PRESCRIBING INFORMATION

EMERADE™
Sterile epinephrine solution for injection in pre-filled pen
0.15 mg, 0.3 mg and 0.5 mg

Catecholamine / Sympathomimetic
ATC Code: C01CA24

Bausch Health, Canada Inc.
2150 St. Elzéar West
Laval, Quebec
H7L 4A8

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Intramuscular injection to be injected into anterolateral aspect of the thigh. Do not inject into the buttock.	The pre-filled pen contains 0.5 mL of 1 mg/mL epinephrine solution. EMERADE 0.15 mg delivers a single dose of 0.15 mL containing 0.15 mg of epinephrine (as hydrogen tartrate). EMERADE 0.3 mg delivers a single dose of 0.3 mL containing 0.3 mg of epinephrine (as hydrogen tartrate). EMERADE 0.5 mg delivers a single dose of 0.5 mL containing 0.5 mg of epinephrine (as hydrogen tartrate).	Sodium chloride, Sodium meta-bisulfite, Disodium edetate, Hydrochloric acid (for adjustment of pH), Water for injection

INDICATIONS AND CLINICAL USE

EMERADE is 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 and age (see **DOSAGE AND ADMINISTRATION** section).

EMERADE is 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 to loss of intravascular fluid volume and hypotension during anaphylactic reactions.

EMERADE is designed as emergency supportive therapy only and not as a replacement or substitute for subsequent medical or hospital care, nor are they intended to supplant insect venom hyposensitization.

Clinical Signs and Symptoms of Anaphylaxis

Anaphylaxis is a serious, acute, allergic reaction that may cause death. 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.

1% to 2% of the general population is 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 (especially poorly controlled 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: shortness of breath, respiratory arrest

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, tachycardia, and 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 depend on 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 lifesaving when used as directed immediately following exposure to an allergen.

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. 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. 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

EMERADE is intended for immediate administration as emergency supportive therapy and 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.

General

All patients who are prescribed EMERADE 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 EMERADE in case support is needed in the emergency situation.

Patients with a history of anaphylaxis are at risk for subsequent episodes and even death. EMERADE should be used in emergency situations as life-sustaining treatment. 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 EMERADE auto-injector prescription. The patient must urgently seek medical assistance for further treatment after using EMERADE.

EMERADE injection is not intended as a substitute for medical attention or hospitable care. In conjunction with the administration of epinephrine, the patient should seek appropriate medical care. More than two sequential doses of epinephrine should only be administered under direct medical supervision (See **DOSAGE AND ADMINISTRATION** section).

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 epinephrine not reaching the muscle tissue resulting in a suboptimal effect.

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

Injection-Related Complications

EMERADE is designed to minimize the risk of unintentional injection.

EMERADE should ONLY be injected into the anterolateral aspect of the thigh (see **DOSAGE AND ADMINISTRATION - Dosing Considerations**).

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 EMERADE 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
To minimize the risk of injection related injury when administering EMERADE 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 EMERADE 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 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 occur from pulmonary edema resulting from peripheral constriction and cardiac stimulation.

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

Sensitivity/Resistance

EMERADE contains sodium meta-bisulfite which can cause allergic reactions including anaphylaxis and bronchospasm in sensitive individuals particularly in those with a history of

asthma. All those patients should be carefully instructed in which circumstances EMERADE must be used.

Nevertheless, epinephrine is the drug of choice of serious allergic reactions and the presence of sulfite in this product should not deter administration of the drug treatment of serious allergic or other emergency situations, even if the patient is sulfite-sensitive.

Reproduction

There are no studies available to determine epinephrine's potential effect on fertility.

Special Populations

Pregnant Women
There are no adequate or well-controlled studies of epinephrine during pregnancy. Epinephrine should be used in pregnancy only if the potential benefit to the mother outweighs the possible risk to the fetus.

Nursing Women
Epinephrine is distributed into breast milk. Because of its poor oral bioavailability and short half-life, any adrenaline in breast milk is unlikely to affect the nursing infant.

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.

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

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

ADVERSE REACTIONS

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 patients with asthma, 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**).

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 WARNING AND PRECAUTIONS section).

Side-effects of epinephrine in general are associated with the α- and β-receptor activity of Epinephrine. The following table is based upon experience with the use of epinephrine, but the frequency of adverse reaction cannot be estimated.

