

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-640

MEDICAL REVIEW

Medical Officer's Review of NDA 21-640
Amendments 22

**NDA 21,640
Amendment 22**

Submission Date: May 4, 2004
Review Date: May 5, 2004

Sponsor:

ISTA Pharmaceuticals
15279 Alton Parkway
Suite 100
Irvine, California, 92618

Marvin J. Garrett
(949) 788-5303

Drug:

Vitrase (hyaluronidase for injection)

Pharmacologic Category:

adjuvant

**Dosage Form and
Route of Administration:**

Injection

Submitted:

Changes to the Insert, Vial and Kit Carton
requested by the Agency.

Amendment 22 contains the changes requested by the Agency per a telecon with the sponsor on May 4, 2004. The requested changes address the issues raised by the Office with regards to the pregnancy category and the preclinical animal data contained in the label. The sponsor has accepted all of the changes proposed by the Agency. The revised package insert submitted by the sponsor is attached.

**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.

Vitrasc 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

Vitrasc 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

Distributed by: Allergan Inc. Irvine, CA 92612

Under license from: ISTA Pharmaceuticals, Inc. Irvine, CA 92618

Manufactured by: Cardinal Health Albuquerque, NM 87109

NDA 21-640

Page 8

Comments/Recommendations:

The label submitted by the sponsor is acceptable and recommended for approval.

Jennifer D. Harris, MD
Medical Officer

cc:

NDA 21-640

HFD-550/Div Files

HFD-550/CSO/Gorski

HFD-550/CHEM/Rodriguez

HFD-550/MO/Harris

HFD-550/SMO/Chambers

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/s/

Jennifer Harris
5/5/04 01:54:30 PM
MEDICAL OFFICER

Wiley Chambers
5/5/04 02:47:48 PM
MEDICAL OFFICER

Medical Officer's Review of NDA 21-640
Amendments 17, 21 & 22

NDA 21,640
Amendment 17
Amendment 21
Amendment 22

Submission Date: April 23, 2004
Submission Date: April 30, 2004
Submission Date: May 4, 2004
Review Date: May 5, 2004

Sponsor:

ISTA Pharmaceuticals
15279 Alton Parkway
Suite 100
Irvine, California, 92618

Marvin J. Garrett
(949) 788-5303

Drug:

Vitrase (hyaluronidase for injection)

Pharmacologic Category:

adjuvant

**Dosage Form and
Route of Administration:**

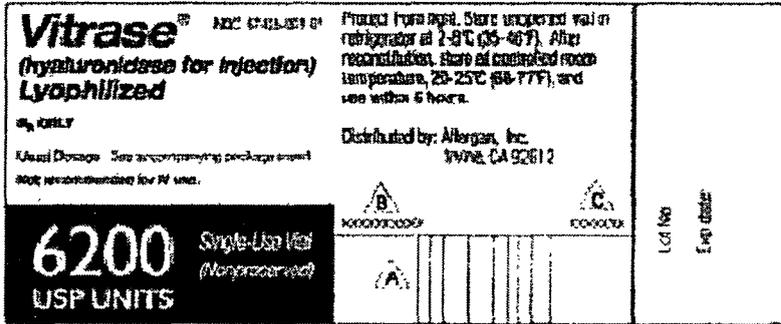
Injection

Submitted:

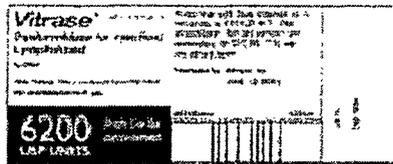
Amendment 17: Draft Mock Labeling for
Vial and Kit Carton
Amendment 21: Revised Mock Labeling for
Vial
Amendment 22 Final Draft Labeling, Insert,
Vial, Kit Carton

Amendment 17 contains draft mock labeling for the vial and kit carton. Based on discussions with the Division concerning the readability of the vial label, the sponsor revised this submission in Amendment 21. Amendment 21 removes all storage condition information and repositions the "Rx only" statement on the vial label. No changes were made to the kit carton in this amendment. After further discussions with the sponsor based on input from the Office, the sponsor has made further revisions to the vial and carton to add the source of the hyaluronidase (Ovine) to the labels. Additionally, the font sizes on the vial label have been revised further to enhance readability.

Vial and Kit Carton Label submitted in Amendment 17:

