2 DOSAGE AND ADMINISTRATION

Inject Adrenalin® intramuscularly or subcutaneously into the anterolateral aspect of the thigh, or subcutaneously into a gluteal muscle, or scapular area. The most appropriate location for administration because of its location, size, and availability of blood flow. Injection into (or near) smaller muscles, such as in the deltoid, is not recommended due to possible differences in absorption associated with this use.

Do not administer repeated injections of epinephrine at the same site, as the resulting vasocstruction may cause tissue necrosis.

Do not inject into buttocks, digits, hands, or feet (5.1).

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia, have been reported following epinephrine injection. Advise patients to seek medical care if they develop signs or symptoms of infection (5.2). Muscle collapse or severe weakness may also produce ventricular arrhythmias, particularly in patients with underlying heart disease.

5 WARNINGS AND PRECAUTIONS

5.1 Incorrect Locations of Injection

Injection into the anterolateral aspect of the thigh (vastus lateralis muscle) is the most appropriate location for administration because of its location, size, and availability of blood flow. Injection into (or near) smaller muscles, such as in the deltoid, is not recommended due to possible differences in absorption associated with this use.

Do not administer repeated injections of epinephrine at the same site, as the resulting vasocstruction may cause tissue necrosis.

Do not inject into buttocks, digits, hands, or feet (5.1).

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia, have been reported following epinephrine injection. Advise patients to seek medical care if they develop signs or symptoms of infection (5.2). Muscle collapse or severe weakness may also produce ventricular arrhythmias, particularly in patients with underlying heart disease.

5.2 Serious Infections at the Injection Site

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia, have been reported following epinephrine injection 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 of epinephrine. Local washing with alcohol may reduce presence of bacteria on the skin, alcohol cleansing does not kill bacterial spores. To decrease the risk of Clostridium infection, do not inject Adrenalin® into the buttocks (see Warnings and Precautions (5.1)). Advise patients to seek medical care if they develop signs or symptoms of infection, such as persistent redness, warmth, swelling, or tenderness, at the epinephrine injection site.

5.3 Disease Interactions

Some patients may be at greater risk for developing adverse reactions after surgery, anephric syndrome, severe stress, trauma, weakness, dizziness, sweating, palpitations, pain, nausea and vomiting, headache, and respiratory difficulties. These symptoms occur in some persons receiving therapeutic doses of epinephrine, but are more likely to occur in patients with heart disease, hypertension, or hyperthyroidism (see Warnings and Precautions (5.3)).

Due to the lack of randomized, controlled clinical trials of epinephrine for the prevention of anaphylaxis, the true incidence of adverse reactions associated with the systemic use of epinephrine is difficult to determine. Adverse reactions reported in observational trial cases, case reports, and studies are listed below by body system:

Cardiovascular: angina, arrhythmias, hypertension, palpitations, palpitating, paresthesia, syncope, tachycardia, tachyarrhythmias, tachycardia, ventricular tachycardia, ventricular fibrillation, and vasodilation. Patients with Parkinson’s disease may experience psychomotor agitation or notice a temporary worsening of symptoms. Epinephrine is a vasoconstricting agent and may be at greater risk of developing adverse reactions after surgery, anephric syndrome, severe stress, trauma, weakness, dizziness, sweating, palpitations, pain, nausea and vomiting, headache, and respiratory difficulties. These symptoms occur in some persons receiving therapeutic doses of epinephrine, but are more likely to occur in patients with heart disease, hypertension, or hyperthyroidism (see Warnings and Precautions (5.3)).

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Due to the lack of randomized, controlled clinical trials of epinephrine for the prevention of anaphylaxis, the true incidence of adverse reactions associated with the systemic use of epinephrine is difficult to determine. Adverse reactions reported in observational trial cases, case reports, and studies are listed below by body system:
In mice, teratogenic effects (including embryonic lethality) were observed at approximately 3 times the maximum recommended intramuscular or subcutaneous dose (on a mg/gm basis at maternal subcutaneous dose of 1 mg/kg/day for 10 days). These effects were not seen in mice at approximately 2 times the maximum recommended daily intramuscular or subcutaneous dose (on a mg/gm basis at a subcutaneous maternal dose of 0.5 mg/kg/day for 10 days).

In hamsters, teratogenic effects were observed at approximately 2 times the maximum recommended intramuscular or subcutaneous dose (on a mg/gm basis at a subcutaneous maternal dose of 0.5 mg/kg/day for 4 days).