These symptoms and signs usually subside quickly, especially with rest, quiet and recumbence.

System organ	Adverse reaction
Cardiac disorders	Tachycardia, arrhythmia, palpitations, angina pectoris, myocardial infarction, prolonged QTc interval, stress cardiomyopathy
Vascular disorders	Hypertension, vasoconstriction, peripheral ischemia, intracranial haemorrhage
Respiratory disorders	Bronchospasm, pulmonary oedema
Nervous system disorders	Headache, dizziness, tremor, syncope
Metabolic and nutrition disorders	Hyperglycaemia, hypokalemia, acidosis
Psychiatric disorders	Anxiety, hallucination
Gastrointestinal disorders	Nausea, vomiting
General disorders	Hyperhidrosis, asthenia

EMERADE contains sodium meta-bisulfite, which may rarely cause severe hypersensitivity reactions.

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 life-threatening allergic reactions.

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 oxidase inhibitors, sodium levothyroxine, and certain antihistamines, notably chlorpheniramine, tripelennamine, and diphenhydramine.

The cardiostimulating and bronchodilating effects of epinephrine are antagonized by beta-adrenergic blocking drugs, such as propranolol. 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 alpha-adrenergic blocking 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 and age. A physician who prescribes EMERADE 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.
An initial dose should be administered as soon as symptoms of anaphylaxis are recognized.

Recommended Dose and Dosage Adjustment

The effective dose is usually in the range 0.005-0.01 mg/kg bodyweight

Pediatric Population

Use in children: EMERADE 0.5 mg is not recommended for use in children.

- *Children between 15 kg and 30 kg bodyweight:* The usual dose is 0.15 mg.
- *Children over 30 kg bodyweight:* The usual dose is 0.3 mg.
- *Adolescent patients over 30 kg bodyweight:* The dosage recommendations for adult patients should be followed.

Adults

- Individuals under 60 kg bodyweight: The recommended dose is 0.3 mg.
- Individuals over 60 kg bodyweight: The recommended dose is 0.3 to 0.5 mg depending on clinical judgement.

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, a second injection with an additional EMERADE may be administered 5 – 15 minutes after the first injection. It is recommended that the patients are prescribed two EMERADE pens 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 EMERADE auto-injector:

- As EMERADE 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.

EMERADE is 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 (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 EMERADE 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 EMERADE. The

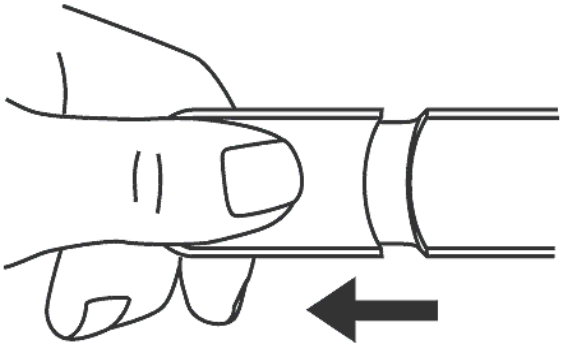
physician should review with the patient, in detail, the **PATIENT MEDICATION INFORMATION** section and operation of the auto-injector.

Actual demonstration of the injection technique by a physician or a pharmacist is recommended. The instructions for use must be carefully followed in order to avoid accidental injection. EMERADE should only be used for injection in the outer thigh.

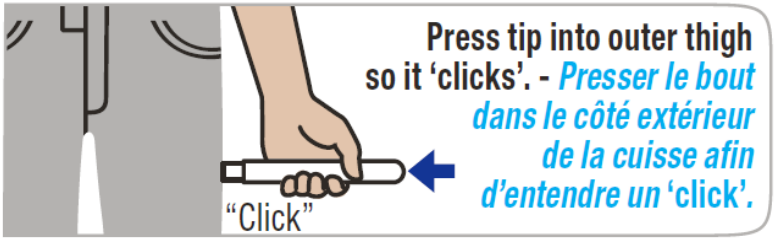
The injection occurs when EMERADE is pressed gently into the thigh

Instructions for use:

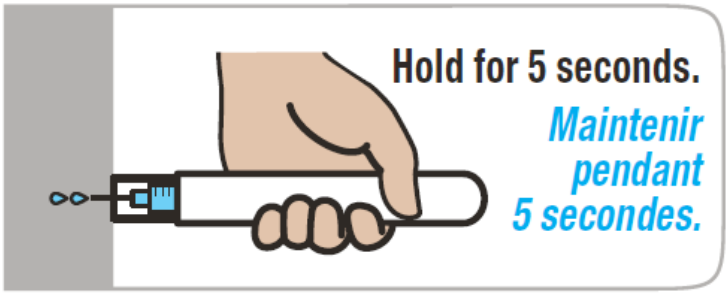
EMERADE should be used for intramuscular injection only on the outer thigh (see **WARNINGS AND PRECAUTIONS**). The injection occurs when the triggering cylinder is gently pressed into the thigh. This can be done through clothing due to the 25 mm needle length.



1. Remove the needle shield.
EMERADE is easy to use. EMERADE has an obvious opening at the needle end; and none at the opposite end. Therefore, there is no risk that the patient turns EMERADE backwards and injects incorrectly.



2. Press EMERADE gently against the outer side of the thigh. A click can be heard when the injection goes into the muscle.



3. Hold EMERADE against the thigh for about 5 seconds. Lightly massage the injection site afterwards.

Seek immediate medical help.

When the injection is completed the plunger is visible in the inspection window by lifting the label.

Some liquid may remain in the auto-injector after the injection. The auto-injector cannot be re-used. Talk to your pharmacist or physician about how to properly dispose of your expired EMERADE.

EMERADE is intended only for emergency treatment.

You must always contact your doctor or go to the nearest hospital for further treatment. Inform your doctor that you have taken an injection of epinephrine. Take the used auto-injector with you.

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 result in 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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 in relieving 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.

Pharmacodynamics

Epinephrine is the natural active sympathomimetic hormone from the adrenal medulla. It stimulates both the α- and β-adrenergic receptors. Epinephrine is the first choice for emergency treatment of severe allergic reactions and idiopathic or exercised-induced anaphylaxis.

Epinephrine has a potent vasoconstrictive effect through its α-adrenergic stimulation. This effect counteracts the vasodilatation and increased vascular perfusion, leading to low intravascular flow and hypotension, which are the main pharmacotoxicological effects in the anaphylactic shock.

By stimulating of β-receptors in the lungs, epinephrine produces a potent bronchodilator effect with relief of wheezing and dyspnea. Epinephrine also relieves pruritus, urticaria and angioedema associated to anaphylaxis.

Pharmacokinetics

The oral bioavailability of epinephrine is poor, owing to its rapid and extensive metabolism in the gut and liver. Epinephrine is, however, well absorbed systemically when administered by intramuscular (IM) or subcutaneous (SQ) routes. Epinephrine is distributed throughout the body. Epinephrine crosses the placenta but does not penetrate the blood-brain barrier to a great extent.

Epinephrine will distribute into breast milk.

The half-life of epinephrine in plasma is about 2 to 3 minutes. However, when epinephrine is injected subcutaneous or intramuscularly the absorption is retarded by local vasoconstriction and thus the effects can last longer than as predicted by half-life. Massage around the injection site is advised to accelerate absorption.

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

Subcutaneous administration of epinephrine is no longer the route of choice for patients in shock, because absorption and achievement of therapeutic plasma concentrations can be significantly delayed.

Circulating epinephrine is metabolized in the liver and other tissues by the enzymes COMT and MAO. Inactive metabolites are excreted in the urine.

STORAGE AND STABILITY

Shelf life 18 months.

Store at room temperature (15°C to 25°C). Do not freeze.

EMERADE should always be carried if at risk for anaphylaxis.

Keep in the original package a durable case to protect the auto-injector and the labelling. Keep out of reach and sight of children.

The solution can be examined through the inspection window at any time by lifting the label. Discard and replace EMERADE if the solution is discolored or contains particles.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

EMERADE consists of a pre-filled syringe made of glass with a polyisoprene rubber plunger in an auto-injector. The pre-filled syringe contains 0.5 mL of 1 mg/mL epinephrine sterile solution.

EMERADE is available in three fixed doses:

EMERADE 0.15 mg single use pre-filled pen delivers a single dose of 0.15 mL containing 0.15 mg of epinephrine (as epinephrine hydrogen tartrate).

EMERADE 0.3 mg single use pre-filled pen delivers a single dose of 0.3 mL containing 0.3 mg of epinephrine (as epinephrine hydrogen tartrate).

