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RESEARCH**

APPLICATION NUMBER:

21-859

MEDICAL REVIEW

Original Application – M.O. Review #2

Submitted: September 14, 2005
Received: September 14, 2005
Review completed: September 14, 2005
Reviewer: Rhea A. Lloyd, M.D.

Proposed Trade Name: Hylenex recombinant

Established Name: hyaluronidase human injection

Sponsor: Halozyme Therapeutics, Inc.,
11588 Sorrento Valley Road, Suite 17
San Diego, CA 92121

Contact: Don Kennard
858-794-8889 ext. 208

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: The sponsor has submitted final package insert labeling based upon discussion with the Division at the September 6, 2005 teleconference.

The sponsor has revised the trade name from “Hylenex” to “Hylenex recombinant” and established name to “hyaluronidase human injection”.

The attached carton and container labeling was submitted in the original submission dated March 18, 2005.

CLINICAL REVIEW

Application Type NDA
Submission Number 21-859
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Letter Date March 18, 2005
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Reviewer Name Rhea A. Lloyd, MD
Review Completion Date September 21, 2005

Established Name (Hyaluronidase Human Injection)
(Proposed) Trade Name HYLENEX™ recombinant
Therapeutic Class Protein enzyme
Applicant Halozyme Therapeutics, Inc.
11588 Sorrento Valley Rd.,
Suite 17
San Diego, CA 92121

Don Kennard
858-794-8889 ext. 208

Priority Designation P

Dosage Form

Injectable solution

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.

Intended Population

Patients in all age groups including neonates.

Formulation

Ingredient	Unit Formula 1 mL vial (mg)
rHuPH20 (recombinant human hyaluronidase)	~150U
Sodium Phosphate Dibasic Dihydrate	1.78
Sodium Hydroxide	4.2
Albumin (Human)	1
Calcium Chloride Dihydrate	0.40
Sodium Chloride	8.5
Edetate Disodium Dihydrate	1
Water for Injection	qs to 1mL

Reviewer's Comment:

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

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

HYLENEX recombinant is recommended for approval from a clinical perspective with the labeling changes identified in this review. NDA 21-859 HYLENEX recombinant (hyaluronidase human injection) is submitted under Section 505(b)(2) of the Food Drug and Cosmetics Act with Wydase® (NDA 6-343) designated as the reference listed drug.

The indications in the proposed labeling in this review are supported by the USP monograph test for hyaluronidase and 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 conclusions of the DESI report were published in the Federal Register on September 23, 1970 (35 FR 14800-1). Wydase® was included in the DESI Review Studies and found to be effective for the DESI review indications. Additionally, NDA 21-859 relies upon supportive evidence from the published literature and the Phase I Safety Trial (R04-0851) sponsored by Halozyme Therapeutics, Inc.

The drug substance in HYLENEX is a recombinant human hyaluronidase, rHuPH20. rHuPH20 is manufactured in chemically defined media that does not include any animal derived ingredients and therefore carries less potential risk of disease transmission from animal pathogenic agents.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No postmarketing risk management activity is recommended given the reported event profile of hyaluronidase over the past 50 years.

1.2.2 Required Phase 4 Commitments

No Phase 4 commitments are required.

1.2.3 Other Phase 4 Requests

There are no Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Established Name	hyaluronidase human injection
(Proposed) Trade Name	HYLENEX™ recombinant
Therapeutic Class	Protein enzyme

Hyaluronidase products have been used clinically in the US for over 50 years. Hyaluronidase cleaves hyaluronic acid which is a major component of the extracellular matrix of all mammalian tissues. The principal use of hyaluronidase during this time has been as an adjuvant to increase the absorption and dispersion of other drugs.

HYLENEX recombinant (hyaluronidase human injection) is a 150 USP enzymatic unit formulation composed of a protein enzyme that is prepared from a recombinant human form of hyaluronidase, rHuPH20. It is administered as an injection but not for intravenous use. The safety and efficacy is supported by the USP monograph test for hyaluronidase and the conclusions from 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

1.3.2 Efficacy

The efficacy of HYLENEX recombinant 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. C

Wydase®, the reference listed drug, was included in the DESI Review Studies and found to be effective for the DESI review indications. Published literature for hyaluronidase is also consistent with the DESI evaluation. There are no unresolved efficacy issues.

The hyaluronidases are a family of beta, 1-4 glucosaminidases that depolymerize hyaluronic acid (HA) and chondroitin sulfate. A gene for the expression of PH-20 is present in the genome of all mammals. Hyaluronidases present in extracts from mammalian testes are encoded by the PH-20 gene. The recombinant human form of PH-20 possesses the same enzymatic activity, as compared to the United States Pharmacopeia (USP) Hyaluronidase Reference Standard, in spreading factor function and dermal layer reconstitution. This test is a surrogate for the proposed indications because the test evaluates the same action *in vitro* as would occur in the human body. Thus, references to the DESI findings are appropriate.