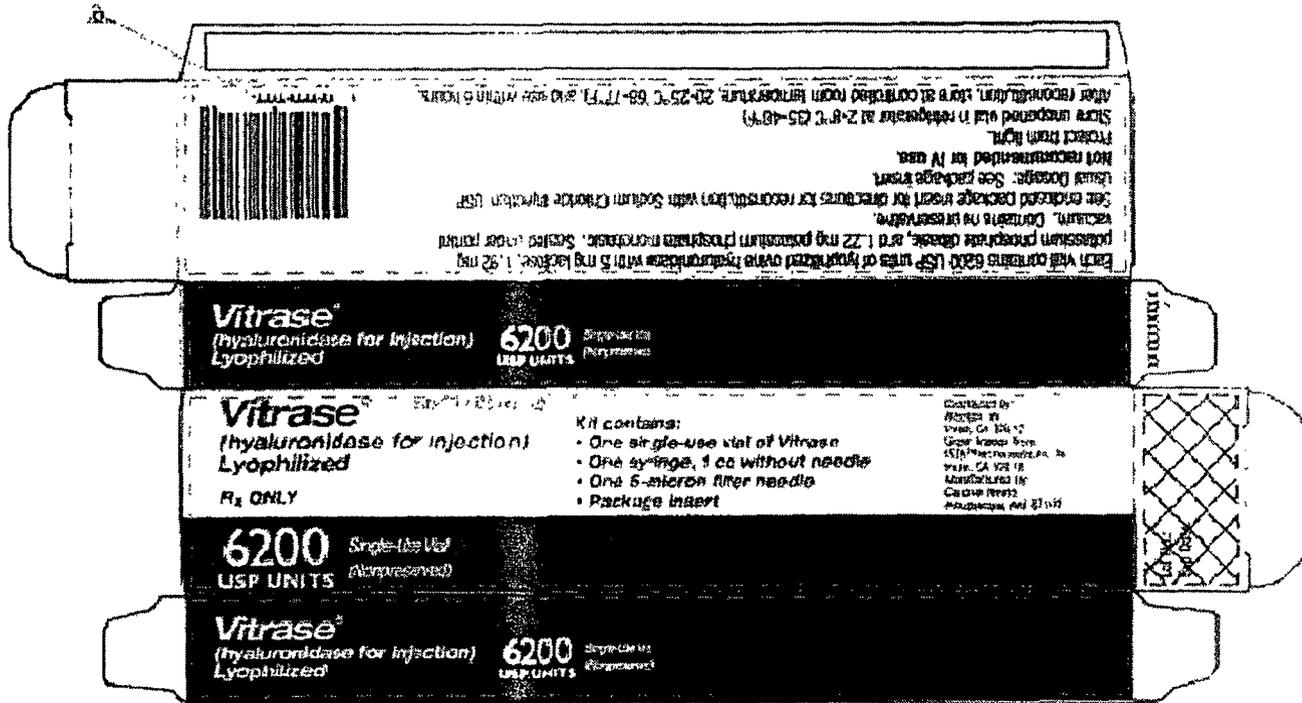


Label shown at 200%



Label shown at 100%

BEST POSSIBLE COPY



Each vial contains 6200 USP units of hyaluronidase (with 15 mg lactose, 1.92 mg potassium phosphate dibasic, and 1.22 mg potassium phosphate monobasic). Sterile, single vial, lyophilized. Contains no preservative. See enclosed package insert for directions for reconstitution with Sodium Chloride Injection, USP. Usual Dosage: See package insert. Not recommended for IV use. Product from BSN. Store unopened vial in refrigerator at 2-8°C (35-40°F). After reconstitution, store at controlled room temperature, 20-25°C (68-77°F), and use within 6 hours.

Vitraser
(hyaluronidase for injection)
Lyophilized

6200 USP UNITS

Single-use Vial
(Unpreserved)

Vitraser
(hyaluronidase for injection)
Lyophilized

6200 USP UNITS

Single-use Vial
(Unpreserved)

Rx ONLY

Kit contains:

- One single-use vial of Vitraser
- One syringe, 1 cc without needle
- One 6-gauge filter needle
- Package insert

Manufactured by
BSN
15151
Covina, CA 91724
Manufactured in
Covina, CA, USA

Vitraser
(hyaluronidase for injection)
Lyophilized

6200 USP UNITS

Single-use Vial
(Unpreserved)

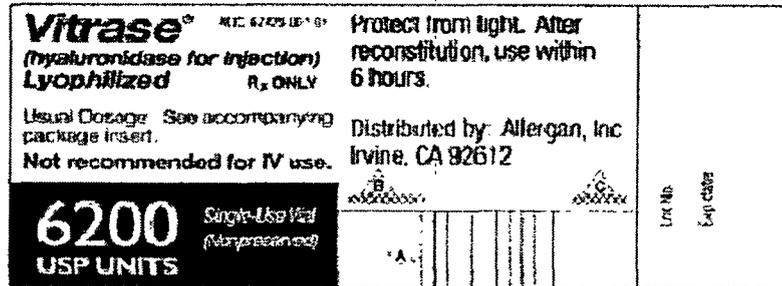
INKS



PMS 287 BLACK

© 2000 BSN, a division of BSN Corporation, BSN
The area with BSN denotes a sterile part number and copy code

Revised vial label submitted in Amendment 21:



Label shown at 200%



Label shown at 100%

 Replace with barcode

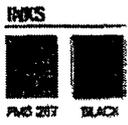
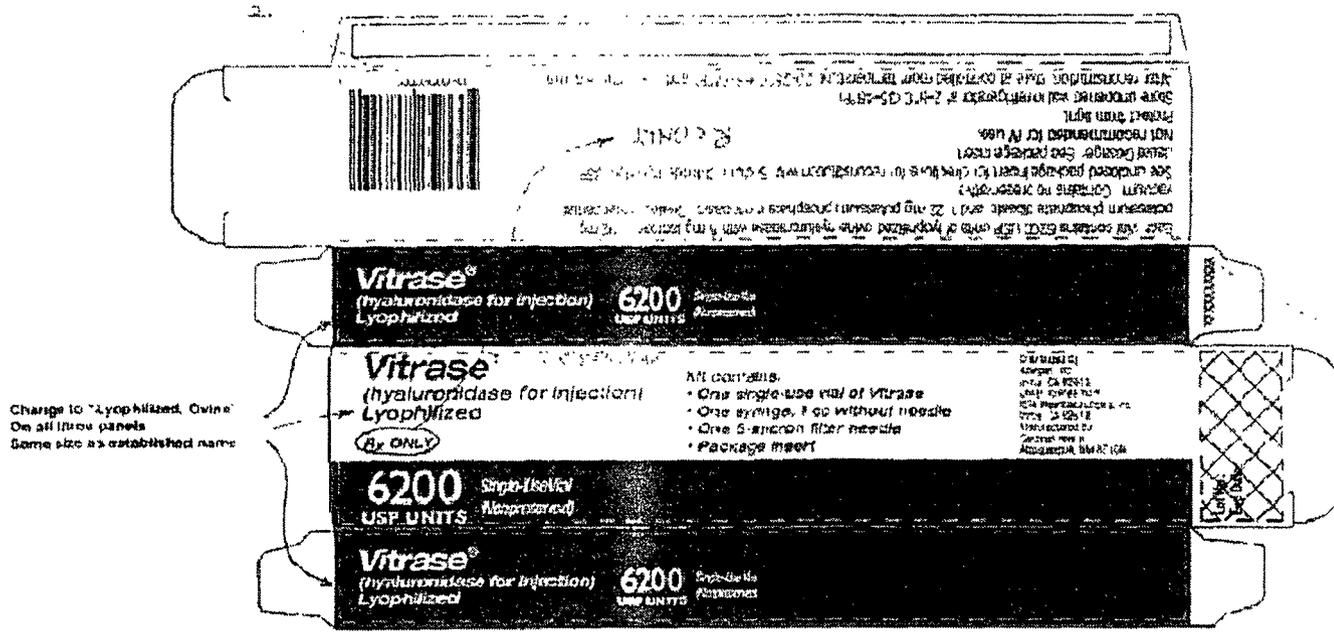
 Denotes placement of label part number and copy code

INXS



FMS 287

Final Draft Vial and Kit Carton Label submitted in Amendment 22:



1. MCN number is correct per carton area.
2. The text is in the correct font and size.

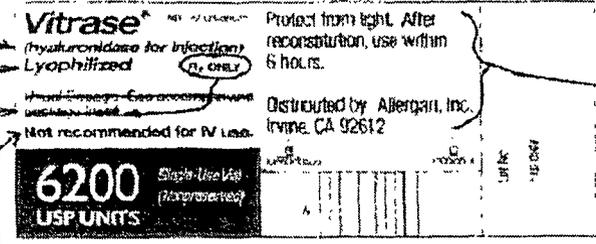
1. Established name to be 1/2 size of trade name

2. Change to "Lyophilized, Ovine". Same size as established name.

3. Remove phrase "Usual Dosage..."

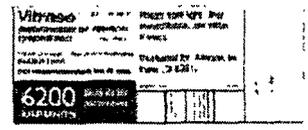
4. Move Rx Only, down and to the left margin. Make font larger.

