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*APPLICATION NUMBER:*  
**21-716**

**MEDICAL REVIEW**

**M.O. Review #4**  
**Pre-approval Safety Conference for NDA 21-716**

**Meeting Date:** June 22, 2005

**Review completed:** July 15, 2005

**Reviewer:** Lucious Lim, M.D., M.P.H.

**Proposed Tradename:** Hydase

**Established Name:** hyaluronidase injection

**Sponsor:** Prima Pharma, Inc.  
3443 Tripp Court  
San Diego, California 92121  
(858) 259-0717  
Contact: Anthony Dziabo

**Pharmacologic Category:** protein enzyme

**Proposed Indication:** 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.

**Dosage Form and Route of Administration:** solution for injection

**Pre-approval safety meeting for NDA 21-716:**

On June 22, 2005, the clinical team and representatives from the Office of Drug Safety met to discuss NDA 21-716's safety data. Following a discussion of the safety data, the submitted labeling was found to be adequate. It was determined that no risk management plan was indicated.

**Recommended Regulatory Action:**

NDA 21-716 is recommended for approval 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 with the labeling submitted.

Lucious Lim, M.D., M.P.H.  
Medical Officer

cc HFD-520/Div Files  
HFD-520/CSO/Gorski  
HFD-520/CHEM/Rodriguez  
HFD-520/CHEM TL/Ng  
HFD-520/PHARM/Chen  
HFD-430/DDRE/Bonnel  
HFD-520/MO/Lim  
HFD-520/CTL/Boyd  
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7/20/05 10:08:25 AM  
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**M.O. Review #3**  
**Amendment to Original NDA 21-716**

**Submitted:** January 12, 2005; June 30, 2005

**Received:** January 14, 2005; July 1, 2005

**Review completed:** July 7, 2005

**Reviewer:** Lucious Lim, M.D., M.P.H.

**Proposed Tradename:** Hydase

**Established Name:** hyaluronidase injection

**Sponsor:** Prima Pharma, Inc.  
3443 Tripp Court  
San Diego, California 92121  
(858) 259-0717  
Contact: Anthony Dziabo

**Pharmacologic Category:** protein enzyme

**Proposed Indication:** 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.

**Dosage Form and Route of Administration:** solution for injection

**Submitted:**

Submitted is the applicant's response to the approvable letter issued by the agency on April 21, 2004. These submissions are responses to CMC deficiencies and revised labeling based on previous review and discussion with the applicant.

**Reviewer's Comments:**

*The applicant has accepted all recommended changes to the labeling as requested by the Division. The submitted labeling (package insert and container and carton labeling) is acceptable.*

## Revised Package Insert Labeling as Requested by the Division

### **Hydase™** (hyaluronidase injection)

#### **DESCRIPTION**

Hydase™ is a preparation of purified bovine testicular hyaluronidase, a protein enzyme. The exact chemical structure of this enzyme is unknown. However, the amino acid sequence for the primary structure of the enzyme has been deduced from the sequence of purified peptides.

Hydase™ (hyaluronidase injection) is supplied as a sterile, colorless, odorless, ready for use solution. Each vial contains 150 USP units of hyaluronidase per mL with 8.5 mg sodium chloride, 1 mg edetate disodium, 0.4 mg calcium chloride, monobasic sodium phosphate buffer, sodium hydroxide to adjust the pH, and sterile water.

Hydase™ has an approximate pH of 6.9 and an osmolality of 275 to 305 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 C<sub>1</sub> of the glucosamine moiety and C<sub>4</sub> 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 anti-bodies. 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 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**

Hydase™ 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 Hydase™ (hyaluronidase 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 Hydase™ 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 Hydase™ to determine reproductive effects. No adequate and well controlled studies have been conducted with Hydase™ in pregnant women. Hydase™ 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 later growth, development, and functional maturation of the infant.

### **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 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 overhydration 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**

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

**Absorption and Dispersion of Injected Drugs**

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

It is recommended that appropriate references be consulted regarding physical or chemical incompatibilities before adding Hydase™ 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 Hydase™ (hyaluronidase injection) into rubber tubing close to needle.

An alternate method is to inject Hydase™ under skin prior to clysis. 150 U will facilitate absorption of 1,000 mL or more of solution. As with all parenteral fluid therapy, observe effect closely, with same precautions for restoring fluid and electrolyte balance as in intravenous injections. The dose, the rate of injection, and the type of solution (saline, glucose, Ringer 's, etc.) must be adjusted carefully to the individual patient. When solutions devoid of inorganic electrolytes are given by hypodermoclysis, hypovolemia may occur. This may be prevented by using solutions containing adequate amounts of inorganic electrolytes and/or controlling the volume and speed of administration.

Hydase™ 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 U of Hydase™ (hyaluronidase 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**

Hydase™ (hyaluronidase injection) is supplied sterile as 150 USP units of hyaluronidase per mL in a 2 mL clear glass vial and gray rubber stopper with blue flip off aluminum seal.

