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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HYLENEX recombinant safely and effectively. See full prescribing information for HYLENEX recombinant.

HYLENEX recombinant (hyaluronidase human injection) for infiltration use, for interstitial use, for intramuscular use, for intraocular use, for peribulbar use, retrobulbar use, for soft tissue use and for subcutaneous use
Initial U.S. Approval: 2005

INDICATIONS AND USAGE

HYLENEX recombinant is an endoglycosidase indicated as an adjuvant

- in subcutaneous fluid administration for achieving hydration (1.1)
- to increase the dispersion and absorption of other injected drugs (1.2)
- in subcutaneous urography for improving resorption of radiopaque agents (1.3)

DOSAGE AND ADMINISTRATION

- See Full Prescribing Information for all approved routes of administration. (2.1)
- Subcutaneous fluid administration:
  Inject 150 U HYLENEX recombinant prior to subcutaneous fluid administration. It will facilitate absorption of 1,000 mL or more of solution. The dosage of subcutaneous fluids administered is dependent upon the age, weight, and clinical condition of the patient as well as laboratory determinations. The rate and volume of subcutaneous fluid administration should not exceed those employed for intravenous infusion. (2.2)
- Increasing dispersion and absorption of injected or subcutaneously infused drugs:
  Inject 50-300 U (most typically 150 U) HYLENEX recombinant prior to drug administration. Alternatively, add 50-300 U (most typically 150 U) HYLENEX recombinant to the injection solution. (2.3)
- Subcutaneous Urography:
  Inject 75 U HYLENEX recombinant subcutaneously over each scapula, followed by injection of the contrast medium at the same sites. (2.4)

DOSAGE FORMS AND STRENGTHS

- 150 USP units/mL single dose vials (3)

CONTRAINDICATIONS

- Hypersensitivity (4)

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 Halozyme Therapeutics, Inc. at 1-877-877-1679 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 dispersion and absorption 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, 14)

See 17 for PATIENT COUNSELING INFORMATION
Revised: XX/2015

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 Important Administration Instructions
2.2 Subcutaneous Fluid Administration
2.3 Dispersion and Absorption of Injected Drugs
2.4 Subcutaneous Urography
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
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
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Important Precautions Regarding HYLENEX recombinant
17.2 What Patients Should Know About Adverse Reactions
17.3 Patients Should Inform Their Doctors If Taking Other Medications

***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

HYLENEX recombinant is indicated as an adjuvant in subcutaneous fluid administration for achieving hydration.

1.2 Dispersion and Absorption of Injected Drugs

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

1.3 Subcutaneous Urography

HYLENEX recombinant is indicated as an adjunct in subcutaneous urography for improving resorption of radiopaque agents.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

HYLENEX recombinant should not be administered intravenously. Its effects relative to dispersion and absorption of other drugs are not produced when it is administered intravenously because the enzyme is rapidly inactivated.

HYLENEX recombinant may be administered for infiltration use, interstitial use, intramuscular use, intraocular use, peribulbar use, retrobulbar use, soft tissue use or subcutaneous use.

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration.

Always use aseptic precautions. Lightly pinch the skin up into a small mound and insert the needle/catheter into the subcutaneous space. Inject HYLENEX recombinant through the catheter hub or injection port closest to the needle/catheter. Begin administration of solution. Solution should start in readily.

2.2 Subcutaneous Fluid Administration

Inject 150 U of HYLENEX recombinant prior to start of subcutaneous fluid administration to facilitate absorption of up to 1,000 mL or more of solution. As with all parenteral fluid therapy, observe effect closely, with the 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,

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Ringer's, etc.) must be adjusted carefully to the individual patient. When solutions devoid of inorganic electrolytes are administered subcutaneously, 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.

HYLENEX recombinant may be added to small volumes of solution, such as fluid replacement solutions or solutions of drugs for subcutaneous injection. Subcutaneous fluids should be administered as directed by a physician. The dosage of subcutaneous fluids administered is dependent upon the age, weight, and clinical condition of the patient as well as laboratory determinations. 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 and the rate of administration should not be greater than 2 mL per minute.

2.3 Dispersion and Absorption of Injected Drugs

Hylenex can be used to enhance the dispersion and absorption of other injected or subcutaneously infused drugs by pre-administration of HYLENEX recombinant or by adding 50-300 U, most typically 150 U hyaluronidase, to the injection solution prior to infiltration use, interstitial use, intramuscular use, intraocular use, retrobulbar use, soft tissue use or subcutaneous use.

2.4 Subcutaneous Urography

The subcutaneous route of administration of urographic contrast media may be considered when intravenous administration cannot be successfully accomplished, particularly in infants and small children. With the patient prone, inject 75 U of HYLENEX recombinant 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

HYLENEX recombinant is contraindicated in patients with known hypersensitivity to hyaluronidase or any of the excipients in HYLENEX recombinant. A preliminary skin test for hypersensitivity to HYLENEX recombinant 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 HYLENEX recombinant if sensitization occurs.

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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. It is not for topical use.

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 mild local injection site reactions such as erythema and pain. Hyaluronidase has been reported to enhance the adverse reactions associated with co-administered drug products. Edema has been reported most frequently in association with subcutaneous fluid administration. Allergic reactions (urticaria or 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 HYLENEX recombinant to a solution containing another drug.