5. Make phrase "Not Recommended..." in larger font



Label shown at 200%

6. Right text area enlarged to largest font possible.



Label shown at 100%

A. Replace with barcode

B. Indicates placement of label text number and copy code



Comments/Recommendations:

The vial and kit carton labels contained in Amendment 22 are acceptable and recommended for approval.

Jennifer D. Harris, MD
Medical Officer

CC:

NDA 21-640
HFD-550/Div Files
HFD-550/CSO/Gorski
HFD-550/CHEM/Rodriguez
HFD-550/MO/Harris
HFD-550/SMO/Chambers

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/s/

Jennifer Harris
5/5/04 01:50:58 PM
MEDICAL OFFICER

Wiley Chambers
5/5/04 02:08:55 PM
MEDICAL OFFICER

Medical Officer's Review of NDA 21-640
120-day Safety Update

NDA 21-640
Amendment 20

Submission: 4/27/04
Review Completed: 4/28/04

Proposed Tradename:

Vitrase (hyaluronidase for injection)

Generic Name:

ovine hyaluronidase

Sponsor:

ISTA Pharmaceuticals
15279 Alton Parkway
Suite 100
Irvine, California 92618

Pharmacologic Category:

adjuvant

Proposed Indication:

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.

Submitted:

120-day Safety Update

The safety information submitted in the original NDA and subsequent amendments is current. There is no new safety information to report in this safety update.

Recommendations:

The original conclusions reached in the NDA review remain unchanged. NDA 21-640 is recommended for approval.

Jennifer D. Harris, M.D.
Medical Officer

NDA 21-640
HFD-550/Div Files
HFD-550/MO/Harris
HFD-550/SMO/Chambers
HFD-725/Biostats/Rahman
HFD-550/Chem/Rodriguez
HFD-550/PharmTox/ChenZ
HFD-550/PM/Gorski

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/s/

Jennifer Harris
4/29/04 04:23:22 PM
MEDICAL OFFICER

Wiley Chambers
4/30/04 04:49:28 PM
MEDICAL OFFICER

**Medical Officer's Review of NDA 21-640
Financial Disclosure**

NDA 21-640
Amendment 14

Submission: April 22, 2004
Review Completed: April 23, 2004

Proposed Tradename:

Vitrase (hyaluronidase for injection)

Generic Name:

ovine hyaluronidase

Sponsor:

ISTA Pharmaceuticals
15279 Alton Parkway
Suite 100
Irvine, California 92618

Pharmacologic Category:

adjuvant

Submitted:

Financial disclosure statements for investigators for study ISTA-VIT-CS04: Clinical Evaluation of Hypersensitivity Reaction to Vitrase (hyaluronidase for injection).

Financial disclosure statements have been submitted for the following individuals.

*principle investigator, sensitization evaluator
investigator, sensitization evaluator
investigator, test article administrator
investigator, test article administrator*

ISTA Pharmaceuticals has certified that they have not entered into any financial arrangement with the listed clinical investigators. They have also certified that neither the investigators nor their spouses or dependent children have any financial interests in ISTA Pharmaceuticals or Vitrase. Therefore, there is no cause to question the results of this study based on monetary gain.

Recommendations:

The original conclusions reached in the NDA review remain unchanged. NDA 21-640 is recommended for approval.

Jennifer D. Harris, MD
Medical Officer

cc

NDA 21-640
HFD-550/Div Files
HFD-550/CSO/Gorski
HFD-550/CHEM/Rodriguez
HFD-550/MO/Harris

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Jennifer Harris
4/28/04 08:16:16 AM
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Wiley Chambers
4/29/04 04:13:30 PM
MEDICAL OFFICER

Medical Officer's Review of NDA 21-640
Amendments 12 and 15

NDA 21,640
Amendment 12
Amendment 15

Submission Date: April 13, 2004
Submission Date: April 22, 2004
Review Date: April 23, 2004

Sponsor:

ISTA Pharmaceuticals
15279 Alton Parkway
Suite 100
Irvine, California, 92618

Marvin J. Garrett
(949) 788-5303

Drug:

Vitrase (hyaluronidase for injection)

Pharmacologic Category:

adjuvant

Dosage Form and
Route of Administration:

Injection

Submitted:

Amendment 12: Revised Draft Labeling for
Insert, Vial Label, Kit Carton
Amendment 15: Draft Labeling, Package
Insert

Amendment 12 submitted by the sponsor requests wording to be added to the adverse event section concerning events reported as a result of _____ of Vitrase.

Following is the subsequent draft label submitted by the sponsor in Amendment 15. Reviewer recommended deletions are delineated in the comments column and additions are in red within the review.

7 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

Comments/Recommendations:

The label submitted by the sponsor are acceptable. The label is recommended for approval.

**Jennifer D. Harris, MD
Medical Officer**

cc:

NDA 21-640
HFD-550/Div Files
HFD-550/CSO/Gorski
HFD-550/CHEM/Rodriguez
HFD-550/MO/Harris
HFD-550/SMO/Chambers

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/s/

Jennifer Harris
4/26/04 01:30:58 PM
MEDICAL OFFICER

Wiley Chambers
4/27/04 08:57:21 AM
MEDICAL OFFICER

**Medical Officer's Review of NDA 21-640
Amendment 11**

NDA 21-640
Medical Officer's Review

Submission: 3/31/04
Review Completed: 4/2/04

Proposed Tradename:

Vitrise (hyaluronidase for injection)

Generic Name:

ovine hyaluronidase

Sponsor:

ISTA Pharmaceuticals
15279 Alton Parkway
Suite 100
Irvine, California 92618

Pharmacologic Category:

adjuvant

Proposed Indication:

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.

Submitted:

Study report ISTA-VIT-CS04, the Clinical Evaluation of Hypersensitivity Reaction to Vitrise which is in response to the Agency's Discipline Review Letter dated February 4, 2004. The protocol for this study was submitted the division as a Special Protocol Assessment on January 13, 2004.

Title: Clinical Evaluation of Hypersensitivity Reaction to Vitrase (hyaluronidase for injection)

Principle Investigator: Karl Beutner, M.D., Ph.D.
Solano Clinical Research
635 Anderson Road
Suites 15 and 17
Davis, California 95616

Objective: The objective of this study was to rule out (with 95% confidence) a greater than 10% incidence of hypersensitivity to Vitrase following a single intradermal injection of 3 USP units Vitrase. Less than or equal to a 10% hypersensitivity response was considered acceptable.