NDC 059690-019-01, 1 mL in a 2mL vial, as single use vials.

NDC 059690-019-06, 6 x 1 mL in a 2mL vial, as single use vials.

NDC 059690-019-24, 24 x 1 mL in a 2mL vial, as single use vials.

Not Recommended for IV Use.

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

DO NOT FREEZE.

**Rx Only**

**PrimaPharm, Inc.**  
3443 Tripp Court 26072  
San Diego, CA 92121 USA  
[www.primapharm.net](http://www.primapharm.net)

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\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

**Reviewer's Comments:**

*Mock-up for the 24 x 1 mL in a 2 mL vial carton labeling is provided in the submission.  
This mock-up is acceptable.*

**Recommended Regulatory Action:**

NDA 21-716 is recommended for approval 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.

It is recommended that NDA 21-716 be approved with the labeling submitted.

Lucious Lim, M.D., M.P.H.  
Medical Officer

cc HFD-520/Div Files  
HFD-520/CSO/Gorski  
HFD-520/CHEM/Rodriguez  
HFD-520/CHEM TL/Ng  
HFD-520/PHARM/Chen  
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TO: NDA 6-343, NDA 7-933, NDA 9-201, NDA 9-380  
NDA 21-593, NDA 21-640, NDA 21-665, NDA 21-716

FROM: Wiley A. Chambers, M.D.  
Deputy Director  
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

THROUGH: Gary J. Buehler  
Director  
Office of Generic Drugs

DATE: October 28, 2004

SUBJECT: Exclusivity Determination

This memo explains a decision by the Food and Drug Administration (FDA or Agency) to grant new chemical entity (NCE) status to Ista's hyaluronidase product, Vitrase (NDA 021640) and, consequently, to grant Vitrase 5-year marketing exclusivity under section 505(c)(3)(D) and 505(j)(5)(D) of the Federal Food, Drug, and Cosmetic Act (FDCA or Act).<sup>1</sup> This decision has been made based on consultations between this Division and the Office of Generic Drugs.

### Summary

Hyaluronidase protein products have not been fully characterized. The Agency has decided that NCE status, from which five-year exclusivity arises, is appropriate, because we have inadequate information to determine whether any active moiety in a (non-recombinant) hyaluronidase product is the same as any previously approved active moiety.

NCE status depends on whether a product contains a previously approved active moiety. Until the proteins are fully characterized, the Agency will generally presume (in the absence of persuasive evidence to the contrary) that each new naturally sourced (non-recombinant) protein product does not necessarily contain any of the same active moieties as a previously approved naturally sourced protein product.

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<sup>1</sup> Initially, FDA concluded that Vitrase was eligible for 3-year exclusivity, notified the company of this determination on or about September 2, 2004, and provided it and the pending applicants an opportunity to comment on the exclusivity determination. The Agency based this initial conclusion on a judgment that all hyaluronidase could be viewed as containing some or all of the same active moieties, and that Vitrase, therefore, would be entitled to 3-year exclusivity for performing required product-specific clinical allergenicity studies. The Agency had not decided what the scope of that exclusivity would be. Amphastar Pharmaceuticals, Inc. provided comments on this initial determination in letters dated September 10 and 20, 2004; Halozyme Therapeutics, Inc. submitted comments in a letter dated October 1, 2004, and comments were submitted on behalf of PrimaPharm, Inc. in a letter dated October 4, 2004. The Agency has taken into account all comments received.

Under this presumption, the Agency anticipates that all naturally sourced hyaluronidase products will receive NCE status. As NCE products, each hyaluronidase product would, therefore, receive 5-year marketing exclusivity. Since each would receive this exclusivity, however, the exclusivity would not block the submission and approval of 505(b)(2) applications for any other naturally sourced hyaluronidase product (unless an adequate showing was made that the next product contains at least one of the same active moieties as in the previously approved product).

The statute and regulations are silent on whether to grant NCE status to protein products that have not been fully characterized. While it may be unlikely that each product would prove to be an NCE if fully characterized, applying a presumption in favor of NCE status to protein products that have not been fully characterized, and, consequently, granting each five-year exclusivity, is permissible.

As a general matter, the Agency would likely impose substantial clinical safety and efficacy data requirements on each application to market a naturally sourced protein product for which the active moieties have not been fully characterized, akin to the requirements FDA would typically impose to support an application for an NCE.

In light of the generally substantial data requirements for NCEs, the data requirements for hyaluronidase products for the uses for which it has been approved to date are somewhat unusual. For the approval of these hyaluronidase products, the Agency and the applicants are able to rely not only on a Drug Efficacy Study Implementation (DESI) determination and on a long marketing history to assess the products' efficacy and safety (other than with regard to allergenicity, for which the Agency requires product-specific clinical data), but also on an in vitro assay to assess the activity levels of specific products. To obtain approval to market hyaluronidase for its current uses, each applicant generally must provide only equivalent clinical allergenicity data. These characteristics do not preclude treating each hyaluronidase as a separate NCE, however, until such time as the Agency receives sufficient evidence to demonstrate sameness of an active moiety.<sup>2</sup>

Therefore, FDA will apply a presumption in favor of NCE status to naturally sourced hyaluronidase products until full characterization occurs.