7.1 Incompatibilities

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

Admixture stability studies have shown that 2% lidocaine with 1:100,000 or 1:200,000 epinephrine is incompatible with hyaluronidase due to the presence of sodium metabisulfite, a common additive in anesthetic products containing epinephrine.

7.2 Drug-Specific Precautions

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

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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.

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. In an embryo-fetal study, mice have been dosed daily by subcutaneous injection with recombinant human hyaluronidase at dose levels up to 2,200,000 U/kg. The study found no evidence of teratogenicity. Reduced fetal weight and increased numbers of fetal resorptions were observed, with no effects found at a daily dose of 360,000 U/kg, which represents several orders of magnitude over the suggested human dose range of 50-300 U of HYLENEX recombinant (0.8-5 U/kg in a 60 kg subject).

In a pre- and postnatal development study, mice have been dosed daily by subcutaneous injection with recombinant human hyaluronidase at dose levels up to 1,100,000 U/kg. The study found no adverse effects on sexual maturation, learning and memory of offspring, or their ability to produce another generation of offspring.

It is also not known whether HYLENEX recombinant can cause fetal harm when administered to a pregnant woman. HYLENEX recombinant should be given to a pregnant woman 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.

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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

Clinical hydration requirements for children can be achieved through administration of subcutaneous fluids facilitated with HYLENEX recombinant.

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

HYLENEX recombinant is a purified preparation of the enzyme recombinant human hyaluronidase. HYLENEX recombinant is produced by genetically engineered Chinese Hamster Ovary (CHO) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). The purified hyaluronidase glycoprotein contains 447 amino acids with an approximate molecular weight of 61,000 Daltons.

HYLENEX recombinant is supplied as a sterile, clear, colorless, nonpreserved, ready-for-use solution. Each mL contains 150 USP units of recombinant human hyaluronidase with 8.5 mg sodium chloride, 1.4 mg dibasic sodium phosphate, 1 mg albumin human, 1.5 mg L-methionine, 0.2 mg polysorbate 80, and hydrochloric acid and sodium hydroxide added for pH adjustment.

HYLENEX recombinant has an approximate pH of 7.0 and an osmolality of 280 to 340 mOsm/kg.

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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 C1 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.

The reconstitution of the dermal barrier removed by intradermal injection of hyaluronidase (20, 2, 0.2, 0.02, and 0.002 U/mL) to adult humans indicated that at 24 hours the restoration of the barrier is incomplete and inversely related to the dosage of hyaluronidase; 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 hyaluronidase 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 components in blood of a number of mammalian species bring about the inactivation of hyaluronidase.

Studies have demonstrated that hyaluronidase is antigenic; repeated injections of relatively large amounts of hyaluronidase preparations may result in the formation of neutralizing antibodies.

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Hyaluronidase is found in most tissues of the body. Long-term animal studies have not been performed to assess the carcinogenic or mutagenic potential of hyaluronidase.

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. In addition, when recombinant human hyaluronidase was administered to cynomolgus monkeys for 39 weeks at dose levels up to 220,000 U/kg, no evidence of toxicity to the male or female reproductive system was found through periodic monitoring of in-life parameters, e.g., semen analyses, hormone levels, menstrual cycles, and also from gross pathology, histopathology and organ weight data.

14 CLINICAL STUDIES

HYLENEX recombinant facilitated the administration of subcutaneous fluids in pediatric patients with mild to moderate dehydration in an open-label, multicenter, single arm study in fifty-one (51) patients. A subcutaneous injection of 1 mL (150 U) of HYLENEX recombinant was immediately followed by subcutaneous infusion of isotonic fluids in either the mid-anterior thigh or the inter-scapular area of the upper back.

The safety and flow rate of subcutaneously administered Lactated Ringer's (LR) solution with and without HYLENEX recombinant was evaluated in a prospective, randomized, double-blinded, placebo-controlled, within-subject, single-center study in fifty-four (54) healthy volunteers. The mean HYLENEX recombinant facilitated infusion rate was 464 mL/hr versus 118 mL/hr for the saline control ($p < 0.001$, paired t-test).

16 HOW SUPPLIED/STORAGE AND HANDLING

HYLENEX recombinant is supplied sterile as 150 USP units of nonpreserved recombinant human hyaluronidase per mL in a single-use glass vial.

HYLENEX recombinant is supplied in the following packaging:

1 mL Single Dose Vial (NDC 18657-117-01) available in boxes of 4 (NDC 18657-117-04) or 10 (NDC 18657-117-10)

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

DO NOT FREEZE.

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17 PATIENT COUNSELING INFORMATION

17.1 Important Precautions Regarding HYLENEX recombinant

Instruct patient that HYLENEX recombinant 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

Patients should be advised that 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

Instruct patients that they may not receive furosemide, the benzodiazepines, phenytoin, dopamine and/or alpha agonists with HYLENEX recombinant. These medications have been found to be incompatible with hyaluronidase.

Patients should be advised that if they are taking salicylates (e.g., aspirin), steroids (e.g., cortisone or estrogens), or antihistamines, they may need to be prescribed larger amounts of hyaluronidase for equivalent dispersing effect.

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