstances under which epinephrine should be used:

Cardiovascular
Epinephrine use should be avoided in patients with cardiogenic, traumatic, or hemorrhagic shock; cardiac dilation; and/or cerebral arteriosclerosis.

Epinephrine should be used with caution in patients with cardiac arrhythmias, coronary artery or organic heart disease, hypertension, or in patients who are on medications that may sensitize the heart to arrhythmias, e.g., digitalis, diuretics, or anti-arrhythmics. In such patients, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias.

Patients with hypertension or hyperthyroidism are prone to more severe or persistent effects.

Endocrine and Metabolism
Patients with diabetes may develop increased blood glucose levels following epinephrine administration.

Neurologic
Epinephrine use should be avoided in patients with organic brain damage.

Patients with Parkinson's disease may notice a temporary worsening of symptoms after treatment with epinephrine.

Ophthalmologic
Epinephrine use should be avoided in patients with narrow-angle glaucoma.

Respiratory
There is a significantly increased risk of respiratory symptoms in patients with concomitant asthma, especially if poorly controlled. These patients are at increased risk of death from anaphylaxis.

Fatalities may also occur from pulmonary edema resulting from peripheral constriction and cardiac stimulation.

There is also a risk for adverse reactions after the administration of adrenaline to patients with hyperthyroidism, phaeochromocytoma, severe renal impairment, prostate adenoma, hypercalcaemia, hypokalaemia, and in elderly patients and pregnant women.

Sensitivity
This product contains sodium metabisulfite, a substance which may cause allergic-type reactionsincluding anaphylactic symptoms or mild to severe asthmatic episodes in certain susceptible persons.

Nevertheless, epinephrine is the drug of choice for serious allergic reactions and 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.

Reproduction
No studies have been conducted to determine epinephrine's potential effect on fertility.

Special Populations

Geriatrics (>65 years of age):
Elderly patients with hypertension, coronary artery disease or cardiac arrythmias are particularly at risk for epinephrine overdose. More careful monitoring and avoidance of epinephrine overdose is recommended for these patients.

Pediatrics (patients 15-30 kg):
There are no data to suggest a difference in safety or effectiveness of epinephrine between adults and children in this weight group.

See **DOSAGE AND ADMINISTRATION** section for dosage requirements based on weight.

Pregnancy:
Although there are no adequate and well-controlled studies in pregnant women, epinephrine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Adverse reactions of epinephrine include transient, moderate anxiety; feelings of over stimulation; apprehensiveness; restlessness; tremor; weakness; shakiness; dizziness; sweating; tachycardia; palpitations; pallor; nausea and vomiting; headache; and/or respiratory difficulties. Ventricular arrhythmias may follow administration of epinephrine. While these symptoms occur in some patients treated with epinephrine, they are likely to be more pronounced in patients with hypertension or hyperthyroidism. These signs and symptoms usually subside rapidly, especially with bed rest.

Some patients may be at greater risk of developing adverse reactions after epinephrine administration. These include elderly individuals, pregnant women, and patients with diabetes. Patients with coronary artery disease are prone to more severe or persistent effects, and may experience angina. Cases of takotsubo (stress) cardiomyopathy have been reported in patients treated with epinephrine. Patients with epinephrine-triggered takotsubo cardiomyopathy are predominantly women and are younger than the typical takotsubo cardiomyopathy patient. These events are characterized by rapid onset of symptoms after epinephrine administration and high complication rates, mostly in the form of cardiogenic shock and acute pulmonary edema. The prognosis is however good with complete recovery in most cases.

Excessive doses cause acute hypertension. Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease.

Arrhythmias, including fatal ventricular fibrillation, have been reported, particularly in patients with underlying cardiac disease or those receiving certain drugs (see **DRUG INTERACTIONS**).

Lacerations, bent needles, and embedded needles have been reported with epinephrine auto-injectors when epinephrine has been injected into the thigh of young children who are uncooperative and kick or move during the injection (see **WARNING AND PRECAUTIONS** section).

Injection into the buttock has resulted in cases of gas gangrene.

Accidental injections can lead to injury at the injection site resulting in bruising, bleeding, discoloration, erythema or skeletal injury.