## **Hyaluronidase**

CDER and OCC have reviewed the history of hyaluronidase products to determine the eligibility for exclusivity of Ista's Vitrase. The threshold question is whether the product is a new chemical entity eligible for five year exclusivity under 21 CFR 314.108.

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<sup>2</sup> Providing each applicant with the same NCE exclusivity, and thus the same opportunity for approval, is also equitable in light of their equivalent data burdens. Should applicants seek approval for another use of hyaluronidase each likely would be required to provide a full suite of clinical safety and efficacy data.

Mammalian testicular hyaluronidase has been marketed for over 50 years. DESI findings established its effectiveness for three indications (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 Agency considers a current USP in vitro assay a valid surrogate for enzymatic activity of hyaluronidase for these three uses. Accordingly, the Agency considers this assay sufficient to demonstrate the efficacy of specific hyaluronidase products for these uses. In addition, the Agency considers mammalian testicular hyaluronidase safe, except for product-specific allergenicity, on the basis of available literature and a review of adverse event reports showing very few adverse events for hyaluronidase from various sources and in various formulations. As a result, the Agency only requires submittal of product-specific clinical allergenicity data to support marketing of hyaluronidase for these uses, and only if human safety data are otherwise unavailable for the specific product.<sup>3</sup>

At one time, there were ten legally marketed hyaluronidase products with NDAs. The last of these, Wyeth's Wydase, was withdrawn from the market about three years ago. FDA approved a 505(b)(2) applications for Ista Pharmaceuticals' (ovine sourced) Vitrase on May 4, 2004 and has now also approved Amphastar's (bovine sourced) Amphadase (submitted June 6, 2003) on October 26, 2004. The Agency currently is reviewing two other 505(b)(2) applications for natural, mammalian testicular sourced hyaluronidase: C

↵ and PrimaPharm Inc.'s (bovine sourced) Hydase (submitted October 17, 2003).

The specific animal source of the hyaluronidase for each previously marketed hyaluronidase drug product is not known. Wydase was labeled as bovine-sourced hyaluronidase. However, it is uncertain what the species sources were for other approved mammalian testicular hyaluronidase products (equine, ovine, bovine, etc). Although naturally occurring hyaluronidases have never been fully characterized with respect to chemical structure and impurities, the Agency understands that the amino acid sequence of a hyaluronidase molecule varies based both on the species and the tissue from which it is sourced. Further, it is unknown whether the amino acid sequence for the various types of proteins present in particular tissue may themselves vary (i.e., whether the known types of proteins are, in fact, categories of proteins that may vary in their amino acid sequence as well). In addition, the Agency has information indicating not only that hyaluronidase varies by species and tissue source, but also that the particular proteins in a given batch may vary from batch to batch.

### Grounds for New Chemical Entity Status

Agency regulations (21 CFR 314.108(a)) define "new chemical entity" (NCE) as:

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<sup>3</sup> For a more complete discussion of hyaluronidase, including its safety and effectiveness, see Steven Galson's May 5, 2004 letter responding to the October 23, 2003 citizen petition filed by Baxter Healthcare Corporation (docket 2003P-0494).

a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act.

They define "active moiety" as:

. . . the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

In short, NCEs can contain only previously unapproved (new) active moieties. In assessing whether a molecule is a new active moiety, FDA considers the covalently bonded portions of the molecule. When this approach is applied to protein products such as hyaluronidase, the Agency looks to the entire amino acid sequence as the active moiety. Accordingly, if the amino acid sequence of a molecule differs from that of a previously approved molecule, that molecule is a new active moiety. For a drug to be an NCE, none of the active moieties it contains can previously have been approved under 505(b).

### **Five-Year Exclusivity**

FDA's implementing regulations for marketing exclusivity at 21 CFR 314.108 provide that an approved new chemical entity is entitled to marketing exclusivity, under which no applicant may submit a 505(b)(2) application or abbreviated new drug application (ANDA) for a drug product that contains an active moiety found in the NCE for five years from the date of approval of the NCE (or for four years if the subsequent application includes a certification challenging a patent listed for the approved drug).<sup>4</sup> As a general matter, this exclusivity works to delay competitors from marketing a drug with the same active moiety, though not in all cases. For example, it does not delay approval of 505(b)(2) applications and ANDAs submitted to the Agency before the approval of the NCE, nor does it delay approval of a full NDA for the drug (supported entirely by data either developed by the applicant or to which the applicant has a right of reference). In fact, neither Amphadase nor either of the currently pending applications for hyaluronidase would be blocked by five-year exclusivity for Vitrase, even if it were shown that their proteins had the exact same amino acid sequence as those in Vitrase, because the Agency has interpreted five-year exclusivity to block only Agency acceptance, not approval, of applications. 54 Fed. Reg. 28,872, 28,901 (July 10, 1989).