Study Design: This was a Phase I, single center, single-dose, open-label, placebo controlled study of Vitrase's potential to produce a hypersensitive skin reaction in normal healthy volunteer subjects. Each subject received a single intradermal injection of 3 USP units Vitrase. Evidence of population hypersensitivity rate less than or equal to 10% was considered acceptable.

Test Articles:

The investigational test article was 3USP units of Vitrase in 30 microliters of sterile saline administered by intradermal injection. The control test article was 30 microliters of sterile saline (vehicle diluent for Vitrase) administered by intradermal injection. Vitrase was injected at one prepared site on the ventral surface of the left forearm and saline was injected at a marked location at least 10cm distal to the injection site for Vitrase.

Study Population – Inclusion and Exclusion Criteria

Inclusion Criteria

- Healthy male or female subjects at least 18 years of age
- Willing/able to return for all required study visits
- Willing/able to follow instructions of the study investigator and his/her staff
- Agree to avoid disallowed medications throughout the duration of the study
- For women capable of becoming pregnant: must agree to have urine pregnancy test performed at screening (must be negative), and must agree to use a medically acceptable form of birth control throughout the study duration and for at least one week prior to and after completion of the study. Women considered capable of becoming pregnant include all females who have experienced menarche and have not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).

- Signed informed consent form approved by Institutional Review Board.

Exclusion Criteria

- Have a known hypersensitivity to hyaluronidase (any source)
- Have a known hypersensitivity to bee sting
- Atopic individuals assessed by medical history
- Topical or systemic corticosteroids within 30 days of study entry
- Concurrent use of antihistamines or anti-inflammatory drugs, topical or systemic, during the study (treatment and follow-up stages)
- Have chronic urticaria or dermatography
- Have any active or chronic/recurrent disease likely to affect immune function
- Have a known blood dyscrasia or bone marrow suppression, a diagnosis of peptic ulcer disease, inflammatory bowel disease, or ulcerative colitis, or any uncontrolled/unstable pulmonary, cardiac, vascular, autoimmune, hepatic, renal, or central nervous system disease
- Have a history of abuse of alcohol/drugs within 6 months prior to the screening visit
- Are pregnant or nursing/lactating
- Have participated in any other trial of an investigational drug or device within 30 days prior to enrollment

Study Masking

Treatment was open-label, both to the investigator and the patient.

Outcome Variable

A positive reaction to injected test article was defined as a wheal with pseudopods appearing within five minutes after injection, persisting for 20-30 minutes and accompanied by localized itching. Transient vasodilation (e.g., erythema) at an injection site was not considered a positive reaction. A subject assessed by the investigator or sub-investigator as having evidence of hypersensitivity at the Vitrase injection site, but not at the saline injection site, was considered to be positive for Vitrase hypersensitivity (a responder). A subject with negative assessments at both injection sites, positive assessments at both sites, or positive saline assessment with negative Vitrase assessment was considered to be negative for Vitrase hypersensitivity (a non-responder).

**APPEARS THIS WAY
ON ORIGINAL**

Study Schedule

Visit No.	1	2	2
Procedures	Screening (Day -3 to - 1)	Day 1 Baseline	Day 1 Post injection
Treatment Days		X	
Informed Consent	X		
Medical History/ Demographics	X		
Inclusion/ Exclusion Criteria		X	
Physical Examination	X		
Vital Signs (BP, HR, RR, temperature)	X		
Urine Pregnancy Test ^a	X		
Concomitant Medications		X	
Vitrase and Saline injection		X	
Assess Adverse Events			X
Assess hypersensitivity response			X
Discharge from the Study			X

^aApplies only to females capable of becoming pregnant.

Subject Disposition and Demographics

Seventy-six (76) people were screened and sixty-five (65) subjects were enrolled and treated with test articles. All enrolled subjects completed the study.

Baseline Demographics

Number of Subjects	65
Age	
Mean	23.5
STD	8.5
Median	21
Range	(18-55)
Gender	
Male	45 (69%)
Female	20 (31%)
Race	
Caucasian	36 (55%)
American Indian	0
Hispanic	3 (5%)
African American	2 (3%)
Asian or Pacific Islander	15 (23%)
Other	9 (14%)

Outcome Results

		Vitrase Injection Site N (%)	Saline Injection Site N (%)
Wheal with psuedopods at 5 minute post-injection?	yes	4 (6%)	6 (9%)
	no	61 (94%)	59 (91%)
Wheal with psuedopods persist for 20 to 30 minutes post-injection with localized itching?	yes	0	0
	no	65 (100%)	65 (100%)
Positive Responder? (evidence of sensitization reaction at Vitrase Injection site and Absence of reaction at saline injection site)	Yes	0	
	no	65 (100%)	

Reviewer's Comments:

All four of the subjects (subject No. 003, 004, 005, and 006) who had a positive reaction in the Vitrase group at 5 minutes also had a positive reaction to the saline injection. Per the protocol defined statistical evaluation, this was not considered a positive response. None of these subjects had a persistent reaction that lasted 20-30 minutes post-injection. Subject 006 had a history of asthma and allergy to sulfa drugs. There were no common traits identified among these subjects based on the review of the history and physical information provided.

Safety Evaluation

There were no adverse events or serious adverse events reported during the study.

Conclusions/Recommendations:

There were no type I hypersensitivity reactions observed during this trial. The results rule out (with 95% confidence) a greater than 10% incidence of hypersensitivity to Vitrase following a single intradermal injection of 3 USP units.

It is recommended that the hypersensitivity test section of the label reflect the method and amount of Vitrase used for testing in this trial.

Jennifer D. Harris, M.D.
Medical Officer

NDA 21-640
HFD-550/Div Files
HFD-550/MO/Harris
HFD-550/SMO/Chambers
HFD-725/Biostats/Rahman
HFD-550/Chem/Rodriguez
HFD-550/PharmTox/ChenZ
HFD-550/PM/Gorski

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Wiley Chambers
4/7/04 11:46:47 AM
MEDICAL OFFICER

Medical Officer's Review of NDA 21-640
Amendment 8

**NDA 21,640
Amendment 8**

Submission Date: March 5, 2004
Received Date: March 8, 2004
Review Date: March 31, 2003

Sponsor:

ISTA Pharmaceutacals
15279 Alton Parkway
Suite 100
Irvine, California, 92618

Marvin J. Garrett
(949) 788-5303

Drug:

Vitrase (hyaluronidase for injection)

Pharmacologic Category:

adjuvant

**Dosage Form and
Route of Administration:**

Injection

Submitted:

Revised Labeling

Following is the revised labeling submitted by the sponsor. Reviewer recommended deletions are delineated in the comments column and additions are in red within the review.