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 in the thigh. 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** section).

The potential for epinephrine to produce these types of adverse reactions does not contraindicate its use in an acute life-threatening allergic reaction.

DRUG INTERACTIONS

Overview
There are no known contraindications to the use of epinephrine in a life-threatening allergic reaction.

Drug-Drug Interactions
Epinephrine should be used with caution in patients who are on medications that may sensitize the heart to arrhythmias, e.g., digitalis, diuretics, or anti-arrhythmics. In such patients, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias.

Caution is advised in patients receiving cardiac glycosides or diuretics, since these agents may sensitize the myocardium to beta-adrenergic stimulation and make cardiac arrhythmias more likely.

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

The cardiostimulating and bronchodilating effects of epinephrine are antagonized by betaadrenergic blocking drugs, such as propranolol. Anaphylaxis may be made worse by beta blockers because these drugs decrease the effectiveness of epinephrine.

The vasoconstricting and hypertensive effects of epinephrine are antagonized by alphaadrenergicblocking drugs, such as phentolamine.

Phenothiazines may also reverse the pressor effects of epinephrine.

Deaths have been reported in asthmatic patients treated with epinephrine following the use of isoproterenol, orciprenaline, salbutamol, and long acting beta agonists.

Drug-Lifestyle Interactions
Cocaine sensitizes the heart to catecholamines (as does uncontrolled hyperthyroidism), and epinephrine use in these patients should be cautious.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dosage in any specific patient should be based on body weight. A physician who prescribes ANAPEN® or ANAPEN® JUNIOR should take appropriate steps to ensure that the patient thoroughly understands the

indications and use of the device. The physician should review with the patient, in detail, the **CONSUMER INFORMATION** section and operation of the auto-injector.

Recommended Dose and Dosage Adjustment

The effective dose is usually in the range 0.005-0.01 mg/kg body weight.

ANAPEN®:
The ANAPEN® auto-injector is intended for intramuscular administration in adults and children who weigh 30 kg or more.

ANAPEN® auto-injector delivers a single intramuscular dose of 0.3 mg epinephrine in a 0.3mL volume (0.3 mg/0.3 mL).

ANAPEN® JUNIOR:
The ANAPEN® JUNIOR auto-injector is intended for pediatric intramuscular administration in children who weigh between 15 kg and 30 kg.

ANAPEN® JUNIOR auto-injector delivers a single intramuscular dose of 0.15 mg epinephrine in a 0.3 mLvolume (0.15 mg/0.3 mL).

For children weighing more than 30 kg, ANAPEN® auto-injector 0.3 mg (adult formulation) is recommended.

Since the dose of epinephrine delivered from ANAPEN® JUNIOR is fixed at 0.15 mg, the physician can consider other forms of injectable epinephrine if doses lower than 0.15 mg are felt to be necessary (e.g., for children weighing less than 15 kg).

Administration

An initial dose should be administered as soon as symptoms of anaphylaxis are recognised. In the absence of clinical improvement or if deterioration occurs after the initial treatment, a second injection with an additional ANAPEN® auto-injector may be administered 5 – 15 minutes after the first injection. It is recommended that patients are prescribed two ANAPEN® or ANAPEN® JUNIOR auto-injectors which they should carry at all times.

All individuals receiving emergency epinephrine must be immediately transported to hospital, ideally by ambulance, for evaluation and observation even if symptoms appear to be improving.

The patient/carer should be informed that following each use of ANAPEN® and ANAPEN® JUNIOR auto-injector:

- As ANAPEN® and ANAPEN® JUNIOR auto-injector is designed as emergency treatment only, the patient should be advised to always seek medical help immediately.
- Conscious patients should preferably lie flat with feet elevated but sit up if they have breathing difficulties. Unconscious patients should be placed on their side in the recovery position.
- The patient should if possible remain with another person until medical assistance arrives.

ANAPEN® and ANAPEN® JUNIOR are intended for intramuscular use in the anterolateral aspect of the thigh, through clothing if necessary. Do not inject into the buttock.