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<sup>4</sup> Congress defined the scope of the five-year exclusivity by stating that it applies only to drug products "no active ingredient (including any ester or salt of the active ingredient) of which has been approved . . ." under section 505(b) of the Act. 21 U.S.C. 505(c)(3)(D), (j)(5)(D). Based on Congress's having been aware of the Agency's then-existing classification system for drugs and the Congressional intent not to grant exclusivity for "minor" variations from previously approved compounds, the Agency has interpreted this statutory language to limit the exclusivity to products that contain no previously approved active moieties. 54 Fed. Reg. 28,897-98 (July 10, 1989). The current regulatory definition for active moiety appears to track the definition used by the Agency when the Hatch-Waxman amendments were enacted. See 21 CFR 314.108(a); "Drug Classification and Priority Review Policy" 2 (SMG CDER # 4820.3) (1984) (which also states that "[t]he active moiety is the entire molecule or ion, not the "active site").

### **Presumption in Favor of NCE Status**

For certain protein products, the specific identity of the active moiety/ies has not been shown. As reflected above, the Act and the Agency's regulations are silent on whether to grant NCE status and exclusivity to such products. It also appears that the Agency has not previously expressly considered what presumption to apply regarding new chemical entity status if the active moieties in a protein product have not been fully characterized. Now having considered the issue, the Agency believes it is reasonable to presume that the proteins in these products are not the same unless sufficient information is available to determine that they are. It bears noting in this regard that NDA applicants are not required to characterize non-recombinant, large molecule, biologically derived products to obtain marketing approval, and subsequent applicants bear the burden of showing their products to be sufficiently similar to warrant reliance on data submitted in support of the prior product's application.

A survey of regulatory treatment for other previously approved protein products provides limited guidance as to whether past practice comported with a presumption in favor of NCE status.<sup>5</sup> Previously approved products considered include surfactants, calcitonins, secretins, glucagons, menotropin and urofollitropin, pancrelipase and insulins. Often, naturally sourced protein products are old and, therefore, either they were not eligible for NCE status or available information on the basis for granting or not granting NCE status is limited. In at least two instances, however, the Agency did not grant NCE status in a circumstance where it might have been presumed under the presumption now under consideration (menotropin/urofollitropin and pancrelipase).

### **Implications of Presumption**

The five-year exclusivity arising from the presumption in favor of NCE status may not provide meaningful protection to some naturally sourced products containing proteins that have not been fully characterized, since each will receive NCE exclusivity that effectively blocks no other. In some cases (such as hyaluronidase, as discussed), no applicant may need to make a substantial research investment, as each is able to rely, at least largely, on existing data based on marketing experience, literature, a DESI finding, etc. However, if such long-term use has not occurred, applicants will likely have to develop their own substantial clinical safety and efficacy data if the proteins cannot be fully characterized to enable reliance on a prior applicant's data.

In the past, the Agency tended to review naturally sourced products at a grosser level, focusing less on the potential significance for safety and efficacy of the particular structure of active moieties. Increasingly, however, the Agency has come to believe that those differences can be important.<sup>6</sup> As a consequence, the Agency imposes more product-specific data

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<sup>5</sup> The information on previously approved protein products relied upon for this memorandum was provided by the Office of Generic Drugs and other CDER entities.

<sup>6</sup> The Agency is focusing attention on related issues under its general program assessing approval standards for follow-on biologically derived products, under which the Agency continues to consider citizen petitions and other

requirements now, even for relatively well understood but not fully characterized naturally sourced products. For example, the Agency has published draft guidance on product-specific safety and efficacy clinical requirements for naturally sourced pancreatic extract products. Similarly, the Agency now requires product-specific allergenicity data for hyaluronidase (as discussed above). In other words, even for older types of naturally sourced products, if they have not been fully characterized, new applicants may each have to generate their own product-specific data that no other applicant can rely upon. Further, in the absence of substantial experience due to long-term marketing or other generalizable data does not exist, as a general matter, the Agency would require each applicant to submit essentially its own full set of product-specific clinical safety and efficacy data for naturally sourced products containing proteins that have not been fully characterized. In other words, each applicant would likely be treated essentially as an applicant typically would in seeking approval for an entirely new chemical entity.

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DIRECTOR  
Gary Buehler

**CLINICAL REVIEW #2 of NDA 21-716**

**M.O. Review #2  
Clinical Amendment to Original NDA**

Submitted: September 15, 2004  
Received: September 17, 2004  
Review completed: October 14, 2004  
Reviewer: Lucious Lim, M.D., M.P.H.

