CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-665

MEDICAL REVIEW(S)

M.O. Review #4
Labeling Amendment to Original NDA 21-665

Submitted:	August 12, 2004
Received:	August 13, 2004
Review completed:	August 13, 2004
Reviewer:	William M. Boyd, M.D.
Proposed Tradename:	Amphadase
Established Name:	hyaluronidase injection
Sponsor:	Amphastar Pharmaceuticals, Inc. 11570 Sixth Street Rancho Cucamonga, California 91730 Contact: Stephen A. Campbell 909-980-9484 ext. 2019
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:

Submitted is revised labeling based on previous review and discussion with the applicant. A final, revised package insert and final, revised container and carton labeling were submitted by the applicant on August 12, 2004.

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

6 Draft Labeling Page(s) Withheld

CLINICAL REVIEW #3 of NDA 21-665

M.O. Review #3
Clinical Amendment to Original NDA

Submitted:	April 23, 2004
Received:	April 26, 2004
Review completed:	July 13, 2004
Reviewer:	William M. Boyd, M.D.

Proposed Tradename: Amphadase

Established Name: hyaluronidase injection

Sponsor: Amphastar Pharmaceuticals, Inc.
11570 Sixth Street
Rancho Cucamonga, California 91730

Contact: Stephen A. Campbell
909-980-9484 ext. 2019

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.

Table of Contents

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Pending ongoing labeling negotiations with the applicant, NDA 21-665 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 API-H001-CLN-A. The 95% confidence interval for allergenicity of Amphadase 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

Amphastar submitted NDA 21-665 for Amphadase (hyaluronidase injection) on June 6, 2003.

Amphadase (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 indication for use as an aid in retrobulbar and cone injection infiltrative anesthesia in ocular surgery is supported by the DESI evaluation; however, [redacted] it was not included in approved indications.

The hyaluronidases are a family of β, 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.

Amphastar received a not approvable letter dated January 7, 2004, which listed a clinical deficiency requesting that the level of allergenicity be evaluated in a clinical trial of a representative population of patients.

Amphastar submitted a study report for Clinical Protocol API-H001-CLN-A, a Randomized, Double-Blinded, Placebo and Active Controlled Study for Evaluation of the Allergenicity of Amphadase in Health Volunteers Using Intradermal Skin Test, on April 23, 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 API-H001-CLN-A. The allergenicity level of Amphadase 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. Review #1 signed December 8, 2003.

B. State of Armamentarium for Indication(s)

See M.O. Review #1 signed December 8, 2003.

C. Important Milestones in Product Development

See M.O. Review #1 signed December 8, 2003.

D. Other Relevant Information N/A

E. Important Issues with Pharmacologically Related Agents

See M.O. Review #1 signed December 8, 2003.

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

See M.O. Review #1 signed December 8, 2003.

III. Human Pharmacokinetics and Pharmacodynamics

See M.O. Review #1 signed December 8, 2003.

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 API-H001-CLN-A.

B. Tables Listing the Clinical Trials in this Amendment

Table 1 – Clinical Trials

Protocol Number	API-H001-CLN-A
Study Design	Multicenter, Double-Masked, Randomized, Placebo and Active Controlled
Study Period	3/15/04 – 4/6/04
No. Sites	Three
No. Subjects	162 enrolled
Status	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.

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 API-H001-CLN-A.

B. Description of Patient Exposure
Clinical Protocol API-H001-CLN-A exposed 162 enrolled subjects to a skin test utilizing an intradermal injection of Amphadase, positive control, and a negative control.

C. Methods and Specific Findings of Safety Review
The submitted clinical study report was reviewed in its entirety. The allergenicity level of Amphadase is less than the limit set of 10%.

Individual Study Review

Study API-H001-CLN-A

Title: A Randomized, Double-Blinded, Placebo and Active Controlled Study for Evaluation of the Allergenicity of Amphadase in Healthy Volunteers Using Intradermal Skin Test

Objective: The primary endpoint for this study is the "allergenicity of Amphadase" by means of an intradermal skin testing. A positive reaction consists of the entire phenomenon as follows:

i. reaction appearing within 30 minutes of drug placement;
ii. a wheal (> 8mm) with or without pseudopods;
iii. reaction accompanying erythema; and
iv. reaction accompanying localized itching.