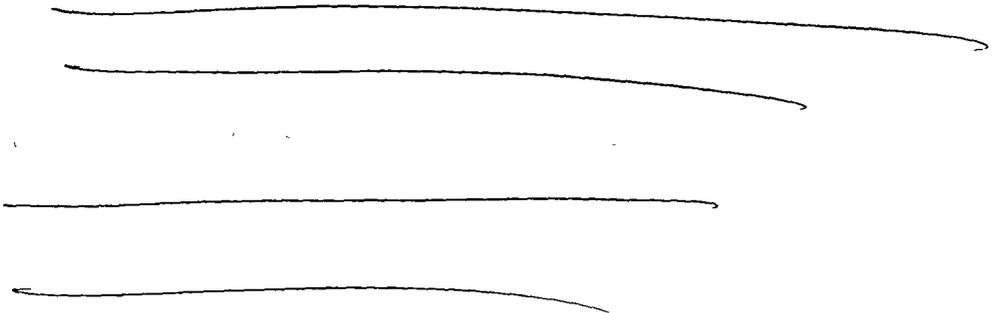
**Vitrase
(hyaluronidase for injection)**

DESCRIPTION

.....

.....

6 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.



Comments/Recommendations:

The changes submitted by the sponsor are acceptable. The label is recommended for approval after deleting the reference to the _____ in the Description section.

Jennifer D. Harris, MD
Medical Officer

cc:
NDA 21-640
HFD-550/Div Files
HFD-550/CSO/Gorski
HFD-550/CHEM/Rodriguez
HFD-550/MO/Harris
HFD-550/SMO/Chambers

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Wiley Chambers
4/7/04 12:25:05 PM
MEDICAL OFFICER

CLINICAL REVIEW of NDA 21-640

Original Application

Submitted: August 4, 2003
Received: August 7, 2003

Review completed: December 1, 2003

Reviewer: Jennifer D. Harris, MD

Proposed Name: Vitrase (ovine hyaluronidase)
Established Name: Hyaluronidase for injection

Sponsor: Ista Pharmaceuticals
15279 Alton Parkway
Suite 100
Irvine, California 92618

Contact: Marvin J. Garrett
(949) 727-0833

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Executive Summary

I. Recommendations

A. Recommendation on Approvability

NDA 21-640 is recommended for approval from a clinical prospective with the labeling identified in this review. The indication as described in the labeling proposed in this review is supported by Agency's evaluation of the National Academy of Sciences-National Research Council, Drug Efficacy Study Group's reports hyaluronidase (DESI 6343, 6714, 7933) as well as other available evidence. The conclusion was published in the Federal Register on September 23, 1970 (35 FR 14800-1).

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

No additional Phase 4 studies are recommended. There are no additional recommended risk management steps for this product.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Vitrase (hyaluronidase for injection) — Units is a protein enzyme prepared from ovine testicular tissue. It is administered as an injection but not for intravenous use. The safety and efficacy is supported by the DESI evaluation for use 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.

B. Efficacy

The efficacy is supported by the DESI evaluations of hyaluronidase (mammalian origin) (DESI 6343, 6714, 7933) for use 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. The

Published literature for hyaluronidase is consistent with the DESI evaluation. There are no other drug products approved for these indications. There are no unresolved efficacy issues.

Executive Summary Section**C. Safety**

Hyaluronidase injection and hyaluronidase for injection have been safely marketed for over 50 years with millions of uses per year. The safety is supported by the DESI evaluation for use 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.

There are no new safety concerns or relevant adverse events that have not previously been included in the labeling. The most serious labeled adverse events have been hypersensitivity reactions including anaphylactic-like reactions. These events vary in severity. In several large published series, the frequency of reported events has been less than 0.1%. The more severe events occur even less frequently. Furosemide, the benzodiazepines and phenytoin have been found to be incompatible with hyaluronidase. Hyaluronidase should not be used to enhance the absorption and dispersion of dopamine and/or alpha agonist drugs because of the potential enhancement of their pharmacologic effects. Hyaluronidase should not be used intravenously because it is inactivated by blood product constituents. It should not be used on the cornea of the eye because the structural changes are not predictable.

D. Dosing

Established dosing has been in the range of 50 to 300 units. The most typical dose is 150 units. Careful dose ranging studies have never been conducted.

E. Special Populations

Although there have been suggestions in the literature of differences due to age and racial factors, the differences have never been supported by the data in clinical studies. There are no known differences in dose response due to age, gender, racial or ethnic factors. Studies supporting the proposed indications have been conducted in pediatric patients including premature infants.

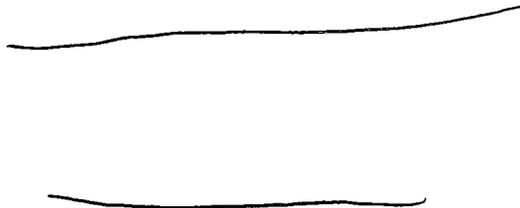
Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Vitrace (Hyaluronidase for injection) — Units is a protein enzyme prepared from ovine testicular tissue. It is administered as an injection but not for intravenous use. The sponsor's proposed use 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. The product would be indicated for all age groups including neonates.

B. State of Armamentarium for Indication(s)



The labeled indications as described in the Federal Register Notice following the DESI review, included:

1. For use as an adjunct to increase the absorption and dispersion of other injected drugs;
2. For hypodermoclysis;
3. As an adjunct in subcutaneous urography for improving the resorption of radiopaque agents.

C. Important Milestones in Product Development

Vitrace (hyaluronidase for injection), was originally submitted in October, 2002 (NDA 21-414,) for the indication of clearance of vitreous hemorrhage. An approvable letter was issued and there have been no additional studies submitted to the agency to support a vitreous hemorrhage indication.

This current NDA for Vitrace (hyaluronidase for injection) has been submitted to the agency for the indications supported in the DESI review for hyaluronidase.

Clinical Review Section

The DESI Reviews (3) were completed in late 1960s; and these reviews supported the effectiveness of this drug product for use as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; as an adjunct in subcutaneous urography for improving resorption of radiopaque agents;

D. Other Relevant Information

Vitrax (hyaluronidase for injection) received marketing approval for ophthalmic intravitreal injection on November 13, 1998 in Mexico. However, it has not been marketed to date.

