VITRASE- hyaluronidase, ovine injection, solution
Bausch & Lomb Incorporated

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VITRASE® (hyaluronidase injection) Ovine, 200 USP Units/mL safely and effectively. See full prescribing information for VITRASE®.

VITRASE® (hyaluronidase injection) Ovine, 200 USP Units/mL
Initial U.S. Approval: 2004

RECENT MAJOR CHANGES

• Dosage and Administration (2) – 03/2012
• Contraindications (4) – 03/2012

INDICATIONS AND USAGE

• VITRASE is indicated as an adjuvant in subcutaneous fluid administration for achieving hydration (1.1)
• to increase the dispersion and absorption of the other injected drugs (1.2)
• in subcutaneous urography for improving resorption of radiopaque agents. (1.3)

DOSAGE AND ADMINISTRATION

Draw the desired amount of VITRASE into the syringe to obtain target hyaluronidase activity (USP Units) according to table. (2)

- Subcutaneous Fluid Administration: Inject 200 Units of VITRASE prior to clysis. 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. (2.1)
- Increasing absorption and dispersion of injected drugs: Add 50 – 300 Units (most typically 150 units) of VITRASE to the injection solution. Consultation of references on physical or chemical incompatibilities is recommended. (2.2)
- Subcutaneous Urography: With the patient prone, inject 75 Units of VITRASE subcutaneously over each scapula, followed by injection of the contrast medium at the same sites. (2.3)

DOSAGE FORMS AND STRENGTHS

Ovine hyaluronidase: 200 USP units/mL single use 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 Bausch & Lomb at 1-800-323-0000, 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: 10/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Subcutaneous Fluid Administration

VITRASE® (hyaluronidase injection) is indicated as an adjuvant in subcutaneous fluid administration for achieving hydration.

1.2 Dispersion and Absorption of Injected Drugs

VITRASE is indicated as an adjuvant to increase dispersion and absorption of other injected drugs.

1.3 Subcutaneous Urography

VITRASE is indicated as an adjuvant 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.

VITRASE (hyaluronidase 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.

Draw the desired amount of VITRASE into the syringe to obtain the target Hyaluronidase Activity (USP Units) according to the table below.

Amount of VITRASE Solution Withdrawn Per Target Hyaluronidase Activity

Target Hyaluronidase Activity (USP Units)	Volume Withdraw from Vial (mL)
50 Units	0.25 mL
75 Units	0.38 mL
150 Units	0.75 mL
200 Units	1.0 mL

After admixture with drug, store at 15-25°C (59-77°F) and use within 6 hours.

2.1 Subcutaneous Fluid Administration (Hypodermoclysis)

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

An alternate method is to inject VITRASE under skin prior to clysis. 200 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.

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

3 DOSAGE FORMS AND STRENGTHS

Ovine hyaluronidase 200 USP Units/mL single use vials

4 CONTRAINDICATIONS

VITRASE (hyaluronidase injection) is contraindicated in patients with known hypersensitivity to hyaluronidase or any other ingredient in the formulation. A preliminary skin test for hypersensitivity to VITRASE can be performed. The skin test is made by intradermal injection of approximately 0.02 mL (4 Units) of a 200 Units/mL solution *[see Dosage and Administration (2)]*. 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 VITRASE if sensitization occurs.

5 WARNINGS AND PRECAUTIONS

5.1 Spread of Localized Infection

Hyaluronidase should not be injected into or around infected or acutely inflamed area because of the danger of spreading to a localized infection. Hyaluronidase should not be used to reduce the swelling of bites or stings.

5.2 Ocular Damage

VITRASE® (hyaluronidase injection) should not be applied directly to the cornea.

5.3 Enzyme Inactivation with Intravenous Administration

VITRASE 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 VITRASE (hyaluronidase injection) 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 absorption and dispersion 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.

7.3 Local Anesthetic Agent

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 incidences of systemic reaction.

7.4 Salicylates, Cortisone, ACTH, Estrogens, 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: Animal reproduction studies have not been conducted with VITRASE. Human studies on the effect of intravaginal hyaluronidase in sterility due to oligospermia indicated the hyaluronidase may have aided conception. Thus, it appears that hyaluronidase may not adversely affect fertility in females. VITRASE (hyaluronidase injection) 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.

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 VITRASE have been established in pediatric patients. Use of

VITRASE 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 VITRASE.

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

VITRASE is a preparation of purified ovine testicular hyaluronidase, a protein enzyme. The exact chemical structure of this enzyme is unknown.

VITRASE (hyaluronidase injection) is supplied as a sterile, non-preserved, colorless solution with a pH of 6.4 to 7.2. Each mL contains 200 USP units of ovine hyaluronidase with 0.93 mg lactose, 0.36 mg potassium phosphate dibasic, 0.23 mg potassium phosphate monobasic, and 9.0 mg sodium chloride.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

12.2 Pharmacodynamics

In the absence of hyaluronidase, material injected subcutaneously spreads 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 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.

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 from the production of organ-specific antibodies against this enzyme following repeated injections.

16 HOW SUPPLIED/STORAGE AND HANDLING

VITRASE® (hyaluronidase injection) Ovine is supplied sterile as 200 USP Units/mL of ovine hyaluronidase non-preserved, 1.2 mL in a single-use 2 mL glass vial with a rubber stopper and aluminum seal.

- NDC 24208-002-01

Storage

- Protect from light.
- Store unopened vial in refrigerator at 2°-8°C (35°-46°F).
- Do not freeze.

17 PATIENT COUNSELING INFORMATION

17.1 Important Precautions Regarding VITRASE

Instruct patient that VITRASE is being used to increase the dispersion and absorption of fluids or other injected drugs, as appropriate to the intended use.