1.3.3 Safety

NDA 21-859 HYLENEX recombinant (hyaluronidase human injection) is submitted under Section 505(b)(2) of the Food Drug and Cosmetics Act. Wydase® (NDA 6-343) is designated as the reference listed drug. Wydase® was included in the DESI Review Studies and found to be safe for the DESI review indications. 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.

A single Phase 1 clinical safety trial, R04-0851 was performed. The objective of the study was to evaluate the allergic sensitivity of patients to HYLENEX recombinant (hyaluronidase human injection) and to determine that less than 10% of patients would have a positive test reaction to HYLENEX recombinant. None of the patients exhibited a positive skin test result. There are no new safety concerns or relevant adverse events that have not previously been included in other hyaluronidase 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.

1.3.4 Dosing Regimen and Administration

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.

1.3.5 Drug-Drug Interactions

No drug-drug interaction analyses were performed. 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.

1.3.6 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

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supporting the proposed indications have been conducted in pediatric patients including premature infants.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Hylenex recombinant (hyaluronidase human injection) 150 USP units/mL is a protein enzyme prepared by biotechnology techniques. rHuPH20, in HYLENEX recombinant, is a biotechnology product manufactured in chemically defined media devoid of fetal calf serum or other animal derived constituents.

It is administered as an injection but is not for intravenous use. The applicant's proposed indication is the same as the hyaluronidase DESI review 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 resorptions of radiopaque agents.

The product would be indicated for all age groups including neonates.

2.2 Currently Available Treatment for Indications

There are three animal derived hyaluronidase products currently approved for the hyaluronidase DESI review indications: Vitrase NDA 21-640, Wydase 6-343 and Amphadase NDA 21-665.

2.3 Availability of Proposed Active Ingredient in the United States

The following were approved or permitted in the past:

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.

2.4 Important Issues With Pharmacologically Related Products

Not applicable.

2.5 Presubmission Regulatory Activity

The Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (DAAODP) provided guidance on the criteria for demonstrating the efficacy of HYLENEX recombinant in pre-Investigational New Drug meetings with the sponsor. The guidance confirmed that efficacy could be demonstrated by showing that the specific activity of HYLENEX recombinant meets the in vitro assay established in the United States Pharmacopeia for hyaluronidase. CMC test methods for the drug substance and the drug product were developed as part of the HYLENEX recombinant development program to meet the criteria given by the Division. These methods demonstrate the hyaluronidase activity of the recombinant human hyaluronidase rHuPH20 drug substance. These methods also demonstrate the hyaluronidase activity of rHuPH20 in the HYLENEX recombinant drug product and utilize the USP Reference Standard in determining enzymatic activity values.

NDA 21-859 was submitted with the clinical data requested by the DAAODP as documented in the minutes of a Pre-IND meeting held on January 26, 2004.

2.6 Other Relevant Background Information

Hylenex recombinant (hyaluronidase human injection) has not been marketed in any foreign countries.

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3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Drug Product Composition

Ingredient	Unit Formula 1-mL vial (mg)
rHuPH20 (recombinant human hyaluronidase)	~150 IU
rHuPH20 Overage (recombinant human hyaluronidase)	
Sodium Phosphate Dibasic Dihydrate	1.78
Sodium Hydroxide	4.2
Albumin (Human)	1.0
Calcium Chloride Dihydrate	0.40
Sodium Chloride	8.5
Edetate Disodium Dihydrate	1.0
Water for Injection	qs to 1.0 mL
Other Components	

Regulatory Drug Product Specification

Test	Acceptance Criteria
Description	Clear, colorless solution
Assay and Identity	
rHuPH20 Content	report results
Impurity	report results
Particulate Matter	
pH	6.5 – 8.0
Osmolality	290 – 350 mOsm/kg
Bacterial Endotoxins	
Sterility	sterile

Reviewer's Comment:

rHuPH20 content should be specified. The specific upper limits of impurities should be specified.

At the time of this review, the chemistry reviewer recommends an rHuPh20 overage c

3.2 Animal Pharmacology/Toxicology

From the Pharmacology/Toxicology standpoint, the NDA is recommended for approval with labeling changes included in this review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

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

The submitted clinical study report, clinical protocol, and literature reports related to clinical trial, R04-0851 were reviewed. This study was conducted in the United States under IND 66,888 and is evaluated in this Medical Officer's review. This study was to evaluate patient sensitivity to Hylenex recombinant (hyaluronidase human injection).

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4.2 Tables of Clinical Studies

**Table 4.2-1 R04-0851
 US Safety Study**

Study No. Start Date/ End Date	Study Objective	Population Studied	Design	Doses, Frequency of Dosing	Primary Endpoint	# Pts Treated, Age Range, Mean Age (yrs)	Sex, Race
R04-0851 December 20, 2004/ January 19, 2005 and December 27, 2004/ January 26, 2005	To determine sensitivity to rHuPH20 to be < 10%	Healthy volunteers	Single blinded, single-center, single arm, negative control	0.1 mL HYLENEX (15U) and 0.1 mL 0.5% NaCl Single intradermal injection of each in either forearm	Reaction to injection	100 patients 18 - 70 yrs 37.3 yrs	25 % Male 75 % Female 80 % Caucasian 12 % Black 3 % Asian 3 % American Indian 2 % Other

4.3 Review Strategy

This application was submitted in accordance with Sect. 505(b)(2) of the Federal Food, Drug and Cosmetics Act. This review was conducted by re-reviewing the DESI findings and conclusions, reviewing all submitted literature references, conducting a Medline search and reviewing all relevant articles.