E. Important Issues with Pharmacologically Related Agents

Not applicable

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

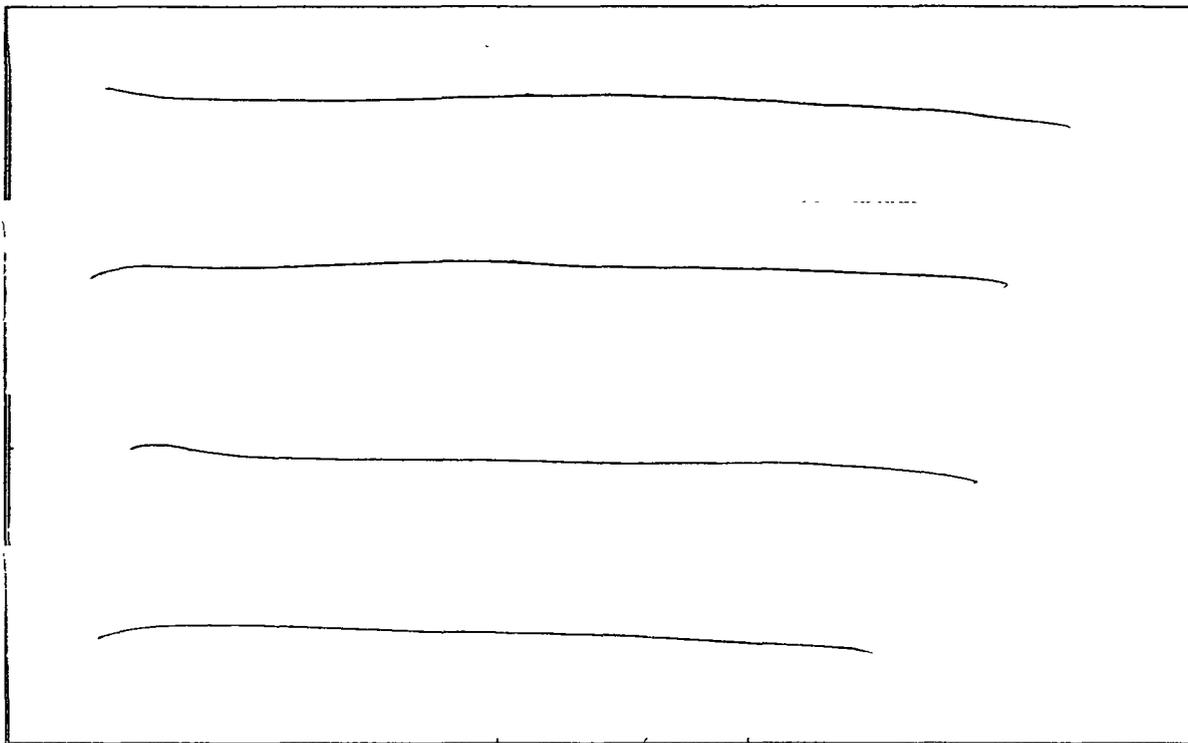
Drug Product Composition

Ingredients	Amount/mL
Ovine Hyaluronidase	— USP units *
Potassium Phosphate Dibasic USP/EP	1.92 mg
Monobasic, Potassium Phosphate, NF/EP	1.22 mg
Lactose Monohydrate NF/EP	5.0 mg
Water for Injection USP/EP	QS

Regulatory Drug Product Specification

Test	Method	Release Specification

Clinical Review Section



There are no other clinically relevant issues related to Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews.

Ovine versus Bovine

The hyaluronidases are a family of β , 1-4 endoglucosaminidases that depolymerize hyaluronic acid (HA) and chondroitin sulfate. Multiple literature studies have demonstrated that a single gene for PH-20 is present in the genome of mammals. The hyaluronidases present in extracts from mammalian testes are all encoded by the PH-20 gene. No significant differences between the mammalian sources of hyaluronidase in activity have been identified.

The USP monographs groups all mammalian hyaluronidases into the same monograph.

III. Human Pharmacokinetics and Pharmacodynamics

Clinical Review Section

A. Pharmacokinetics

Hyaluronidase acts locally. No new pharmacokinetic or bioavailability studies have been conducted. Hyaluronidase is inactivated by the components found in blood.

B. Pharmacodynamics

This section is not applicable for this product. Hyaluronidase acts locally and is inactivated with systemic distribution. Plasma levels do not correlate with clinical efficacy or ocular safety.

IV. Description of Clinical Data and Sources

A. Overall Data

The data sources reviewed for the purposes of this clinical review included the evaluation reports of the DESI reviews (6343, 6714 and 7933), postmarketing reports and literature reports.

B. Tables Listing the Clinical Trials

No new clinical studies have been submitted.

C. Postmarketing Experience

This drug has not been marketed. There is no post marketing experience with this drug.

FDA Spontaneous Reporting System

The events listed below are all reported ADRs with a frequency of 2 or more, in which hyaluronidase was either the primary or secondary drug listed. It should be noted that hyaluronidase was never the only drug involved, and the distribution consisted of tens of millions of doses over 50 years.

SOC	PT	Total Events	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
General Disorders	Drug Ineffective	67	0	50	0	0	0	0	50
General Disorders	Injection Site Reaction NOS	42	0	42	0	0	0	0	42
Skin And Subcutaneous Tissue	Face Oedema	26	0	20	12	2	0	0	8
Skin And Subcutaneous Tissue	Dermatitis NOS	23	0	23	0	0	0	0	23
Eye Disorders	Conjunctivitis	23	0	23	2	0	0	0	23
Eye Disorders	Blindness	20	0	18	2	14	0	0	2
Eye Disorders	Eye Disorder NOS	14	0	14	1	3	0	0	11
Eye Disorders	Pupillary Disorder NOS	14	0	14	4	4	0	0	6