**Proposed Tradename:** Hydase

**Established Name:** Hyaluronidase injection

**Sponsor:** Prima Pharma, Inc.  
3443 Tripp Court  
San Diego, California 92121  
(858) 259-0717  
Contact: Anthony Dziabo

**Pharmacologic Category:** Protein enzyme

**Proposed Indication:** 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.

**Dosage Form and  
Route of Administration:** Solution for injection

**Reviewer's Comments:**

*The italicized text within this review is intended to represent the comments and conclusions of this reviewer.*

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Executive Summary Section

**Executive Summary**

**I. Recommendations**

**A. Recommendation on Approvability**

Pending ongoing labeling negotiations with the applicant, NDA 21-716 is recommended for approval 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 potential safety issues related to the level of allergenicity have been adequately evaluated in Clinical Protocol 04-113. The 95% confidence interval for allergenicity of Hydase is less than the limit set at 10%.

**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**

PrimaPharm submitted NDA 21-716 for Hydase (hyaluronidase injection) on October 15, 2003.

Hydase (hyaluronidase injection) 150 USP units/mL is a protein enzyme prepared from bovine 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. □

The hyaluronidases are a family of  $\beta$ , 1-4 endoglucosaminidases that depolymerize hyaluronic acid (HA) and chondroitin sulfate. The hyaluronidase drug products are partially purified preparations of mammalian testicular tissue and cannot currently be fully characterized.

PrimPharm received a not approvable letter dated April 21, 2004, which listed a clinical deficiency requesting that the level of allergenicity be evaluated in a clinical trial of a representative population of patients.

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PrimPharm submitted a study report for Clinical Protocol 04-113, an open label, single-center clinical study to evaluate the allergenicity of Hydase in healthy volunteers on September 15, 2004.

**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. There are no unresolved efficacy issues.

**C. Safety**

The potential safety issues related to the level of allergenicity have been adequately evaluated in Clinical Protocol 04-113. The allergenicity level of Hydase is less than the limit set of 10%.

**D. Dosing**

No change to the current dosing regimen is proposed in this submission.

**E. Special Populations**

There are no known differences with respect to age, gender, race, or hepatic impairment.

**Clinical Review**

**I. Introduction and Background**

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

See M.O. Original NDA Review signed March 31, 2004.

**B. State of Armamentarium for Indication(s)**

See M.O. Original NDA Review signed March 31, 2004.

**C. Important Milestones in Product Development**

See M.O. Original NDA Review signed March 31, 2004.

**D. Other Relevant Information N/A**

**E. Important Issues with Pharmacologically Related Agents**

See M.O. Original NDA Review signed March 31, 2004.

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

See M.O. Original NDA Review signed March 31, 2004.

**III. Human Pharmacokinetics and Pharmacodynamics**

See M.O. Original NDA Review signed March 31, 2004.

# CLINICAL REVIEW #2 of NDA 21-716

## Clinical Review Section

### IV. Description of Clinical Data and Sources

#### A. Overall Data

The overall data reviewed in this clinical amendment consisted of a single clinical study report for Clinical Protocol 04-113.

#### B. Tables Listing the Clinical Trials in this Amendment

**Table 1 – Clinical Trials**

<b>Protocol Number</b>	<b>04-113</b>
<b>Study Design</b>	Single-center, Open-label
<b>Study Period</b>	7/13/04 – 7/15/04
<b>No. Sites</b>	One
<b>No. Subjects</b>	100 enrolled
<b>Status</b>	Completed

#### C. Postmarketing Experience

The product has not been marketed in the United States.

#### D. Literature Review

There was no significant new information found in the published literature.

### V. Clinical Review Methods

#### A. How the Review was Conducted

The submitted clinical study report was reviewed in its entirety.

#### B. Overview of Materials Consulted in Review

The clinical study report was submitted in paper format.

#### C. Overview of Methods Used to Evaluate Data Quality and Integrity

The data was reviewed for consistency with other applications in this class.

#### D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trial was conducted in accordance with accepted ethical standards.

#### E. Evaluation of Financial Disclosure

There are no investigators with a financial interest in the drug product that is the subject of this clinical protocol.

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**VI. Integrated Review of Efficacy**

**Brief Statement of Conclusions**

The efficacy of the drug product was well established in the previous M.O. clinical reviews. No information has been submitted which would alter those conclusions.

**VII. Integrated Review of Safety**

**A. Brief Statement of Conclusions**

The potential safety issues related to the level of allergenicity have been adequately evaluated in Clinical Protocol 04-113.

**B. Description of Patient Exposure**

Clinical Protocol 04-113 exposed 100 enrolled subjects to a skin test utilizing an intradermal injection of Hydase.

**C. Methods and Specific Findings of Safety Review**

The submitted clinical study report was reviewed in its entirety. The allergenicity level of Hydase is less than the limit set of 10%.

**Individual Study Review**

**Study 04-113**

**Title:** Evaluation of Sensitivity to Hydase (Hyaluronidase Injection, USP) 150 USP Units/mL

**Objective:** The objective of this study was to evaluate the sensitivity of subjects to Hydase, hyaluronidase injection, and to verify that less than 10% of patients tested would have a positive reaction to Hydase.