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

VITRASE. 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.

Distributed by: Bausch & Lomb
Incorporated, Tampa, FL 33637

Manufactured by: Alliance Medical
Products, Inc., CA 92618

9295100

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

NDC 24208-002-01

VITRASE®
(hyaluronidase injection)
Ovine

Rx only

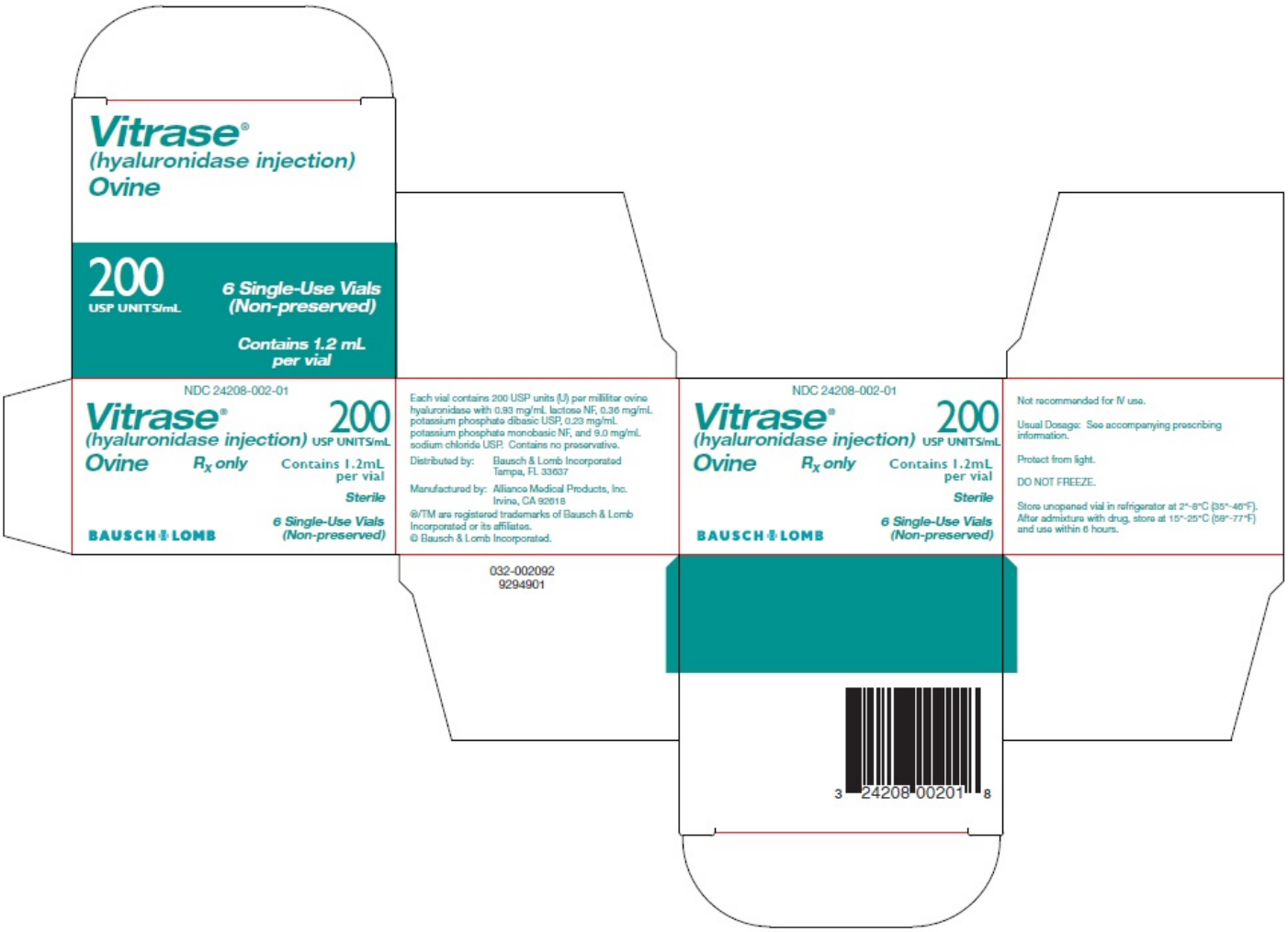
200 USP UNITS/mL

Contains 1.2 mL per vial

Sterile

6 Single-Use Vials
(Non-preserved)

BAUSCH+LOMB



VITRASE

hyaluronidase, ovine injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:24208-002
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HYALURONIDASE, OVINE (UNII: 64R4OHP8T0) (HYALURONIDASE, OVINE - UNII:64R4OHP8T0)	HYALURONIDASE, OVINE	200 [USP'U] in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
LACTOSE (UNII: J2B2A4N98G)	0.93 mg in 1 mL
POTASSIUM PHOSPHATE, DIBASIC (UNII: CI71S98N1Z)	0.36 mg in 1 mL
POTASSIUM PHOSPHATE, MONOBASIC (UNII: 4J9FJ0HL51)	0.23 mg in 1 mL
SODIUM CHLORIDE (UNII: 451W47IQ8X)	9.0 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:24208-002-01	6 in 1 CARTON		
1		1.2 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021640	02/01/2005	

Labeler - Bausch & Lomb Incorporated (196603781)

Establishment

Name	Address	ID/FEI	Business Operations
Bausch & Lomb Incorporated		807927397	MANUFACTURE(24208-002)

Establishment

Name	Address	ID/FEI	Business Operations
Alliance Medical Products, Inc		102688657	ANALYSIS(24208-002) , LABEL(24208-002) , MANUFACTURE(24208-002) , PACK(24208-002)

Revised: 10/2012 Bausch & Lomb Incorporated