CLINICAL REVIEW NDA 21-640

Clinical Review Section

SOC	PT	Total Events	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
Respiratory/Thoracic	Apnea	12	0	12	8	1	0	1	8
General Disorders	Injection Site Necrosis	12	0	10	0	2	0	0	8
General Disorders	Edema NOS	12	0	6	0	3	0	0	3
Eye Disorders	Eyelid Ptosis	12	0	12	0	0	0	0	12
Vascular Disorders	Hypertension NOS	11	1	11	4	1	0	0	7
General Disorders	Pain NOS	11	0	11	1	1	0	0	9
Gastrointestinal Disorder	Vomiting NOS	11	0	6	2	0	0	0	4
Respiratory/Thoracic	Dyspnea	10	0	6	2	0	0	2	2
Eye Disorders	Visual Acuity Reduced	10	0	10	2	6	0	0	2
Immune System Disorders	Hypersensitivity NOS	9	0	9	2	1	0	0	7
Eye Disorders	Eyelid Edema	9	0	9	3	3	0	0	3
Respiratory/Thoracic	Pulmonary Edema NOS	8	0	8	6	0	0	4	2
General Disorders	Injection Site Edema	8	0	8	0	2	0	0	6
Gastrointestinal Disorder	Nausea	8	0	6	2	0	0	0	4
General Disorders	Malaise	7	0	2	1	0	0	0	1
Vascular Disorders	Hypotension NOS	6	0	4	3	0	0	0	4
Skin And Subcutaneous Tissue	Angioneurotic Oedema	6	0	6	0	0	0	0	6
Skin And Subcutaneous Tissue	Urticaria NOS	6	0	4	0	0	0	0	4
Psychiatric Disorders	Confusional State	6	0	4	4	0	0	0	0
General Disorders	Injection Site Inflammation	6	0	6	0	0	0	0	6
General Disorders	Injection Site Mass	6	0	6	0	0	0	0	6
Eye Disorders	Amaurosis Fugax	6	0	6	0	0	0	0	6
Eye Disorders	Corneal Edema	6	0	6	0	6	0	0	0
Eye Disorders	Exophthalmos NOS	6	0	6	6	0	0	0	0
Eye Disorders	Iris Disorder NOS	6	0	6	0	6	0	0	0
Eye Disorders	Ophthalmoplegia NOS	6	0	6	2	0	0	0	4
Eye Disorders	Panophthalmitis	6	0	5	3	1	0	0	2
Eye Disorders	Pigment Dispersion Syndrome	6	0	6	0	6	0	0	0
Eye Disorders	Retinal Haemorrhage	6	0	6	0	4	0	0	2
Cardiac Disorders	Bradycardia NOS	6	0	4	2	0	0	0	3
Skin And Subcutaneous Tissue	Sweating Increased	5	0	2	2	0	0	0	0
Nervous System	Convulsions NOS	5	0	5	2	1	0	0	3
Eye Disorders	Eye Pain	5	0	3	3	0	0	0	0
Vascular Disorders	Vasodilatation	4	0	4	2	0	0	0	4
Psychiatric Disorders	Thinking Abnormal	4	2	2	0	0	0	0	0
Nervous System	Syncope Vasovagal	4	0	0	0	0	0	0	0
Nervous System	Visual Field Defect NOS	4	0	4	2	2	0	0	0
Immune System Disorders	Drug Hypersensitivity	4	0	4	4	0	0	0	0
General Disorders	Pyrexia	4	0	4	3	0	0	1	2
Eye Disorders	Amblyopia	4	0	4	0	1	0	0	3
Eye Disorders	Eye Haemorrhage NOS	4	0	4	2	0	0	0	2
Eye Disorders	Eye Movement Disorder NOS	4	0	4	2	0	0	0	2
Eye Disorders	Mydriasis	4	0	4	0	0	0	0	4
Eye Disorders	Vision Blurred	4	0	4	0	2	0	0	2
Eye Disorders	Visual Disturbance NOS	4	0	4	0	2	0	0	2
Eye Disorders	Vitreous Haemorrhage	4	0	4	0	4	0	0	0
Ear And Labyrinth Disorders	Tinnitus	4	0	4	0	0	0	0	4
Cardiac Disorders	Tachycardia NOS	4	0	4	3	1	0	0	1
Skin And Subcutaneous	Pruritus	3	0	3	0	0	0	0	3

CLINICAL REVIEW NDA 21-640

Clinical Review Section

SOC	PT	Total Events	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
Tissue									
Skin And Subcutaneous Tissue	Purpura NOS	3	0	0	0	0	0	0	0
Skin And Subcutaneous Tissue	Rash Erythematous	3	0	3	3	0	0	0	1
Psychiatric Disorders	Nervousness	3	0	2	0	0	0	0	2
Nervous System	Loss Of Consciousness	3	0	3	1	0	0	2	1
Nervous System	Paraesthesia	3	0	3	1	1	0	0	1
Investigations	Blood Pressure Increased	3	0	3	1	0	0	1	2
Eye Disorders	Eye Burns NOS	3	0	3	0	3	0	0	2
General Disorders	Chest Pain	3	0	3	2	0	0	1	2
General Disorders	Localised Edema	3	0	3	3	0	0	0	0
Gastrointestinal Disorder	Abdominal Pain NOS	3	0	1	1	0	0	0	1
Gastrointestinal Disorder	Dysphagia	3	0	3	2	0	0	0	1
Eye Disorders	Papilloedema	3	0	3	0	0	0	0	3
Blood And Lymphatic System	Eosinophilia	2	0	2	2	0	0	0	0
Vascular Disorders	Haemorrhage NOS	2	0	1	0	0	0	0	1
Skin And Subcutaneous Tissue	Cold Sweat	2	0	2	2	0	0	0	0
Skin And Subcutaneous Tissue	Vitiligo	2	0	2	0	0	0	0	2
Respiratory/Thoracic	Hypoventilation	2	0	2	1	0	0	0	1
Respiratory/Thoracic	Tachypnoea	2	0	2	1	0	0	1	1
Renal And Urinary Disorders	Pollakiuria	2	0	2	0	0	0	0	2
Psychiatric Disorders	Mental Status Changes	2	0	2	2	0	0	2	0
Nervous System	Disorders Akinesia	2	0	2	1	0	0	0	1
Nervous System	Cerebrovascular Accident	2	0	2	2	0	0	0	0
Nervous System	Dizziness	2	0	1	1	0	0	1	0
Nervous System	Dysarthria	2	0	2	0	0	0	0	2
Nervous System	Intracranial Haemorrhage NOS	2	2	2	0	0	0	0	0
Nervous System	Neurological Disorder NOS	2	0	2	0	0	0	0	2
Nervous System	Paralysis NOS	2	0	2	0	0	0	0	2
Nervous System	Peripheral Neuropathy NOS	2	0	2	1	1	0	0	0
Nervous System	Stupor	2	0	2	0	0	0	0	2
Nervous System	Tremor	2	0	2	1	0	0	0	1
Nervous System	Trismus	2	0	2	0	0	0	0	2
Musculoskeletal And Connective Tissue	Back Pain	2	0	2	0	0	0	0	2
Investigations	Blood Pressure Decreased	2	0	2	1	0	0	0	1
Investigations	Computerised Tomogram Abnormal	2	0	2	1	0	0	0	1
Investigations	Intraocular Pressure Increased	2	0	2	2	0	0	0	0
Investigations	Oxygen Saturation Decreased	2	0	2	0	0	0	0	2
Investigations	Pupillary Light Reflex Tests Abnormal	2	0	2	1	0	0	0	1
Injury, Poisoning	Bhster	2	0	2	2	0	0	0	2
Injury, Poisoning	Delayed Recovery From Anaesthesia	2	0	2	0	0	0	2	0
Injury, Poisoning	Medication Error	2	0	1	0	0	0	0	1
Infections And Infestation	Eye Infection Staphylococcal	2	0	2	2	0	0	0	0
Infections And Infestation	Infection NOS	2	0	2	2	0	0	0	1

