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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights not include all the information needed to use AMPHADASE® safely and effectively. See full prescribing information for AMPHADASE®.

Amphadase® (hyaluronidase injection)
Initial U.S. Approval: 2005

----------RECENT MAJOR CHANGES----------
- Dosage and Administration (2) --- 3/2012
- Contraindications, Hypersensitivity (4.1) --- 3/2012
- Warnings and Precautions, Spread of Localized Infections (5.1) --- 3/2012
- Warnings and Precautions, Ocular Damage (5.2) --- 3/2012
- Warnings and Precautions, Enzyme Inactivation with Intravenous Administration (5.3) --- 3/2012

----------INDICATIONS AND USAGE----------
Amphadase® is indicated as an adjuvant
- in subcutaneous fluid administration for achieving hydration (1.1)
- to increase absorption and dispersion of other injected drugs (1.2)
- in subcutaneous urography for improving resorption of radiopaque agents (1.3)

----------DOSAGE AND ADMINISTRATION----------
• Subcutaneous Fluid Administration
Insert needle with aseptic precautions. With tip lying free and movable between skin and muscle, begin clysis; fluid should start in readily without pain or lump. Then inject Amphadase® (hyaluronidase injection) into rubber tubing close to needle. (2.1)
• Absorption and Dispersion of Injected Drugs
Absorption and dispersion of other injected drugs may be enhanced by adding 50-300 Units, most typically 150 U hyaluronidase, to the injection solution. (2.2)
• Subcutaneous Urography
The subcutaneous route of administration of urographic contrast media is indicated when intravenous administration cannot be successfully accomplished, particularly in infants and small children. With the patient prone, 75 U of Amphadase® (hyaluronidase injection) is injected subcutaneously over each scapula, followed by injection of the contrast medium at the same sites. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
150 USP units/mL single dose vials (3)

----------CONTRAINDICATIONS----------
Hypersensitivity (4.1)

----------WARNINGS AND PRECAUTIONS----------
- Spread of Localized Infection (5.1)
- Ocular Damage (5.2)
- Enzyme Inactivation with Intravenous Administration (5.3)

----------ADVERSE REACTIONS----------
Allergic and anaphylactic-like reactions have been reported, rarely (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amphastar Pharmaceuticals, Inc. at 1-800-423-4136 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- Furosemide, the benzodiazepines and phenytoin are incompatible with hyaluronidase (7.1)
- Hyaluronidase should not be used to enhance the absorption and dispersion of dopamine and/or alpha agonist drugs (7.2)
- Local anesthetics: Hyaluronidase hastens onset and shortens duration of effect, increases incidence of systemic reactions (7.3)
- Large doses of salicylates, cortisone, ACTH, estrogens or antihistamines may require larger amounts of hyaluronidase for equivalent dispersing effect (7.4)

----------USE IN SPECIFIC POPULATIONS----------
Pediatric Use: The dosage of subcutaneous fluids administered is dependent upon the age, weight, and clinical condition of the patient. For premature infants or during the neonatal period, the daily dosage should not exceed 25 mL/kg of body weight, and the rate of administration should not be greater than 2 mL per minute. Special care must be taken in pediatric patients to avoid over hydration by controlling the rate and total volume of the infusion. (2.1, 8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised 3/2012

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

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Subcutaneous Fluid Administration

Amphadase® is indicated as an adjuvant in subcutaneous fluid administration for achieving hydration.

1.2 Dispersion and Absorption of Injected Drugs

Amphadase® is indicated as an adjuvant to increase the dispersion and absorption of other injected drugs.

1.3 Subcutaneous Urography

Amphadase® is indicated as an adjunct in subcutaneous urography for improving resorption of radiopaque agents.

2 DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.1 Subcutaneous Fluid Administration (Hypodermoclysis)

Insert needle with aseptic precautions. With tip lying free and movable between skin and muscle, begin clysis; fluid should start in readily without pain or lump. Then inject Amphadase® (hyaluronidase injection) into rubber tubing close to needle.

An alternate method is to inject Amphadase® under skin prior to clysis. 150 U will facilitate absorption of 1,000 mL or more of solution. As with all parenteral fluid therapy, observe effect closely, with same precautions for restoring fluid and electrolyte balance as in intravenous injections. The dose, the rate of injection, and the type of solution (saline, glucose, Ringer's, etc.) must be adjusted carefully to the individual patient. When solutions devoid of inorganic electrolytes are given by hypodermoclysis, hypovolemia may occur. This may be prevented by using solutions containing adequate amounts of inorganic electrolytes and/or controlling the volume and speed of administration.

Amphadase® may be added to small volumes of solution (up to 200 mL), such as small clysis for infants or solutions of drugs for subcutaneous injection. For infants and children less than 3 years old, the volume of a single clysis should be limited to 200 mL; and in premature infants or during the neonatal period, the daily dosage should not exceed 25 mL/kg of body weight; the rate of administration should not be greater than 2 mL per minute. For older patients, the rate and volume of administration should not exceed those employed for intravenous infusion.