Instruct caregivers to hold the leg of young children firmly in place and limit movement prior to and during injection. Lacerations, bent needles, and embedded needles have been reported with epinephrine

auto-injectors when epinephrine has been injected into the thigh of young children who are uncooperative and kick or move during an injection (see **WARNINGS AND PRECAUTIONS** section).

Patients with a history of severe allergic reactions should be instructed about the circumstances under which epinephrine should be used (see **INDICATIONS AND CLINICAL USE** section).

A physician who prescribes ANAPEN® or ANAPEN® JUNIOR should take appropriate steps to ensure that the patient thoroughly understands the indications and use of the device. The patient's physician or pharmacist should review the package insert in detail with the patient or caregiver to ensure that he/she understands the indications and use of ANAPEN® or ANAPEN® JUNIOR. Actual demonstrationof the injection technique by a physician or a pharmacist is recommended.

A training device for patient instruction purposes is also available. Instruct patients and/or caregivers to use and practice with the Trainer to familiarize themselves with the use of ANAPEN® and ANAPEN® JUNIOR in an allergic emergency.

ANAPEN® and ANAPEN® JUNIOR contain 1.05 mL of solution but deliver **only** a single dose in a volume of 0.3 mL, with 0.75 mL remaining in the unit **after use**.

OVERDOSAGE

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

Overdosage of epinephrine may produce extremely elevated arterial pressure, which may resultin cerebrovascular hemorrhage, particularly in elderly patients. Overdosage sometimes also results in extreme pallor and coldness of the skin, metabolic acidosis, and kidney failure. Suitable corrective measures must be taken in such situations. Epinephrine overdosage can also cause transient bradycardia followed by tachycardia, and these may be accompanied by potentially fatal cardiac arrhythmias. Treatment of arrhythmias consists of administration of a beta-adrenergic blocking drug such as propranolol.

If an epinephrine overdose induces pulmonary edema that interferes with respiration, treatment consists of a rapidly acting alpha-adrenergic blocking drug and/or intermittent positive-pressure respiration.

Premature ventricular contractions may appear within 1 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.

ACTION AND CLINICAL PHARMACOLOGY

Epinephrine acts on both alpha- and beta-adrenergic receptors. Through its action on alpha-adrenergic receptors, epinephrine counters the vasodilation and high vascular permeability that occurs during an anaphylactic reaction that can lead to loss of intravascular fluid volume and hypotension. Through its action on beta-adrenergic receptors, epinephrine causes bronchial smooth muscle relaxation that helps alleviate bronchospasm, wheezing, and dyspnea that may occur during anaphylaxis.

Epinephrine also helps to alleviate pruritus, urticaria, and angioedema, and may be effective inrelieving

gastrointestinal and genitourinary symptoms of anaphylaxis because of its relaxant effects on the smooth muscle of the stomach, intestine, and urinary bladder. Epinephrine contracts the smooth muscle of the uterus.

Epinephrine, when given intramuscularly or subcutaneously, has a rapid onset and short duration of action.

In a pharmacokinetic study in 35 healthy adult subjects, grouped by varying degrees of thickness in the subcutaneous fat layer of the thigh and stratified by gender, a single 0.3 mg/0.3 mL injection at the anterolateral aspect of the mid-thigh was made with an epinephrine Auto-Injector and was compared in crossover design to a manual syringe-delivered dose with needles individualized for delivery to muscle layer. The results indicate no significant differences between subjects with varying thicknesses of subcutaneous fat layer (<15 mm, ≥15 mm and ≤20 mm, or >20 mm skin to muscle distance under maximum compression). Overall adrenaline exposure from 0 to 30 min (AUC 0-30min) for all groups of subjects receiving epinephrine exceeded exposures resulting from syringe delivery. Both inter-subject and intra-subject variability was, however, high in this study and therefore robust conclusions cannot be drawn.

STORAGE AND STABILITY

Shelf-life:

ANAPEN®: 24 months
ANAPEN® JUNIOR: 21 months

Always keep ANAPEN® or ANAPEN® JUNIOR in the outer carton in order to protect from light.

Do not refrigerate or freeze.

Store between 15 - 25°C (59 - 77°F).