Investigators:

Clinical Review Section

Study Design:

This study is a randomized, double-blinded, placebo and active-controlled study in healthy volunteers.

The primary clinical variable will be the level of allergenicity of Amphadase by means of the intradermal skin testing, defined as the incidence of positive skin response to Amphadase: a wheal (> 8mm) with pseudopods accompanying erythema and localized itching appearing within 30 minutes of drug placement. The primary objective of the study will be to show that Amphadase is associated with a significant less allergenicity level compare to the FDA recommended, <10% allergenicity level in terms of the incidence of positive skin response.

Three (3) intradermal injections will be given to each subject. Randomly, each of the following will be administered:

1 injection with the negative control (Saline)
1 injection with the positive control (histamine base 0.1 mg/mL)
1 injection with the test drug, Amphadase (Hyaluronidase 150 USP Units/mL)

Each will be is injected intradermally, in a volume of 0.02 mL, to one of the three injection sites in the subject's forearm (— needle).

The primary efficacy analysis will be performed on a "Per Protocol" population basis. "Per Protocol" subjects are defined as those subjects who had received specified injections of the study drug preparations according to this protocol and the positive control and negative control skin responses are in compliance with the criteria indicated below:

1) The skin response in the positive control site is > 8mm wheal with or without pseudopods formation.
2) The skin response of the negative control site is regularly less than 3 mm wheal/10 mm erythema.

Denoted by p_H, the incidence (%) of positive skin reaction with Amphadase, the statistical hypothesis to be tested is:

$$H_0: p_H = p_0 \text{ vs. } H_a: p_H < p_0 \text{ Where, } p_0 = 10\%$$

The analysis will be based on the 95% two-sided, one-sample binomial test. An exact method will be performed, and the p-value will be calculated for the significance of analyzing the above hypothesis:

$$p - value = \sum_{i=0}^{x} \binom{n}{i} p_0^{\,i} (1 - p_0)^{n-i}$$

where,

n is the number of subjects.
x is the number of positive observation.

This primary analysis will be based on the per-protocol population. The trial will be declared a success if the analysis for Amphadase shows the primary endpoint is statistically significant less than the FDA recommended allergenicity level, 10%.

Inclusion Criteria:

Subjects may be included in the study only if they meet all of the following criteria:

1. Healthy volunteers of either sex;
2. Those without clinically significant cardiovascular gastrointestinal, hepatic, neurological, psychiatric, endocrine, or other major systemic disease that would unduly risk the subject's safety or interfere with the interpretation of results, assessed according to the judgment of the Principal Investigator. A non-inclusive list which would not be exclusionary and define healthy individual for the purposes of this study are:
   - hypothyroidism,
   - stable hypertension except those subjects on beta blockers including ocular preparations,
   - seasonal/perennial allergic rhinitis if able to wash out of antihistamines,
   - stable, mild intermittent asthma (subjects using beta agonists as a monotherapy on an as-needed basis, excluding daily usage),
   - migraine if not taking excluded medications,
   - mild anxiety/depression if not taking excluded medications, and
   - mild arthritic conditions if not taking excluded medications.
3. Willingness and ability to sign an informed consent document;
4. 18 – 80 years of age;
5. Intact skin at the forearm to be administered with study drugs;
6. Female participants are currently practicing effective birth control methods or abstinence.

Exclusion Criteria:

Subjects will be excluded from the study for any of the following reasons:

1. Known allergy, hypersensitivity or contraindications to hyaluronidase, thimerosal, edetate disodium (EDTA);
2. Use of medications within a duration considered to interfere with skin testing. The medications include antihistamines (H1 and H2 antagonists), β-blockers including ocular preparations, tricyclic antidepressants, all asthma therapy excluding PRN beta agonists, polythiazides, monoamine oxidase inhibitors, and immunosuppressive drugs. For example, use of antihistamine medication (H1 antagonists) within 48 hours of skin testing or long-acting antihistamine medication (i.e., hydroxyzine) within 1 week or a duration considered to interfere with skin testing;
3. Known dermographism which may interfere with skin testing.
4. Pregnant or lactating women.