**Investigators:**

Rachel Bittker, MD PRACS Institute, Ltd., Formerly known as DermTech International, 15222-B Avenue of Science, San Diego, CA, (858) 618-1328

**Study Design:**

This study is an open label, single-center study in healthy volunteers.

The primary clinical variable will be the level of allergenicity of Hydase by means of the intradermal skin testing, defined as the incidence of positive skin response to Hydase: a wheal with pseudopods accompanying by localized itching appearing within five minutes of drug placement and persisting for 20-30 minutes. The primary objective of the study will be to show

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that Hydase has an allergenicity level of less than 10% in terms of the incidence of positive skin response.

Each subject will be injected with 0.02 mL of Hydase solution, intradermally in the volar forearm.

A negative response is one in which there is no localized skin reaction and the subject exhibits no systemic reaction.

A positive response consists of a wheal with pseudopods appearing within five minutes post injection, persisting for 20-30 minutes and accompanied by localized itching. Transient vasodilation at the test site, i.e., erythema, is not considered a positive response.

The number of subjects exhibiting a positive response will be reported as a percentage of subjects treated. A 95% two-sided confidence interval will be calculated and reported.

The statistical analysis will be designed to assure that the upper bound of the two-sided confidence interval of the allergic response rate is less than 10%.

The trial will be declared a success if the analysis for Hydase shows the primary endpoint is less than the FDA recommended allergenicity level, 10%.

Inclusion Criteria:

Subjects will be entered or excluded from the study based on the following criteria.

Criteria for Inclusion

1. Subjects 18-85 years of age of either sex
2. Subjects willing and able to comply with the requirements of the study
3. Subjects willing and able to give informed consent

Criteria for Exclusion

1. Subjects who are pregnant or lactating
2. Subjects who have had hyaluronidase treatment within the last 3 months
3. Subjects who were treated with chemotherapy agents or corticosteroids within the past 3 months
4. Subjects with a history of autoimmune disorder
5. Subjects with known sensitivity to hyaluronidase
6. Subjects with a known allergy to proteins
7. Subjects who have a history of dietary beef allergy, undergoing desensitization to beef products or planning to undergo desensitization within the study evaluation period
8. Subjects with severe allergies manifested by a history of anaphylaxis
9. Subjects with a current disease state that can effect immune response (e.g., flu, cancer, HIV)
10. Subjects who are currently treated with immunosuppressive drugs
11. Subjects who have infected/inflamed skin or skin disease in the area of the injection

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12. Subjects who have any skin imperfections such as moles and tattoos at the site of injection

Subject Demographics and Disposition:

**Table 2 – Demographics for Study Population**

Demographics	Study Population
# of Subjects	100
Gender, n (%)	
Male	23 (23.0%)
Female	77 (77.0%)
Ethnicity	
Caucasian	(80) 80.0%
Asian	(2) 2.0%
African American	(10) 10%
Caucasian/Hispanic or Latino	(6) 6%
Native American	(1) 1%
Caucasian/African American	(1) 1%

**Reviewer's Comments:**

*A total of 100 subjects were screened for entering the study; all subjects passed screening and consented for participation. All subjects received study medications and completed the study.*

Primary End Point Analysis

**Table 3 – Level of Allergenicity**

Primary Endpoint	Study Population (All subjects)
# of Subjects	100
Allergenicity: incidence of positive reaction with Hydase, n (%)	0 (0.0%)
Incidence of positive reactions	0 (0.0%)
Incidence of negative reactions	100 (0.0%)

**Table 4 – Skin Reactions Observed at the Post-Injection Observations**

Subject #	5 Minutes	30 Minutes
005	No reaction	Erythema
025	Wheal, pseudopods, erythema	No reaction
030	Erythema	No reaction
035	No reaction	Erythema, wheal
040	Erythema	No reaction
041	Erythema, ecchymosis	Ecchymosis
044	Erythema	No reaction
047	Erythema, ecchymosis	Erythema, ecchymosis
050	Ecchymosis	Ecchymosis
066	Wheal, erythema	Erythema

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079	Erythema	No reaction
082	Erythema	No reaction
091	Ecchymosis	Ecchymosis
093	No reaction	Wheal, erythema
095	Wheal, erythema	Erythema
096	Wheal, erythema	Erythema
097	Ecchymosis	Ecchymosis

**Reviewer's Comments:**

*No subject experienced a positive response. The level of allergenicity of Hydase is less than the FDA recommended allergenicity level of 10%.*

Adverse Events

No deaths were reported.

The Applicant reported the following adverse events from four subjects (4% of the population):

“Subject Number 008 reported a brief “twinge” at their right armpit and a mild heaviness at their right shoulder; both were determined to have an unlikely relationship to the test article.

Subject Number 031 reported slight swelling, erythema, and mild itching at the test site. All symptoms resolved without treatment, and the adverse event was determined to be probably related to the test article.

