CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-640

APPROVED LABELING

Vitrase
(hyaluronidase for injection)
Lyophilized, Ovine

DESCRIPTION

Vitrase is a preparation of purified ovine 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.

Vitrase (hyaluronidase for injection), dehydrated in the solid state under high vacuum with the inactive ingredients listed below, is supplied as a sterile, nonpreserved, white, odorless, amorphous solid. The product is to be reconstituted with Sodium Chloride Injection, USP, before use (see "Dosage and Administration").

Each vial of 6200 USP units contains 5 mg lactose, 1.92 mg potassium phosphate dibasic, and 1.22 mg potassium phosphate monobasic.

The reconstituted solution is clear and colorless with an approximate pH of 6.7 and osmolality of 290 to 310 mOsm.

CLINICAL PHARMACOLOGY

Hyaluronidase is a spreading or diffusing substance, 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 C1 of the glucosamine moiety and C4 of glucuronic acid. This temporarily decreases the viscosity of the cellular cement and promotes diffusion 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 albumen-hyaluronic acid complex as the enzyme cleaves the hyaluronic acid component.

When no spreading factor is present, material injected subcutaneously spreads very slowly, but hyaluronidase causes rapid spreading, provided local interstitial pressure is adequate to furnish the necessary mechanical impulse. Such an impulse is normally initiated by injected solutions. The rate of diffusion is proportionate to the amount of enzyme, and the extent is proportionate to the volume of solution.

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.

The reconstitution of the dermal barrier removed by intradermal injection of hyaluronidase (20, 2, 0.2, 0.02, and 0.002 Units/mL) to adult humans indicated that at 24 hours the restoration of the barrier is incomplete and inversely related to the dosage of enzyme; at 48 hours the barrier is completely restored in all treated areas.

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.

INDICATIONS AND USAGE

Vitrase (hyaluronidase for injection) is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents.

CONTRAINDICATIONS

Hypersensitivity to hyaluronidase or any other ingredient in the formulation is a contraindication to the use of this product.

WARNINGS

Discontinue Vitrase (hyaluronidase for injection) if sensitization occurs.

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

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.

Hyaluronidase should not be applied directly to the cornea.

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

PRECAUTIONS

General

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

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.

Laboratory Tests

A preliminary skin test for hypersensitivity to Vitrase 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 (see "Dosage and Administration"). 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.

Drug Interactions

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.

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.

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.

Pregnancy

Teratogenic Effects --Pregnancy Category C

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

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. It is not known whether hyaluronidase has an effect on the fetus if used during labor; the effect of hyaluronidase on the later growth, development, and functional maturation of the infant is unknown.

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.

Pediatric Use

Hyaluronidase may be added to small volumes of solution (up to 200 mL), such as a small clysis for infants or solutions of drugs for subcutaneous injection. The potential for chemical or physical incompatibilities should be kept in mind. (See "Dosage and Administration.")

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.

During hypodermoclysis, special care must be taken in pediatric patients to avoid over hydration by controlling the rate and total volume of the clysis. (See "Dosage and Administration, hypodermoclysis.")

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

ADVERSE REACTIONS

The most frequently reported adverse experiences have been local injection site reactions. Hyaluronidase has been reported to enhance the adverse events 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.

OVERDOSAGE

Symptoms of toxicity consist of local edema or urticaria, erythema, chills, nausea, vomiting, dizziness, tachycardia, and hypotension. The enzyme should be discontinued and supportive measures initiated immediately.

DOSAGE AND ADMINISTRATION

Vitrase (hyaluronidase for injection) should be administered as discussed below, since its effects relative to absorption and dispersion of other drugs are not produced when it is administered intravenously.

Vitrase is to be reconstituted in the vial to a concentration of 1000 Units/mL of Sodium Chloride Injection, USP by adding 6.2 mL of solution to the vial. Prior to administration, the reconstituted solution should be further diluted to the desired concentration, commonly 150 Units/mL, see table below. The resulting solution should be used immediately after preparation.

A 1 mL syringe and a 5-micron filter needle are supplied in the Vitrase kit. Following reconstitution of Vitrase, as described above, apply the 5-micron filter needle to the 1 mL syringe. Draw the desired amount of Vitrase into the syringe, and dilute according to the table below. Remove the filter needle and apply a needle appropriate for the intended injection.

Desired Concentration	Amount of hyaluronidase reconstituted solution (1000 Units/mL)	Additional Sodium Chloride Injection
50 Units/mL	0.05 mL	0.95 mL
75 Units/mL	0.075 mL	0.925 mL
150 Units/mL	0.15 mL	0.85 mL
300 Units/mL	0.3 mL	0.7 mL

Absorption and Dispersion of Injected Drugs

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

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

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 Vitrase (hyaluronidase for injection) into rubber tubing close to needle.

An alternate method is to inject Vitrase under skin prior to clysis. 150 Units 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.

Vitrase 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.

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 Units of Vitrase (hyaluronidase for injection) is injected subcutaneously over each scapula, followed by injection of the contrast medium at the same sites.

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

HOW SUPPLIED

Vitrase is supplied sterile as 6200 USP units of lyophilized ovine hyaluronidase nonpreserved in a single-use 5 mL glass vial with a rubber stopper and aluminum seal; one 1 mL sterile polycarbonate syringe; and one 5 μm sterile filter needle.

NDC 67425-xxx-xx
Not Recommended for IV Use.
Protect from light.
Store unopened vial in refrigerator at 2-8 °C (35-46 °F). After reconstitution, store at controlled room temperature, 20-25°C (68-77°F), and use within 6 hours.

Rx Only

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