EMERADE 0.5 mg single use pre-filled pen delivers a single dose of 0.5 mL containing 0.5 mg of epinephrine (as epinephrine hydrogen tartrate).

Needle

The syringe in EMERADE has a 25 mm needle. In EMERADE 0.15 mg, the needle protrudes 16 mm at the injection. In EMERADE 0.3 mg and EMERADE 0.5 mg, the needle protrudes 23 mm for the injection.

Package

EMERADE has a durable, plastic outer case to protect the auto-injector and labelling.

Each dosage is differentiated by an appropriate labelling with different colors:

- EMERADE 0.15 mg pre-filled pen is identified in green.
- EMERADE 0.3 mg pre-filled pen is identified in blue.
- EMERADE 0.5 mg pre-filled pen is identified in red.

EMERADE is available in pack sizes of one or 2 pre-filled pens.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

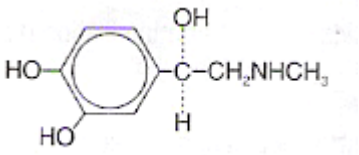
Proper name: Epinephrine hydrogen tartrate or Adrenaline tartrate

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

Molecular formula: $C_{13}H_{19}NO_9$

Molecular mass: 333.29 g/mol

Structural formula:



Physicochemical properties

Description: White or greyish-white crystalline powder.

Solubility: Freely soluble in water, slightly soluble in ethanol.

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 (approximately30 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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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

EMERADE™
Sterile Epinephrine Injection

Read this carefully before you start taking **EMERADE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **EMERADE**.

What is EMERADE used for?
EMERADE is used for the emergency treatment of a sudden, severe and life-threatening allergic reaction. This is type of severe reaction is called anaphylaxis. EMERADE is used in people:

- who are at a higher risk for severe allergic reactions
- with a history of allergic reactions

It is used to treat people with severe allergies to:

- 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.

EMERADE should be used **right away** when you or your child is having a severe allergic reaction. Using it 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.

Some of the warning signs that you or your child may be having a severe allergic reaction are:

- swelling of the throat, lips, tongue or the area around the eyes
- hives
- difficulty breathing or swallowing
- wheezing and cough
- a metallic taste or itching in the mouth
- flushing, itching, or redness of the skin
- stomach cramps, nausea, vomiting, or diarrhea
- an increased heart rate
- decreased blood pressure
- chest pain
- irregular heart beat
- paleness

- a sudden feeling of weakness
- feeling faint
- fear, worry (anxiety) or an overwhelming sense of doom
- collapse
- loss of consciousness

How does EMERADE work?
When you or your child comes into contact with something that you (or they) are allergic to the body releases chemicals to fight against it. For most people the symptoms from this are not serious. But, for some people, when their body releases these chemicals it can lead to life-threatening symptoms.

EMERADE contains epinephrine. This helps to decrease your body's reaction to whatever you are allergic to. Some of the ways it works include:
- relaxing the muscles in your airways. This allows you to breathe more easily.
- helping to reverse the quick and dangerous drop in your blood pressure.
- relaxing the muscles in your stomach, intestines, and bladder.

What are the ingredients in EMERADE?
Medicinal ingredient: Epinephrine as epinephrine hydrogen tartrate
Non-medicinal ingredients: Disodium Edetate, Hydrochloric Acid (to adjust pH), Sodium Chloride, Sodium Meta-Bisulfite and Water for Injection.

EMERADE comes in the following dosage forms:
Solution for Injection in single-use pre-filled pens: 0.15 mg (green), 0.3 mg (blue) and 0.5 mg (red)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take EMERADE. Talk about any health conditions or problems you may have, including if you:
- are allergic to any of the ingredients in EMERADE
- have heart disease
- an irregular heart beat
- have high blood pressure
- have diabetes
- have problems with your thyroid
- have narrow-angle glaucoma
- have depression or other severe mental disorders
- have Parkinson's disease
- have severe kidney disease or a certain type of tumor in the kidney
- have a tumor in the prostate gland
- very high calcium levels in your blood
- very low potassium levels in your blood
- have asthma
- have previously had an allergic reaction

- are pregnant or planning to become pregnant
- are breastfeeding

Other warnings you should know about:

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

Using EMERADE 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.