Subject Number 038 reported stiffness, numbness with tingling, and soreness in her left arm; this event was determined to be likely related to the test article. She also experienced a large bruise after having blood drawn, which was determined not to be related to the test article. All symptoms resolved without treatment.

Subject Number 076 experienced an adverse event in which both arms “fell asleep.” This event was determined not to be related to the test article.”

The Applicant reported the following serious adverse event:

“Two days following the study injection, Subject Number 078, experienced a serious adverse event. The subject reported that she had chest pains and shortness of breath. She was advised to go to the emergency room, but did not elect to go. She then experienced dizziness, sweating, and shortness of breath. Four days following the injection, she was admitted to the hospital and was diagnosed with bilateral pulmonary embolism found on computed tomography (CT) of the chest. The ER doctor thought that this condition was most likely to be related to the subject's use of birth control pills (beginning on [redacted]). The SAE was reported to the IRB and Sponsor. The SAE was determined by the Investigator to be “unlikely related” to the test article. However, the form for reporting SAEs to the IRB did not provide for the category of “unlikely

Clinical Review Section

related,” so for the sake of consistency the Investigator reported the SAE as “possibly related” to the test article.”

**D. Adequacy of Safety Testing**

The potential safety issues related to the level of allergenicity have been adequately evaluated in Clinical Protocol 04-113.

**E. Summary of Critical Safety Findings and Limitations of Data**

See M.O. Original NDA Review signed March 31, 2004.

**VIII. Dosing, Regimen, and Administration Issues**

No change to the current dosing regimen is proposed in this submission.

**IX. Use in Special Populations**

**A. Evaluation of Sponsor’s Gender Effects Analyses and Adequacy of Investigation**

There were no significant differences in safety with respect to gender for safety in this single clinical study.

**B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy**

There were no significant differences in safety with respect age, race, and ethnicity for safety in this single clinical study.

**C. Evaluation of Pediatric Program**

See M.O. Original NDA Review signed March 31, 2004.

**D. Comments on Data Available or Needed in Other Populations**

See M.O. Original NDA Review signed March 31, 2004.

**X. Conclusions and Recommendations**

**A. Conclusions**

The potential safety issues related to the level of allergenicity have been adequately evaluated in Clinical Protocol 04-113. The allergenicity of Hydase is less than the level set of 10%.

**B. Recommendations**

NDA 21-716 is recommended for approval 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. Final labeling will addressed separately in Medical Officer’s Review #3.

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Wiley Chambers  
12/13/04 12:04:53 PM  
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## CLINICAL REVIEW of NDA 21-716

### Original Application

Submitted: October 15, 2003  
Received: October 20, 2003  
Review completed: January 30, 2004  
Reviewer: Lucious Lim, M.D., M.P.H.

**Proposed Tradename:** Hydase

**Established Name:** Hyaluronidase injection

**Sponsor:** Prima Pharma, Inc.  
3443 Tripp Court  
San Diego, California 92121  
(858) 259-0717  
Contact: Anthony Dziabo

**Pharmacologic Category:** Protein enzyme

**Proposed Indication:** 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.

**Dosage Form and  
Route of Administration:** Solution for injection

**Reviewer's Comments:**

*The italicized text within this review is intended to represent the comments and conclusions of this reviewer.*

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**Executive Summary**

**I. Recommendations**

**A. Recommendation on Approvability**

NDA 21-716 is recommended for approval from a clinical prospective with the labeling identified in this review and the following additional comments:

- 1) The hyaluronidases are a family of  $\beta$ , 1-4 endoglucosaminidases that depolymerize hyaluronic acid and chondroitin sulfate. The hyaluronidase drug products are partially purified preparations of mammalian testicular tissue and cannot currently be fully characterized.
- 2) There is no direct clinical data on the use of the Hydase drug product. Clinical study information is needed to provide assurance of the low potential for significant allergic reactions in patients for the proposed indications.
- 3) For hyaluronidase products without human exposure, the level of allergic reactions is recommended to be evaluated using a skin test utilizing an intradermal injection of approximately 0.1 mL (15 U) of a 150 USP Unit/mL to determine if the level is <10%.

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**

Hydase (hyaluronidase injection) 150 USP units/mL is a protein enzyme prepared from bovine testicular tissue. It is administered as an injection but is not for intravenous use. The safety and efficacy of Hydase 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. C

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**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

Other than hyaluronidase, there are no other drug products approved for these indications. There are no unresolved efficacy issues.

**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. There are no unresolved efficacy issues.

**D. Dosing**

Established dosing has been in the range of 30 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**

Hydase (hyaluronidase injection) 150 USP units/mL is a protein enzyme prepared from bovine testicular tissue. It is administered as an injection but is 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)**

NDA 6-343    Wydase (hyaluronidase for Injection) (Baxter)

NDA 6-714    Alidase (Searle)

NDA 7-933    Hyazyme (Abbott)

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**

Hydase (hyaluronidase for injection, [ ] was submitted in July 1948, and permitted on the market on August 19, 1948. [ ]

[ ] The DESI Reviews (3) were completed in late 1960s; and these reviews supported the effectiveness of this drug product for use

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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; and as an aid in retrobulbar and cone injection infiltrative anesthesia in ocular surgery. Hyalase (hyaluronidase for injection) was approved in 1970.