Periodically check to make sure the solution in the auto-injector is not brown in color. Discard and replace if it is discolored or contains a precipitate.

The expiry date is indicated on the label; ANAPEN® or ANAPEN® JUNIOR should not be used after this date. Replace and discard the auto-injector after expiry date.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ANAPEN® and ANAPEN® JUNIOR are designed to provide emergency treatment when medical care is not immediately available.

Highly sensitive individuals should have epinephrine injectable products readily available at all times.

ANAPEN®

Each auto-injector contains: 1.05 mL epinephrine injection 1 mg/mL and is designed to deliver a single dose of 0.3 mg epinephrine in 0.3 mL.

Non-medicinal ingredients: Each auto-injector contains: sodium chloride 6.3 mg, sodium metabisulfite 1.785 mg, hydrochloric acid to adjust pH, and water for injection.

ANAPEN® JUNIOR

Each auto-injector contains: 1.05 mL epinephrine injection 0.5 mg/mL and is designed to deliver a single dose of 0.15 mg epinephrine in 0.3 mL.

Non-medicinal ingredients: Each auto-injector contains: sodium chloride 6.3 mg, sodium metabisulfite 1.785 mg, hydrochloric acid to adjust pH, and water for injection.

PART II: SCIENTIFIC INFORMATION

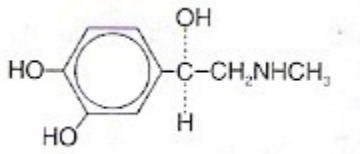
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Epinephrine

Chemical name: 1-(3,4-dihydroxyphenyl)-2-(methylamino)ethanol

Structural formula:



Physicochemical properties: Epinephrine is a sympathomimetic catecholamine. Its naturally occurring *l*-isomer, which is twenty times as active as the *d*-isomer, is obtained in pure form by separation from the synthetically produced racemate.

REPRODUCTION

Teratogenic Effects. Pregnancy Category C

Epinephrine has been shown to have adverse developmental effects in rabbits at a subcutaneous dose of 1.2 mg/kg (approximately 30 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis), in mice at a subcutaneous dose of 1 mg/kg (approximately 7 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis), and in hamsters at a subcutaneous dose of 0.5 mg/kg (approximately 5 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis).

These effects were not seen in mice at a subcutaneous dose of 0.5 mg/kg (approximately 3 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m^2 basis).

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5. Prescribing Information: Epipen® and Epipen Jr®, Mylan Specialty L.P., Date of Revision: April 9, 2020, Submission Control No.: 236785

PART III: CONSUMER INFORMATION
ANAPEN®
Sterile epinephrine injection, Mfr. Std.
Unidose 0.3 mg epinephrine Auto-injector

ANAPEN® JUNIOR
Sterile epinephrine injection, Mfr. Std.
Unidose 0.15 mg epinephrine Auto-injector

This leaflet is Part III of a three-part "Prescribing Information" document published when ANAPEN®, ANAPEN® JUNIOR were approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell youeverything about ANAPEN®, ANAPEN® JUNIOR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

ANAPEN®and ANAPEN® JUNIOR are indicated for the emergency treatmentof anaphylaxis and are intended for people determined to be at risk for serious allergic reactions and for people with a history of anaphylactic reactions.

ANAPEN®and ANAPEN® JUNIOR should be used immediately to treat yourself or your child when experiencing a severe allergic reaction. This is emergency treatment. It does not replace seeing a doctor or going to the hospital.

Anaphylaxis is the term for a severe, life-threatening allergic reaction. A severe allergic reaction occurs when a person is exposed to an allergen (an allergy-causing substance). When the allergen enters the body it triggers the releases of chemicals that can lead to life-threatening symptoms.

Some common allergens include:

- foods like peanuts, tree nuts, shellfish, fish, milk, eggs and wheat
- insect stings like those from bees, wasps, hornets, yellow jackets and fire ants
- insect bites like those from mosquitos and black flies
- certain medicines
- latex
- other allergens (a substance that causes allergies)

These severe allergic reactions can also be caused by exercise, asthma or by unknown causes.