Subject Demographics and Disposition:

Table 2 – Demographics for ITT/Per Protocol Population

Demographics	ITT/Per Protocol Population
# of Subjects	162
Gender, n (%) Male Female	 74 (45.7%) 88 (54.3%)
Mean Age ± SD, years	35.2 ± 1.0
Mean Weight ± SD, kg	81.8 ± 1.6
Ethnicity	
Caucasian	84%
Asian	1.2 %
Black	8%
Hispanic	6.2%
Native American	0%
Other	0.6%

Reviewer's Comments:

A total of 162 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 (ITT/Per-Protocol)

Primary Endpoint	ITT/Per Protocol Population (All subjects)
# of Subjects	162
Allergenicity: incidence of positive reaction with Amphadase, n (%)	8 (5%) (2%, 8%)‡
p-value for hypothesis analysis	0.031*
Incidence of positive reactions with histamine (positive control)	142 (88%)
Incidence of positive reactions with saline (negative control)	3 (2%)

‡ 95% confidence intervals

* $p < 0.05$, reject H_0

Reviewer's Comments:

The level of allergenicity of Amphadase is statistically significantly less than the FDA recommended allergenicity level of 10%.

Among the 162 subjects who received study drug (per-protocol data set), seventeen (17) subjects exhibited false negative reactions and three (3) subjects exhibited both false positive and negative control reactions.

If these subjects are excluded and an additional analysis performed on this population (SAP or "statistical analysis plan population"), the level of allergenicity of Amphadase is still statistically significantly less than the FDA recommended allergenicity level of 10%. See Table 4 below.

Table 4 – Level of Allergenicity (SAP population)

Primary Endpoint	SAP Population (162 – 17 – 3 = 142 subjects)
# of Subjects	142
Allergenicity: incidence of positive reaction with Amphadase, n (%)	7 (5%) (1%, 9%)‡
p-value for hypothesis analysis	0.046*
Incidence of positive reactions with histamine (positive control)	142 (100%)
Incidence of positive reactions with saline (negative control)	0 (0%)

‡ 95% confidence intervals

* $p < 0.05$, reject H_0

Adverse Events

No deaths or serious adverse events were reported.

Table 5 – Adverse Events

Adverse Event	Subject ID
Pruritis (4)	HY-046, -149, -154, -166
Urticaria (5)	HY-046, -149(2), -154, -166
Ecchymosis (1)	HY-042
Rash (3)	HY-149, -154, -166
Gingivitis (1)	HY-185
Throat itching (1)	HY-041

Reviewers' Comments:

The case report form for subject HY-185 (gingivitis), reported the subject complained of "sore gums" 21 minutes after the injections. When the subject awoke the next day, gums were no longer sore. This adverse event is miscoded as gingivitis.

D. Adequacy of Safety Testing

The potential safety issues related to the level of allergenicity have been adequately evaluated in Clinical Protocol API-H001-CLN-A.

E. Summary of Critical Safety Findings and Limitations of Data

See M.O. Review #1 signed December 8, 2003.

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. Review #1 signed December 8, 2003.

D. Comments on Data Available or Needed in Other Populations

See M.O. Review #1 signed December 8, 2003.

X. Conclusions and Recommendations

A. Conclusions

The potential safety issues related to the level of allergenicity have been adequately evaluated in Clinical Protocol API-H001-CLN-A. The allergenicity of Amphadase is less than the level set of 10%.

B. Recommendations

NDA 21-665 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 is addressed separately in Medical Officer's Review #4.

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/s/

William Boyd
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Wiley Chambers
8/19/04 03:22:54 PM
MEDICAL OFFICER

CLINICAL REVIEW #2 NDA 21-665

Original Application – M.O. Review #2

Submitted:	June 6, 2003
Received:	June 13, 2003
Review completed:	December 29, 2003
Reviewer:	William M. Boyd, M.D.