EMERADE contains meta-bisulfite. This can cause allergic reactions and bronchospasms in those with a history of asthma. You should follow your doctor's instructions carefully on when you or child can use EMERADE.

Patients with Parkinson's disease: if you suffer from Parkinson's disease, you may notice that your symptoms may temporarily get worse after using EMERADE.

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

Injection site: You should **ONLY** inject EMERADE into the **outer side of your upper thigh - into the muscle** (see **Instructions for Use**).

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.

When injecting a young child with EMERADE hold their leg firmly in place to limit movement before and during the injection. This will 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 a thick layer of fat under your skin the epinephrine in EMERADE may not reach your muscle tissue. In some cases, this might make EMERADE not work as well.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with EMERADE:

- Drugs used to treat heart rhythm disorders (such as digoxin (also known as digitalis) and quinidine)
- Diuretic drugs. These are also called 'water pills'
- Cardiac glycoside drugs
- Monoamine Oxidase Inhibitors (MAOIs)
- Antihistamines (such as chlorpheniramine, tripelennamine and diphenhydramine
- Beta-adrenergic blocking drugs (such as propanol)
- Alpha-adrenergic blocking drugs (such as phentolamine)
- Phenothiazines
- Isoproterenol, orciprenaline, salbutamol and long acting beta antagonists (LABAs)
- Sodium levothyroxine
- Cocaine

How to take EMERADE:

When you are prescribed EMERADE by your doctor or when you get it from your pharmacist make sure they go through the important information with you and show you how to use it properly.

IMPORTANT NOTE:

Severe, life-threatening allergic reactions (anaphylaxis) can result in death if not treated **right away**. You should talk to your doctor about the warning signs and symptoms of a severe allergic reaction and when to use EMERADE.

If you have been told by your doctor that you or your child is at a higher risk for severe, life-threatening allergic reactions, you should carry EMERADE with you at all times.

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

Use EMERADE exactly how your doctor or pharmacist has 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 EMERADE.

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, remove all food from the mouth right away.

The EMERADE pre-filled-pen:

- is for **single use only. Do not** reuse the pen**.**
- can be injected through clothes.

EMERADE should **ONLY** be injected into the **outer side of your upper thigh - into the muscle**. **Do not** inject it anywhere else. If you do:

- it can cause dangerously high blood pressure or
- you or your child may not get the right dose you or your child needs

Inject EMERADE **right away** if you experience any of the symptoms of a severe allergic reaction, such as swelling of the throat, lips, tongue or around the eyes, trouble breathing or swallowing. It is really important that you get to the hospital after using EMERADE. 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 EMERADE 5 to 15 minutes after the first injection. **Do not inject more than 2 injections right after each other.** It is therefore recommended that you always carry **2** EMERADE pens with you at all times.

Throw away and replace the pen:

- after the expiry date. The expiry date is indicated on the label.
- if the solution in the pen has changed colour or contains particles. You can check the colour of the solution by lifting the label on the pen at the picture of the arrow.
- if there are any signs that pen is leaking.
- if you drop the pen on the ground or in water. The pen is not waterproof.

Usual dose:

Your or your child's dose will be determined by your doctor. It will depend on your weight and your age or your child's weight and age.

Children:
EMERADE 0.5 mg is not recommended for use in children

Children who weigh between 15 kg and 30 kg: 0.15 mg
Children who weigh more than 30 kg: 0.3 mg
Adolescent weighing more than 30 kg: dosing instructions for Adults should be followed

Adults:
Adults who weigh less than 60 kg: 0.3 mg
Adults weighing more than 60 kg: 0.3 mg to 0.5 mg

Instructions for Use:

Follow these instructions carefully.

Step 1:
Remove the needle shield (Figure 1). **Do not** remove the needle shield until you need to use the pen.

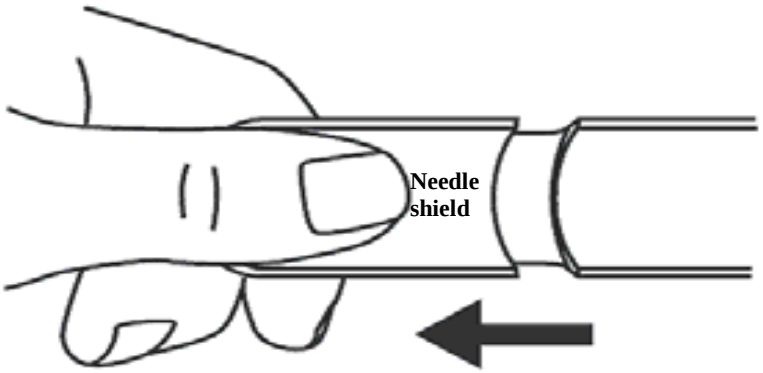

Figure 1

Step 2:
Press the needle (tip) gently against the outer side of the upper thigh – into the muscle. A "**click**" can be heard when the injection goes into the muscle (Figure 2).