**D. Other Relevant Information**

Prima Pharm, Inc., has not marketed Hydase (hyaluronidase injection) in any foreign countries.

**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**

**Table 1 – Drug Product Composition**

Hydase (hyaluronidase injection)	
Description of item	150 USP units/mL
Processed Hyaluronidase	_____
Sodium Chloride USP	_____
Calcium Chloride Dihydrate USP	_____
Disodium Edetate USP	_____
Sodium Phosphate Monobasic Anhydrous USP	_____
Sodium Hydroxide NF	_____
Streile Water for Injection USP	_____

Clinical Review Section

Table 2 – Drug Product Specifications

Testing	Specification
Hyaluronidase Activity	
Container Closure Integrity	

**Reviewer's Comments:**

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

**Mammalian hyaluronidases**

*The hyaluronidases (E.C 3.1.25) are a family of  $\beta$ , 1-4 endoglucosaminidases that depolymerize hyaluronic acid (HA) and chondroitin sulfate. The hyaluronidase drug products are partially purified preparations of mammalian testicular tissue and cannot currently be fully characterized. 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 testicular sources of hyaluronidase in activity have been identified.*

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

**III. Human Pharmacokinetics and Pharmacodynamics**

**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.*

# CLINICAL REVIEW NDA 21-716

## Clinical Review Section

### 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 report

#### B. Tables Listing the Clinical Trials

No new clinical studies have been submitted.

#### C. Postmarketing Experience

##### 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 Edema	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
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 Edema	6	0	6	0	0	0	0	6
Skin And Subcutaneous	Urticaria NOS	6	0	4	0	0	0	0	4

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## Clinical Review Section

SOC	PT	Total Events	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
Tissue									
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 Hemorrhage	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 Hemorrhage 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 Hemorrhage	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 Tissue	Pruritus	3	0	3	0	0	0	0	3
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	Localized 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	Hemorrhage NOS	2	0	1	0	0	0	0	1
Skin And Subcutaneous Tissue	Cold Sweat	2	0	2	2	0	0	0	0

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SOC	PT	Total Events	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
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 Hemorrhage 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	Computerized 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	Blister	2	0	2	2	0	0	0	2
Injury, Poisoning	Delayed Recovery From Anesthesia	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
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 Hemorrhage	2	0	2	0	2	0	0	0
Eye Disorders	Optic Disc Hemorrhage	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 Edema	2	0	2	2	0	0	0	0
Eye Disorders	Parophthalmia	2	0	2	2	0	0	0	0

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SOC	PT	Total Events	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
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 Edema	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.*

#### **D. Literature Review**

There are no submitted literature references.

### **V. Clinical Review Methods**

#### **A. How the Review was Conducted**

*This review was conducted by re-reviewing the DESI findings and conclusions, conducting a Medline search and reviewing all relevant articles.*

#### **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 was reviewed in Datamart. Copies of published articles on hyaluronidase were reviewed (hundreds of articles) 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 is no evidence to the contrary that all trials were conducted in accordance with accepted ethical standards.*

Clinical Review Section

**E. Evaluation of Financial Disclosure**

*There is no reported financial disclosure information. All studies were conducted prior to the implementation of the financial disclosure rules. There are no new studies submitted.*

**VI. Integrated Review of Efficacy**

**A. Brief Statement of Conclusions**

*The published literature is consistent with the DESI evaluation. The USP test to determine USP units may serve as a valid surrogate for efficacy. Other than hyaluronidase, 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**

*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, the drug product has been marketed and used in millions of patients for over 50 years with relatively minimal adverse events.*

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**C. Methods and Specific Findings of Safety Review**

*In addition to the findings in the DESI evaluation, the 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 this and other hyaluronidase products, the safety database is considered large and adequate. However, there is no direct clinical data on the use of the Hydase drug product. Clinical study information is needed to provide assurance of the low potential for significant allergic reactions in patients for the proposed indications. For hyaluronidase products without human exposure, evaluation of the level of allergenicity is recommended.*

**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 15 and 300 units/mL of co-administered drug.*

**IX. Use in Special Populations**

**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.*

## CLINICAL REVIEW NDA 21-716

### Clinical Review Section

#### **X. Conclusions and Recommendations**

##### **A. Conclusions**

NDA 21-716 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 21-716 is not recommended for approval from a clinical prospective until the labeling issues identified in this review are addressed and the level of allergenicity is evaluated using a skin test utilizing an intradermal injection of approximately 0.1 mL (15 U) of a 150 USP Unit/mL to determine if the level is <10%.

#### **XI. Appendix**

##### **A. Other Relevant Materials**

*None.*

##### **B. Individual More Detailed Study Reviews (if performed)**

*None.*

6 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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