Proposed Tradename: Amphadase

Established Name: hyaluronidase injection

Sponsor: Amphastar Pharmaceuticals, Inc.
11570 Sixth Street
Rancho Cucamonga, California 91730

Contact: Stephen A. Campbell
909-980-9484 ext. 2019

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 hyaluronidases are a family of β, 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.

There is no direct clinical data on the use of the Amphadase 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, the level of immunogenicity 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%.

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/s/

William Boyd
12/29/03 11:06:13 AM
MEDICAL OFFICER

Wiley Chambers
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MEDICAL OFFICER

CLINICAL REVIEW of NDA 21-665

Original Application

Submitted:	June 6, 2003
Received:	June 13, 2003
Review completed:	November 23, 2003
Reviewer:	William M. Boyd, M.D.

Proposed Tradename: Amphadase

Established Name: hyaluronidase injection

Sponsor: Amphastar Pharmaceuticals, Inc.
11570 Sixth Street
Rancho Cucamonga, California 91730

Contact: Stephen A. Campbell
909-980-9484 ext. 2019

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.

Table of Contents

Executive Summary

I. Recommendations

A. Recommendation on Approvability

NDA 21-665 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

Amphadase (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 indication for use as an aid in retrobulbar and cone injection infiltrative anesthesia in ocular surgery is supported by the DESI evaluation; however, — , it was not included in approved indications.

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 indication for use as an aid in retrobulbar and cone injection infiltrative anesthesia in ocular surgery is supported by the DESI evaluation; however, — , it was not included in approved indications.

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 ethic 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

Amphadase (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 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 6-392	Hyronase (Schering)
NDA 6-714	Alidase (Searle)
NDA 6-809	Diffusin (Ortho)
NDA 7-933	Hyazyme (Abbott)
NDA 8-619	Enzodase (Squibb)
NDA 8-985	Infiltrase (Armour)
NDA 9-082	Haruadase (Harvey)
NDA 9-201	Hyaluronidase (Cudahy)
NDA 9-380	Hyaluronidase (Worthington)

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 (30 and 60 turbidity reducing units) was submitted in July 1948, and permitted on the market on August 19, 1948. Its name was changed to Hyalase (hyaluronidase for injection) in 1951 with the addition of 1500 unit packages.

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; 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

Amphastar Pharmaceuticals, Inc., has not marketed Amphadase (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

Amphadase (hyaluronidase injection)	
Description of item	150 USP units/mL
Hyaluronidase (amount/mL)	150 USP units*
Sodium Chloride USP (amount/mL)	8.5 mg
Edetate Disodium — USP (amount/mL)	—
Calcium Chloride — amount/mL)	—
Thimerosol NF (amount/mL)	0.1 mg
Monobasic Sodium Phosphate, — (amount/mL)	—
—	—
—	—
—	—

*The USP and NF hyaluronidase units are equivalent to the turbidity-reducing (TR) unit and to the international unit (IU)

Table 2 - Drug Product Specifications

Testing	Specification
pH	6.4 – 7.4
Limit of tyrosine	NMT 0.25 µg/USP unit
Assay	NLT 90% of label claim (150 USP units/mL)
Thimerosol	—
Edetate Disodium	—
—	/
Volume in	NLT —
Sterility	—
Bacterial Endotoxins	NMT 2.30 – /USP unit

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 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

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 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 Tissue	Urticaria NOS	6	0	4	0	0	0	0	4
Psychiatric Disorders	Confusional State	6	0	4	4	0	0	0	0

SOC	PT	Total Events	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
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
Skin And Subcutaneous Tissue	Vitiligo	2	0	2	0	0	0	0	2

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

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

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. 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.

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.

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.

X. Conclusions and Recommendations

A. Conclusions

NDA 21-665 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 21-665 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.

6 Draft Labeling Page(s) Withheld

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

/s/

William Boyd
12/3/03 09:45:09 AM
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