8.2 Labor and Delivery
Use with caution during labor and delivery. Although epinephrine improves maternal hypotension associated with anaphylaxis, it may result in uterine vasoconstriction, decreased uterine blood flow, and fetal anoxia.

8.3 Nursing Mothers
It is not known whether epinephrine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when epinephrine is administered to a nursing woman.

8.4 Pediatric Use
Clinical use data support weight-based dosing for treatment of anaphylaxis in pediatric patients, and other reported clinical experience with the use of epinephrine suggests that the adverse reactions seen in children are similar in nature and extent to those both expected and reported in adults.

8.5 Geriatric Use
Clinical studies for the treatment of anaphylaxis have not been performed in subjects aged 65 and over to determine whether they respond differently from younger subjects. However, other reported clinical experience with use of epinephrine for the treatment of anaphylaxis has identified that geriatric patients may be particularly sensitive to the effects of epinephrine. Therefore, for the treatment of anaphylaxis, consider starting with a lower dose to take into account potential concomitant disease or other drug therapy.

10 OVERDOSAGE
Overdose of epinephrine may produce extremely elevated arterial pressure, which may result in cerebrovascular hemorrhage, particularly in elderly patients. Overdose may also result in pulmonary edema because of peripheral vascular constriction together with cardiac stimulation. Treatment of a rapidly acting α-adrenergic blocking drug and respiratory support.

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

Epinephrine overdosage can also cause transient bradycardia followed by tachycardia and these may be accompanied by potentially fatal cardiac arrhythmias. Premature ventricular contractions may appear within one minute after injection and may be followed by multifocal ventricular tachycardia (preexcitation rhythm). Subsidence of the ventricular effects may be followed by atrial tachycardia and occasionally by atrioventricular block. Treatment of arrhythmias consists of administration of a beta-adrenergic blocking drug such as propranolol.

Overdose sometimes results in extreme pallor and coldness of the skin, metabolic acidosis due to elevated blood lactic acid levels, and kidney failure. Suitable corrective measures must be taken in such situations.

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

11 DESCRIPTION
Adrenalin® (epinephrine injection, USP) is a clear, colorless, sterile solution containing 1 mg/mL (1:1000) epinephrine, packaged as 1 mL of solution in a single-use clear glass vial or 30 mL of solution in a multiple-dose amber glass vial. In the 1 mL vial, each 1 mL of Adrenalin® solution contains 1 mg epinephrine, 7.3 mg sodium chloride, 0.457 mg sodium metabisulfite, 1 mg sodium hydroxide, 2.25 mg tartaric acid, 0.20 mg disodium edetate dihydrate, hydrochloric acid to adjust pH, and water for injection. In the 30 mL vial, each 1 mL of Adrenalin® solution contains 1 mg epinephrine, 6.15 mg sodium chloride, 0.457 mg sodium metabisulfite, 0.920 mg sodium hydroxide, 2.25 mg tartaric acid, 0.20 mg disodium edetate dihydrate, hydrochloric acid to adjust pH, 5.25 mg chlorobutanol as a preservative and water for injection. The pH range is 2.2-5.0.

Epinephrine is a sympathomimetic catecholamine. The chemical name of epinephrine is 1,2-Benzzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (+)-3,4-Dihydroxy-a-(2-(methylamino))ethyl)benzyl alcohol.

The chemical structure of epinephrine is:

\[\text{H} \quad \text{OH} \quad \text{N} \quad \text{CH}_3 \quad \text{OH} \quad \text{OH} \]

The molecular weight of epinephrine is 183.2.

Epinephrine solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Epinephrine acts on both alpha and beta-adrenergic receptors.

12.2 Pharmacodynamics
Through its action on alpha-adrenergic receptors, epinephrine lessens the vasodilation and increased vascular permeability that occurs during anaphylaxis, which can lead to loss of intravascular fluid volume and hypotension. Through its action on beta-adrenergic receptors, epinephrine causes bronchial smooth muscle relaxation and helps alleviate bronchoconspasm, wheezing and dyspnea that may occur during anaphylaxis.

Epinephrine also alleviates pruritus, urticaria, and angioedema and may relieve gastrointestinal and genitourinary symptoms associated with anaphylaxis because of its relaxer effects on the smooth muscle of the stomach, intestine, uterus and urinary bladder.

Epinephrine increases glycogenolysis, reduces glucose uptake by tissues, and inhibits insulin release in the pancreas, resulting in hyperglycemia and increased blood lactic acid [see Warnings and Precautions (5.3)].