2.2 Absorption and Dispersion of Injected Drugs

Absorption and dispersion of other injected drugs may be enhanced by adding 50-300 Units, most typically 150 U hyaluronidase, to the injection solution.

2.3 Subcutaneous Urography

The subcutaneous route of administration of urographic contrast media is indicated when intravenous administration cannot be successfully accomplished, particularly in infants and small children. With the patient prone, 75 U of Amphadase® (hyaluronidase injection) is injected subcutaneously over each scapula, followed by injection of the contrast medium at the same sites.

3 DOSAGE FORMS AND STRENGTHS

150 USP units/mL single dose vials

4 CONTRAINDICATIONS

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4.1 Hypersensitivity

Hypersensitivity to hyaluronidase or any other ingredient in the formulation is a contraindication to the use of this product. A preliminary skin test for hypersensitivity to Amphadase can be performed. The skin test is made by an intradermal injection of approximately 0.02 mL (3 Units) of a 150 Unit/mL solution. A positive reaction consists of a wheal with pseudopods appearing within 5 minutes and persisting for 20 to 30 minutes and accompanied by localized itching. Transient vasodilation at the site of the test, i.e., erythema, is not a positive reaction. Discontinue Amphadase if sensitization occurs.

5 WARNINGS AND PRECAUTIONS

5.1 Spread of Localized Infection

Hyaluronidase should not be injected into or around an infected or acutely inflamed area because of the danger of spreading a localized infection.

Hyaluronidase should not be used to reduce the swelling of bites or stings.

5.2 Ocular Damage

Hyaluronidase should not be applied directly to the cornea.

5.3 Enzyme Inactivation with Intravenous Administration

Hyaluronidase should not be used for intravenous injections because the enzyme is rapidly inactivated.

6 ADVERSE REACTIONS

The following adverse reactions have been identified during post-approval use of hyaluronidase products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The most frequently reported adverse reactions have been local injection site reactions.

Hyaluronidase has been reported to enhance the adverse reactions associated with co-administered drug products. Edema has been reported most frequently in association with hypodermoclysis.

Allergic reactions (urticaria, angioedema) have been reported in less than 0.1% of patients receiving hyaluronidase. Anaphylactic-like reactions following retrobulbar block or intravenous injections have occurred, rarely.

7 DRUG INTERACTIONS

It is recommended that appropriate references be consulted regarding physical or chemical incompatibilities before adding Amphadase® to a solution containing another drug.

7.1 Incompatibilities

Furosemide, the benzodiazepines and phenytoin have been found to be incompatible with hyaluronidase.

7.2 Drug-Specific Precautions

Hyaluronidase should not be used to enhance the dispersion and absorption of dopamine and/or alpha agonist drugs.

When considering the administration of any other drug with hyaluronidase, it is recommended that appropriate references first be consulted to determine the usual precautions for the use of the other drug; e.g., when epinephrine is injected along with hyaluronidase, the precautions for the use of epinephrine in cardiovascular disease, thyroid disease, diabetes, digital nerve block, ischemia of the fingers and toes etc., should be observed.

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7.3 Local Anesthetics

When hyaluronidase is added to a local anesthetic agent, it hastens the onset of analgesia and tends to reduce the swelling caused by local infiltration, but the wider spread of the local anesthetic solution increases its absorption; this shortens its duration of action and tends to increase the incidence of systemic reaction.

7.4 Salicylates, Cortisone, ACTH, Estrogens and Antihistamines

Patients receiving large doses of salicylates, cortisone, ACTH, estrogens or antihistamines may require larger amounts of hyaluronidase for equivalent dispersing effect, since these drugs apparently render tissues partly resistant to the action of hyaluronidase.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. No adequate and well controlled studies have been conducted with Amphadase® in pregnant women. No adequate and well controlled animal studies have been conducted with Amphadase® to determine reproductive effects. Amphadase® should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery

Administration of hyaluronidase during labor was reported to cause no complications: no increase in blood loss or differences in cervical trauma were observed.

8.3 Nursing Mothers

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

8.4 Pediatric Use

The safety and effectiveness of Amphadase have been established in pediatric patients. Use of Amphadase in these patients is supported by evidence from adequate and well-controlled studies. Clinical hydration requirements for children can be achieved through administration of subcutaneous fluids facilitated with Amphadase.

The dosage of subcutaneous fluids administered is dependent upon the age, weight, and clinical condition of the patient as well as laboratory determinations. The potential for chemical or physical incompatibilities should be kept in mind *[see Drug Interactions (7)]*.

The rate and volume of subcutaneous fluid administration should not exceed those employed for intravenous infusion. For premature infants or during the neonatal period, the daily dosage should not exceed 25 mL/kg of body weight, and the rate of administration should not be greater than 2 mL per minute.