CLINICAL REVIEW NDA 21-640

Clinical Review Section

SOC	PT	Total Events	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
Infections And Infestation	Meningitis	2	0	2	0	0	0	2	0
Infections And Infestation	Pharyngitis	2	0	2	0	0	0	0	2
Immune System Disorders	Anaphylactic Reaction	2	0	2	2	0	0	0	0
General Disorders	Condition Aggravated	2	0	2	1	0	0	0	1
General Disorders	Discomfort NOS	2	0	2	0	0	0	0	2
General Disorders	Injection Site Atrophy	2	0	2	0	0	0	0	2
General Disorders	Injection Site Hypersensitivity	2	0	2	0	0	0	0	2
General Disorders	Injection Site Pain	2	0	2	0	0	0	0	2
General Disorders	Tenderness NOS	2	0	2	2	0	0	0	0
Eye Disorders	Blindness Transient	2	0	2	0	0	0	0	2
Eye Disorders	Blindness Unilateral	2	0	2	0	0	0	0	2
Eye Disorders	Ocular Retrobulbar Haemorrhage	2	0	2	0	2	0	0	0
Eye Disorders	Optic Disc Haemorrhage	2	0	2	2	0	0	0	0
Eye Disorders	Optic Nerve Cupping	2	0	2	2	0	0	0	0
Eye Disorders	Optic Nerve Disorder NOS	2	0	2	2	0	0	0	0
Eye Disorders	Orbital Oedema	2	0	2	2	0	0	0	0
Eye Disorders	Parophthalmia	2	0	2	2	0	0	0	0
Eye Disorders	Pupil Fixed	2	0	2	0	0	0	0	2
Eye Disorders	Retinal Artery Occlusion	2	0	2	0	2	0	0	0
Eye Disorders	Retinal Artery Thrombosis	2	0	2	0	0	0	0	2
Eye Disorders	Retinal Exudates	2	0	2	0	2	0	0	0
Eye Disorders	Retinal Oedema	2	0	2	0	2	0	0	0
Eye Disorders	Retinal Vascular Disorder NOS	2	0	2	0	2	0	0	0
Eye Disorders	Uveitis NOS	2	0	2	1	0	0	0	2
Cardiac Disorders	Cyanosis NOS	2	0	2	2	0	0	0	0
Cardiac Disorders	Supraventricular Tachycardia	2	0	2	2	0	0	1	1

Reviewer's Comments: *The most common reports are that the drug product is ineffective. The next most common reported adverse events are consistent with allergic reactions which may have occurred due to hyaluronidase or with the co-administered drug product. Hyaluronidase can increase the capillary permeability caused by an immediate hypersensitivity reaction to another agent.*

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Review Section

- D. Literature Review**
Current literature for hyaluronidase has been reviewed. The published literature is consistent with the DESI evaluation.

V. Clinical Review Methods

- A. How the Review was Conducted**
This review was conducted by re-reviewing the DESI findings and conclusions. A Medline search was also conducted and all relevant articles were reviewed.
- B. Overview of Materials Consulted in Review**
The DESI report is located on microfiche in the CDER library. The findings were published in the Federal Register. The safety database of the marketed products were reviewed in Datamart. Copies of published articles on hyaluronidase were reviewed following a Medline search of hyaluronidase use.
- C. Overview of Methods Used to Evaluate Data Quality and Integrity**
There are no new studies to support this application.
- D. Were Trials Conducted in Accordance with Accepted Ethical Standards**
There were no trials conducted to support this NDA.
- E. Evaluation of Financial Disclosure**
There is no reported financial disclosure information. There are no new studies submitted.

VI. Integrated Review of Efficacy

- A. Brief Statement of Conclusions**
The published literature reviewed is consistent with the DESI evaluation. There are no other drug products approved for these indications. There are no unresolved efficacy issues.
- B. General Approach to Review of the Efficacy of the Drug**
The DESI evaluation and the literature are supportive of the safe and efficacious use of hyaluronidase.
- C. Detailed Review of Trials by Indication**

Clinical Review Section

There were no new clinical studies submitted.

D. Efficacy Conclusions

The efficacy is supported by the DESI evaluation for use 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.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The safety is supported by the DESI evaluation for use 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.

B. Description of Patient Exposure

In addition to the clinical trials used to support the safety and efficacy of hyaluronidase prior to the DESI evaluation, hyaluronidase has been marketed and used in millions of patients for over 50 years with relatively minimal adverse events.

C. Methods and Specific Findings of Safety Review

In addition to the findings in the DESI evaluation, current literature was evaluated. The adverse experiences reported to the agency associated with the use of hyaluronidase have also been reviewed.

D. Adequacy of Safety Testing

Based on the published literature and the marketing history of other hyaluronidase products, the safety database is considered large and adequate.

E. Summary of Critical Safety Findings and Limitations of Data

Hyaluronidase is considered safe when used as labeled.

VIII. Dosing, Regimen, and Administration Issues

Dosing varies with the indication and the amount of co-administered drug product. The usual range is between — and 300 units/mL of hyaluronidase with the co-administered drug.

IX. Use in Special Populations

Clinical Review Section

- A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation**
Gender effects have been investigated. No significant differences have been observed.

- B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy**
Differences based on race have been proposed; however, the data in controlled studies has not supported any differences based on age, race or ethnicity.

- C. Evaluation of Pediatric Program**
The product has been well studied in pediatric patients including neonates.

- D. Comments on Data Available or Needed in Other Populations**
Adequate and well controlled studies in the literature, supports the DESI indications.

X. Conclusions and Recommendations

- A. Conclusions**
NDA 21-640 is supported from a clinical prospective with the labeling identified in this review by the Agency's evaluation of the National Academy of Sciences-National Research Council, Drug Efficacy Study Group's reports on hyaluronidase (DESI 6343, 6714, 7933) as well as other available evidence. The conclusion was published in the Federal Register on September 23, 1970 (35 FR 14800-1).

- B. Recommendations**
NDA 21-640 is recommended for approval from a clinical prospective with the labeling identified in this review.

XI. Appendix

- A. Other Relevant Materials**
None.

- B. Individual More Detailed Study Reviews (If performed)**
None.

7 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jennifer Harris
12/3/03 01:08:32 PM
MEDICAL OFFICER

Wiley Chambers
12/8/03 04:00:13 PM
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