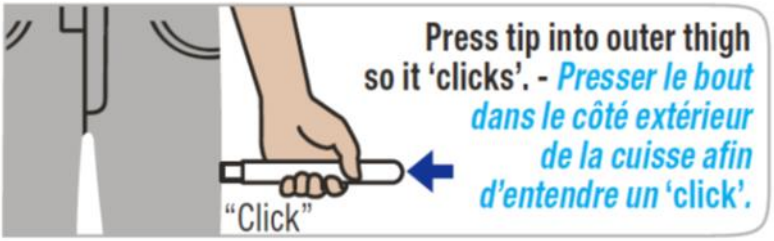

Figure 2

Step 3:
Hold the pen against the thigh for 5 seconds (Figure 3). Lightly massage the injection site afterwards.

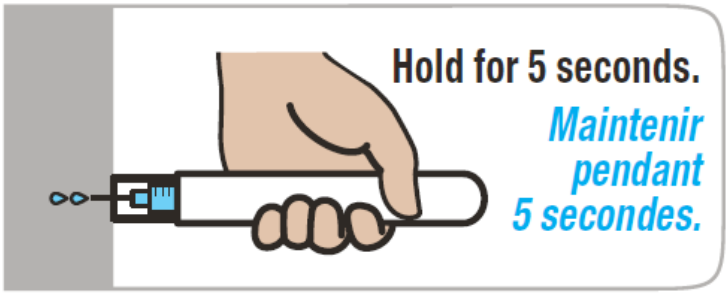

Figure 3

Step 4:
Get medical help right away

- call 911 and get taken to the hospital OR
- go to the nearest hospital (emergency room)
- You should stay with another person, if possible, until you get medical help.
- If you are conscious, you should lie flat with your feet up. If you are having trouble breathing, you should sit up.
- Unconscious patients should be placed on their side.

Step 5:
Repeat steps 1 to 3 if you need to take a second dose 5 to 15 minutes after the first one.

You should take the used EMERADE pen(s) with you. Tell the doctor that you have taken an injection of epinephrine.

After you have finished using the pen:

- You can confirm that you have taken or given a dose of epinephrine because the plunger is now visible. You can check by lifting the label at the picture of the arrow.
- Some solution may remain in the pen.

Overdose:

If you take more than the recommended dose, or inject EMERADE 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
- abnormal heart beat
- difficulty breathing caused by a build-up of fluid in your lungs

What are possible side effects from using EMERADE?
These are not all the possible side effects you or your child may feel when taking EMERADE. If

you or your child experience any side effects not listed here, contact your healthcare professional.

Side effects include:

- Paleness
- Dizziness
- Weakness
- Shaking
- Headache
- Rapid heart beat
- Restlessness
- Anxiety
- Feeling tense
- Fear

Patients who have used EMERADE 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 been seen in kids who 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 heart beats			✓
Chest pain (angina)			✓
Stroke (blurred vision, difficulty speaking, headache, dizziness and weakness)			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

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 by fax; 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.

Storage:

- Keep EMERADE:
  - in the original package - a durable case to protect the pen
  - at room temperature (15°C to 25°C). Do not freeze.
- Keep out of reach and sight of children.
- The expiry date is indicated on the label. Do not use it after this date. Throw it away and replace the pen after this date.
- Every now and then you should inspect the solution in the pen. Throw it away and replace the pen if the solution has changed colour or contains particles or is leaking.

Proper disposal: Talk to your doctor or pharmacist about how to properly dispose of any used or unused EMERADE pens.

If you want more information about EMERADE:

- Talk to your healthcare professional
- Find the full Prescribing Information that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website or by calling the manufacturer's med info line at 1-800-361-4261.

This leaflet was prepared by Bausch Health, Canada Inc.
www.bauschhealth.ca

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