Those who are considered to be at a higher risk of anaphylaxis include people:

- who have previously experienced allergic reactions or anaphylaxis
- who suffer from asthma
- who have food allergies

Anaphylaxis affects multiple body systems: skin, upper and lower respiratory system, intestinal tract, heart and blood vessels.

The most common warning symptoms of anaphylaxis are:

- Hives and swelling

Typical symptoms of anaphylaxis include:

- Swelling of the throat, lips, tongue, or the area around the eyes
- Hives
- Difficulty breathing or swallowing
- Wheezing and cough
- Metallic taste or itching in the mouth
- Flushing, itching, or redness of the skin
- Stomach cramps, nausea, vomiting, or diarrhea
- Increased heart rate
- Decreased blood pressure
- Chest pain
- Irregular heart beat
- Paleness
- Sudden feeling of weakness
- Feeling faint
- Anxiety or an overwhelming sense of doom
- Collapse
- Loss of consciousness

What it does:

ANAPEN® and ANAPEN® JUNIOR contain epinephrine, which is the medication that helps to decrease your body's allergic reaction. Some of the ways it works include:

- Relaxing the muscles in your airways so you can breathe more easily
- Helping to reverse the rapid and dangerous decrease in blood pressure
- Relaxing the muscles in your stomach, intestines, and bladder

What the medicinal ingredient is:

Epinephrine.

What the nonmedicinal ingredients are:

Hydrochloric acid, sodium chloride, sodium metabisulfite, and water for injection.

What dosage forms it comes in:

ANAPEN®: Unidose 0.3 mg epinephrine auto-injector.

ANAPEN® JUNIOR: Unidose 0.15 mg epinephrine auto-injector.

ANAPEN® and ANAPEN® JUNIOR come in disposable, prefilled automatic injection devices. ANAPEN® and ANAPEN® JUNIOR are single-use injectable devices that deliver a fixed dose of epinephrine.

WARNINGS AND PRECAUTIONS

BEFORE you obtain ANAPEN® or ANAPEN® JUNIOR, talk to your doctoror pharmacist about all of your medical conditions, especially ifyou have:

- heart disease
- irregular heartbeat
- high blood pressure
- diabetes
- thyroid conditions
- narrow-angle glaucoma
- depression or other mental disease
- Parkinson's disease
- severe kidney disease
- a tumor on the adrenal gland
- a tumor in the prostate gland
- very high calcium levels in your blood
- very low potassium levels in your blood
- asthma
- previously had an allergic reaction
- an allergy to any of the ingredients in this medication
- also notify your doctor and pharmacist if you are pregnant or breast feeding

ANAPEN® or ANAPEN® JUNIOR is the first line emergency treatment for severe, life-threatening allergic reactions even if you have the above conditions.

Other warnings you should know about:

General: If have you had a severe, life-threatening allergic reaction in the past, you are at a higher risk for having one again. You should carry ANAPEN® or ANAPEN® JUNIOR with you at all times.
You or your child should also wear some form of medical identification bracelet or necklace.

Using ANAPEN® or ANAPEN® JUNIOR does not replace seeing a doctor or going to the hospital. You **must** get medical help **right away** after you or your child has used it.

Patients with Asthma: if you or your child has asthma, and it is not controlled properly, you are at a higher risk of having breathing problems when you have a severe allergic reaction.

ANAPEN® or ANAPEN® JUNIOR contains metabisulfite. This can cause allergic reactions and bronchospasms in those with a history ofasthma. You should follow your doctor's instructions carefullyon when you or child can use ANAPEN® or ANAPEN® JUNIOR.

Injection site: You should **ONLY** inject ANAPEN® or ANAPEN® JUNIOR into the **outer side of your upper thigh - into the muscle** (see Proper Use of this Medication).

Do not inject it into the:

- vein (intravenously (IV))
- buttocks
- hands, fingers, feet and toes

If you do, it can either cause dangerously high blood pressure or you or your child may not get the effect of the emergency treatment that you or they need.

If you accidentally inject it into any of these areas, **go right away** to the nearest hospital (emergency room) for further treatment.