During subcutaneous fluid administration, special care must be taken in pediatric patients to avoid over hydration by controlling the rate and total volume of the infusion *[see Dosage and Administration (2.1)]*.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

11 DESCRIPTION

Amphadase® is a preparation of purified bovine testicular hyaluronidase, a protein enzyme. The exact chemical structure of this enzyme is unknown. However, the amino acid sequence for the primary structure of the enzyme has been deduced from the sequence of purified peptides. Amphadase® (hyaluronidase injection) is supplied as a sterile, clear, colorless, ready for use

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solution. Each vial contains 150 USP units of hyaluronidase per mL with 8.5 mg sodium chloride, 1 mg edetate disodium, 0.4 mg calcium chloride, monobasic sodium phosphate buffer, and not more than 0.1 mg thimerosal (mercury derivative).
Amphadase® has an approximate pH of 6.8 and an osmolality of 295 to 355 mOsm.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hyaluronidase is a dispersion agent, which modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid, a polysaccharide found in the intercellular ground substance of connective tissue, and of certain specialized tissues, such as the umbilical cord and vitreous humor. Hyaluronic acid is also present in the capsules of type A and C hemolytic streptococci. Hyaluronidase hydrolyzes hyaluronic acid by splitting the glucosaminidic bond between Cl of an N-acetylglucosamine moiety and C4 of a glucuronic acid moiety. This temporarily decreases the viscosity of the cellular cement and promotes dispersion of injected fluids or of localized transudates or exudates, thus facilitating their absorption.
Hyaluronidase cleaves glycosidic bonds of hyaluronic acid and, to a variable degree, some other acid mucopolysaccharides of the connective tissue. The activity is measured in vitro by monitoring the decrease in the amount of an insoluble serum albumin-hyaluronic acid complex as the enzyme cleaves the hyaluronic acid component.

12.2 Pharmacodynamics

In the absence of hyaluronidase, material injected subcutaneously disperses very slowly. Hyaluronidase facilitates dispersion, provided local interstitial pressure is adequate to furnish the necessary mechanical impulse. Such an impulse is normally initiated by injected solutions. The rate and extent of dispersion and absorption is proportionate to the amount of hyaluronidase and the volume of solution.
Results from an experimental study, in humans, on the influence of hyaluronidase in bone repair support the conclusion that this enzyme alone, in the usual clinical dosage, does not deter bone healing.

12.3 Pharmacokinetics

Knowledge of the mechanisms involved in the disappearance of injected hyaluronidase is limited. It is known, however, that the blood of a number of mammalian species brings about the inactivation of hyaluronidase.
Studies have demonstrated that hyaluronidase is antigenic: repeated injections of relatively large amounts of this enzyme may result in the formation of neutralizing antibodies.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to assess the carcinogenic or mutagenic potential of hyaluronidase. Hyaluronidase is found in most tissues of the body.
Long-term animal studies have not been performed to assess whether hyaluronidase impaired fertility; however, it has been reported that testicular degeneration may occur with the production of organ-specific antibodies against this enzyme following repeated injections. Human studies on the effect of intravaginal hyaluronidase in sterility due to oligospermia indicated that hyaluronidase may have aided conception. Thus, it appears that hyaluronidase may not adversely affect fertility in females.

16 HOW SUPPLIED/STORAGE AND HANDLING

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Amphadase® (hyaluronidase injection) is supplied sterile as 150 USP units of hyaluronidase per mL in a 2 mL single-use glass vial with a gray rubber stopper and aluminum flip-off seal.

NDC 0548-9090-10, 1 mL vial, 10 vials/carton.
NDC 0548-9090-00, 1 mL vial, 25 vials/carton.

Store unopened in a refrigerator at 2° to 8°C (36° to 46° F).

17 PATIENT COUNSELING INFORMATION

17.1 Important Precautions Regarding Amphadase®

Instruct patient that Amphadase® is being used to increase the dispersion and absorption of fluids or other injected drugs, as appropriate to the intended use.
Instruct patient that there may be mild local injection site signs and symptoms, such as redness, swelling, itching, or pain localized to the site of injection.

17.2 What Patients Should Know About Adverse Reactions

The most frequently reported adverse reactions have been mild local injection site reactions such as redness, swelling, itching, or pain.
Anaphylactic-like reactions, and allergic reactions, such as hives, have been reported rarely in patients receiving hyaluronidases.

17.3 Patients Should Inform Their Doctors If Taking Other Medications

You may not receive furosemide, the benzodiazepines, phenytoin, dopamine and/or alpha agonists with Amphadase®. These medications have been found to be incompatible with hyaluronidase.
If you are taking salicylates (e.g., aspirin), steroids (e.g., cortisone or estrogens), or antihistamines your doctor may need to prescribe larger amounts of hyaluronidase for equivalent dispersing effect.

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