HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do 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

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1 INDICATIONS AND USAGE

1.1 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 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)

1.2 Dispersion and Absorption of Injected Drugs

Absorption and dispersion of injected drugs should not exceed those employed for intravenous infusion. For older patients, the rate and volume of administration may require larger amounts of hyaluronidase for equivalent dispersing effect. (7.4)

2 DOSAGE AND ADMINISTRATION

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; in 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)

2.2 Absorption and Dispersion of Injected Drugs

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; in 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)

3 DOSAGE FORMS AND STRENGTHS

5.2 Ocular Damage

5.1 Spread of Localized Infection

6 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)

Patient Counseling Information

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.

150 USP units/mL single dose vials (3)

Hypersensitivity (4.1)

1 CONTRAINDICATIONS

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

2 DRUG INTERACTIONS

For your convenience, see the full prescribing information listed below:

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

1.1 Subcutaneous Fluid Administration

1.2 Dispersion and Absorption of Injected Drugs

1.3 Subcutaneous Urography

2 DOSAGE AND ADMINISTRATION

2.1 Subcutaneous Fluid Administration

2.2 Absorption and Dispersion of Injected Drugs

2.3 Subcutaneous Urography

2.3 Subcutaneous Urography

2.2 Absorption and Dispersion of Injected Drugs

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

4.1 Hypersensitivity

5 WARNINGS AND PRECAUTIONS

5.1 Spread of Localized Infection

5.2 Ocular Damage

5.3 Enzyme Inactivation with Intravenous Administration

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

7.1 Incompatibilities

7.2 Drug-Specific Precautions

7.3 Local Anesthetics

7.4 Salicylates, Cortisone, ACTH, Estrogens and Antihistamines

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

Revised 5/2014

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

The hyaluronidase (hyaluronidase injection) is supplied as a sterile, clear, colorless, ready for use 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 293 to 355 mOsm.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Hyaluronidase is a dispersion agent, which modifies the permeability of connective tissue. This can be achieved by the hyaluronidase 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 glucosaminobond between C6 of an N-acetylglucosamine moiety and C1 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 the 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 fluids 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
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.

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

17 PATIENT COUNSELING INFORMATION
17.1 Important Precautions
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.

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 antiinhibitors your doctor may need to prescribe larger amounts of hyaluronidase for equivalent dispersing effect.

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