If you inject a young child with ANAPEN® or ANAPEN® JUNIOR hold their leg firmly in place and limit movement before and during the injection to prevent injuries. Ask your healthcare provider to showyou how to properly hold the leg of a young child during injection.

If you have a thick layer of fat under your skin the epinephrine in ANAPEN® or ANAPEN® JUNIOR may not reach your muscle tissue. In some cases this might make ANAPEN® and ANAPEN JUNIOR® not work as well.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with ANAPEN® or ANAPEN® JUNIOR include:

- Heart rhythm medicine, such as digoxin or quinidine (another name for digoxin is digitalis)
- Diuretic medicines ("water pills")
- MAO inhibitors (MAOI), such as selegilline, isocarboxazid, phenelzine sulfate, or tranylcypromine
- Tricyclic antidepressants, such as amitriptyline, doxepin, nortriptyline
- Antihistamines, such as chlorpheniramine, tripelennamine, or diphenhydramine
- Beta-adrenergic blocking drugs, such as propranolol
- Alpha-adrenergic blocking drugs, such as phentolamine
- Ergot alkaloids and phenothiazines
- Isoproterenol, orciprenaline, salbutamol and LABAs
- Thyroid medications (e.g. sodium levothyroxine)
- Cocaine

PROPER USE OF THIS MEDICATION

If you have been told by your doctor that you are at risk for an anaphylactic reaction, carry your ANAPEN® or ANAPEN® JUNIOR with you at all times.

When your doctor prescribes ANAPEN® or ANAPEN® JUNIOR, you must make sure you understand the reason it has been prescribed foryou. You should be confident that you know exactly how and when to use it.

Use ANAPEN® or ANAPEN® JUNIOR exactly how your doctor or pharmacisthas told you. Ask to have the instructions repeated to you if you are unsure about how to use it.

It is recommended that your family members, carers or teachers are also instructed in the correct use of ANAPEN® or ANAPEN® JUNIOR.

There is a training device (Trainer) which you can use to practice.

If you have been stung by an insect, try to remove the stinger with your fingernails. Do not squeeze, pinch or push the stinger deeper into the skin.
If possible, put an ice pack on the area of the sting. Keep yourself warm and avoid exercise.

For allergic reactions caused by foods make sure you remove any remaining food from the mouth immediately.

IMPORTANT NOTE:

Severe, life-threatening allergic reactions (anaphylaxis) can result in death if not treated immediately.

Talk to your doctor about the warning signs and symptoms of anaphylaxis and when to use ANAPEN® or ANAPEN® JUNIOR.

Inject ANAPEN® or ANAPEN® JUNIOR **right away** if you experience any of the symptoms of a severe allergic reaction, such as swelling of thethroat, lips, tongue or around the eyes, trouble breathing or swallowing. You **must** get medical help **right away** after using ANAPEN® or ANAPEN® JUNIOR. You can:

- call 911 and get taken to the hospital OR
- you can have someone take you (or you can take your child) to the nearest hospital emergency room

If you or your child do not feel better or get worse you can inject another dose of ANAPEN® or ANAPEN® JUNIOR 5 to 15 minutes after the first injection.

Do not inject more than 2 injections right after each other.

<u>Usual dose:</u>

ANAPEN® (0.3 mg) should be used for adults and children weighing 30 kg or more.

ANAPEN® JUNIOR (0.15 mg) should be used for children weighing between 15 kg to 30 kg. For children weighing less than 15 kg, call 911.

Directions for Use

Caution:

- Remove ANAPEN® or ANAPEN® JUNIOR from original box before use.
- Never put thumb, fingers or hand over needle end.
- Do not remove grey safety cap until ready for use.

A. Parts of ANAPEN® or ANAPEN® JUNIOR:
Before you use your ANAPEN® or ANAPEN® JUNIOR, you need to know about the parts of the auto-injector. These are shown in the picture below (Figure 1).

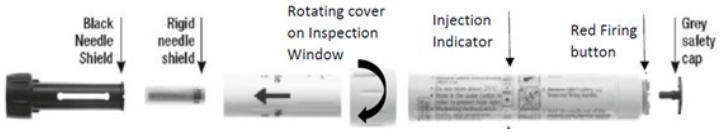


Figure 1

- **Rotating cover on inspection window**:
  You rotate the cover over the solution window to line up the lenses with the solution window on the auto-injector body.

- **Inspection window:**
  You look through the lens into this window before the injection to check that the solution is clear and ready to use.

- **Injection indicator**:
  Before the injection, you can see a white plastic plunger through the window. This means that the auto-injector has not been fired by mistake or tampered with. After the injection, the injection indicator turns red. This indicates that the auto-injector has been fired correctly.

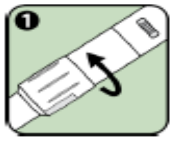
- **Black needle shield (reversible)**:
  This protects the needle when you are not using the auto-injector. You pull the needle shield off before the injection. After the injection, turn the black needle shield around and put it back onto the same end of auto-injector, to cover the needle.

- **Grey safety cap:**
  This covers the red firing button. It stops the button from being pushed by mistake.

Do not remove the black needle shield or the grey safety cap until you need to use your ANAPEN® or ANAPEN® JUNIOR.

B. Checking your ANAPEN® or ANAPEN® JUNIOR:
Before you use your ANAPEN® or ANAPEN® JUNIOR, and on a regular basis, you must check it as follows:

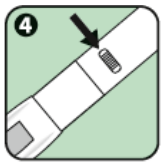
1. Rotate the cover over the solution window fully anticlockwise as indicated by the arrow to line up the lenses with the solution window on the auto-injector body.



2. Look through the lens into the **solution window**. Check that the solution is clear and colourless. If it is cloudy, coloured or contains particles, discard the ANAPEN® or ANAPEN® JUNIOR.

3. Rotate the cover over the solution window fully back clockwise as shown by the arrow, to ensure that the solution window is covered. Put ANAPEN® or ANAPEN® JUNIOR back in the carton until you need to use them.

4. Make sure that the **injection indicator** is not red. If it is red, this means that ANAPEN® or ANAPEN® JUNIOR auto-injector has already been fired and you must discard it.



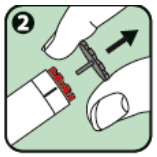
C. Using ANAPEN® or ANAPEN® JUNIOR:

If the black needle shield has been removed, **do not put your thumb, fingers or hand over the open end (needle end) of ANAPEN® or ANAPEN® JUNIOR.**

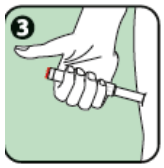
To use ANAPEN® or ANAPEN® JUNIOR, follow the steps below:

1. Remove the black needle shield by pulling hard, in the direction of the arrow. This also removes a grey protective needle shield.

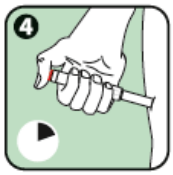
2. Remove the grey safety cap from the red firing button, by pulling as indicated by the arrow.



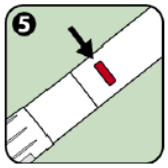
3. Hold the open end (needle end) of ANAPEN® or ANAPEN® JUNIOR against the outer part of your thigh. If necessary, you can use ANAPEN® or ANAPEN® JUNIOR through light clothing, such as denim, cotton or polyester.



4. Press the red firing button so that it clicks. **Keep holding the ANAPEN® or ANAPEN® JUNIOR against your thigh for 10 seconds.** Slowly remove ANAPEN® or ANAPEN® JUNIOR from your thigh. Then gently massage the injection area.



5. **The injection indicator will have turned red**. This shows that the injection is completed.
If the injection indicator is not red, you must repeat the injection with a new ANAPEN® or ANAPEN® JUNIOR.



6. After the injection, the needle sticks out. To cover it, click the wide end of the black needle shield back on the open end (needle end) of ANAPEN® or ANAPEN® JUNIOR (as indicated by the arrow).

7. The injection is now complete.

8. If you are administering ANAPEN® or ANAPEN® JUNIOR to a youngchild, hold the leg firmly in place while administering the injection.

9. Seek medical attention immediately even if the severe allergy symptoms seem to have subsided. Because the effects of epinephrine can wear off and there is a chance of a second reaction, **it is important that you seek medical assistance or go to the emergency room** immediately after using ANAPEN® or ANAPEN® JUNIOR. With a severe, long-lasting allergic reaction, youmay need to administer an additional dose of epinephrine. More than two sequential doses of epinephrine should only be administered under direct medical supervision.

10. **Even if you have sought medical help, you must stay within close proximity to a hospital or where you caneasily call 911 for the next 48 hours.**

Give any used ANAPEN ® orANAPEN® JUNIOR to emergency responders or emergency room personnel.

Do not attempt to reuse ANAPEN® or ANAPEN® JUNIOR after the device has been activated.

Overdose:

If you take more than the recommended dose, or inject the ANAPEN® or ANAPEN® JUNIOR anywhere other than your thigh, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Too much epinephrine can cause dangerously high blood pressure, stroke, or death.

Signs of an overdose include:

- irregular heart beat
- difficulty breathing caused by a build-up of fluid in your lungs

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

ANAPEN® and ANAPEN® JUNIOR are intended to be used immediately to treat yourself or your child when suffering from a severe allergic reaction. This is emergency treatment.

After you use ANAPEN® or ANAPEN® JUNIOR always seek appropriatemedical care. ANAPEN® or ANAPEN® JUNIOR does not replace seeing a doctor or going to the hospital.

The following side effects may occur after using ANAPEN® or ANAPEN® JUNIOR.

- Paleness
- Dizziness
- Weakness
- Shaking
- Headache
- Throbbing
- Restlessness
- Anxiety
- Tenseness
- Fear

Patients who have used ANAPEN® or ANAPEN® JUNIOR 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

Cuts on the skin, bent needles, and needles that remain in the skin after the injection, have happened in young children who do not cooperate and kick or move during an injection.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Difficulty breathing			✓
Increased heart rate (pounding heart)			✓
Irregular or skipped heartbeats			✓
Chest pain (angina)			✓
Stroke (blurred vision, difficulty speaking, headache, dizziness and weakness)			✓

This is not a complete list of side effects. For any unexpected effects while taking ANAPEN® or ANAPEN® JUNIOR, talk to your doctor or pharmacist.

It is important that you seek medical assistance or go to the emergency room immediately after using ANAPEN® or ANAPEN® JUNIOR.

HOW TO STORE IT

- Keep your ANAPEN® or ANAPEN® JUNIOR between 15 - 25°C. Do not refrigerate.
- Do not expose your ANAPEN® or ANAPEN® JUNIOR to direct sunlight.
- Do not keep your ANAPEN® or ANAPEN® JUNIOR in a vehicle during extremely hot or cold weather.
- Always keep your ANAPEN® or ANAPEN® JUNIOR in the original box to protect it from damage.
- The grey safety cap helps to prevent accidental injection. Keep the grey safety cap on until you need to use ANAPEN® or ANAPEN® JUNIOR.
- Occasionally inspect your ANAPEN® or ANAPEN® JUNIOR solution through the inspection window. Replace your ANAPEN® or ANAPEN® JUNIOR if it is discolored or contains solid particles (precipitate) or if there are any signs of leakage. The solution should be clear.
- Discard if there are any signs of damage to the auto-injector or the ANAPEN® or ANAPEN® JUNIOR.
- Do not attempt to take the ANAPEN® or ANAPEN® JUNIOR apart. Replace your ANAPEN® or ANAPEN® JUNIOR before the expiration date or after you use it.
- Talk to your pharmacist or physician about how to properly dispose of your expired ANAPEN® or ANAPEN® JUNIOR.
- Do not place this Consumer Information or any other objects in the original box with your ANAPEN® or ANAPEN® JUNIOR, as this may prevent you from removing your ANAPEN® or ANAPEN® JUNIOR quickly for use.
- Keep out of the reach and sight of children.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or byfax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about ANAPEN® and ANAPEN® JUNIOR:
• Talk to your healthcare professional.
• Find the full Prescribing Information that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the distributor's website www.paladinlabs.com, or by calling 1-888-867-7426.

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