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. These articles were in addition to the articles submitted by the sponsor.

The submitted clinical study reports, clinical protocol, and literature reports related to trial R04-0851 were reviewed. The majority of the application was submitted in the electronic CTD format. Modules 1, 2, and 5 were reviewed in depth.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) was consulted to inspect the only site for the clinical safety study.

There were no discontinuations in this study. There is no evidence which suggests that this trial was not conducted in accordance with accepted ethical standards. There is no evidence to suggest that the applicant did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and protection of human subjects.

4.5 Compliance with Good Clinical Practices

The data from the Phase 1 Safety trial were reviewed for consistency with other applications in this class. No special methods were used.

This trial was conducted under the review of approved Institutional Review Board committee. Investigators used an informed consent form that was appropriate. The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

All patients were completely informed, according to informed consent guidelines, about the pertinent details and purpose of the study. Patients or their legal representatives, read, signed and dated the consent form before taking part in any study activity. A witness and the individual conducting the informed consent discussion also signed and dated the informed consent form. The investigator kept the original signed copies, and provided the patient with a duplicate copy.

4.6 Financial Disclosures

The applicant adequately disclosed financial arrangements with clinical investigators for the Phase 1 Safety trial as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

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

5.2 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.

5.3 Exposure-Response Relationships

This section is not applicable for this product.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

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.

6.1.1 Methods

This review was conducted by re-reviewing the DESI findings and conclusions (6343, 6714 and 7933), reviewing all submitted literature references, conducting a Medline search and reviewing all relevant articles.

The application was submitted in electronic and paper formats. Modules 1, 2, and 5 were reviewed in depth. The submitted clinical study report, clinical protocol, and literature reports related to trial R04-0851 were analyzed in this efficacy review.

The medical reviewer performed a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

6.1.2 General Discussion of Endpoints

This review was conducted by re-reviewing the DESI findings and conclusions of safety and efficacy (6343, 6714 and 7933), reviewing all submitted literature references, conducting a Medline search and reviewing all relevant articles.

The hyaluronidases are a family of beta, 1-4 glucosaminidases that depolymerize hyaluronic acid (HA) and chondroitin sulfate. The recombinant human form of PH20 possesses the same enzymatic activity, as compared to the United States Pharmacopeia (USP) Hyaluronidase Reference Standard, in spreading factor function and dermal layer reconstitution. Thus, references to the DESI findings are appropriate and the USP test for enzymatic activity of hyaluronidase is an appropriate surrogate for efficacy.

6.1.3 Study Design

This review was conducted by re-reviewing the DESI findings and conclusions of safety and efficacy (6343, 6714 and 7933), reviewing all submitted literature references, conducting a Medline search and reviewing all relevant articles.

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).

6.1.4 Efficacy Findings

The DESI evaluation, the enzymatic activity test for hyaluronidase and the literature are supportive of the efficacious use of hyaluronidase.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

The efficacy of HYLENEX recombinant 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.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

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

The application was submitted in electronic and paper formats. Modules 1, 2, and 5 were reviewed in depth. The submitted clinical study report, clinical protocol, and literature reports related to trial R04-0851 were analyzed in this safety review. Refer to Section 10 for the detailed review.

7.1.1 Deaths

No deaths occurred during the development program.

7.1.2 Other Serious Adverse Events

There were no serious adverse events during the development program.

7.1.3 Dropouts and Other Significant Adverse Events

There were no dropouts or other significant adverse events during the development program.

7.1.3.1 Overall profile of dropouts

Not applicable.

7.1.3.2 Adverse events associated with dropouts

Not applicable.

7.1.3.3 Other significant adverse events

There were no serious adverse events during the development program.

7.1.4 Other Search Strategies

Not applicable.

7.1.5 Common Adverse Events

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

7.1.5.1 Eliciting adverse events data in the development program

Not applicable.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Not applicable.

7.1.5.3 Incidence of common adverse events

Refer to Section 7.1.5.4

7.1.5.4 Common adverse event tables

FDA Spontaneous Reporting System

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

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

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

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SOC	PT	Total Events	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
Eye Disorders	Papilloedema	3	0	3	0	0	0	0	3
Blood And Lymphatic System	Eosinophilia	2	0	2	2	0	0	0	0
Vascular Disorders	Haemorrhage NOS	2	0	1	0	0	0	0	1
Skin And Subcutaneous Tissue	Cold Sweat	2	0	2	2	0	0	0	0
Skin And Subcutaneous Tissue	Vitiligo	2	0	2	0	0	0	0	2
Respiratory/Thoracic	Hypoventilation	2	0	2	1	0	0	0	1
Respiratory/Thoracic	Tachypnoea	2	0	2	1	0	0	1	1
Renal And Urinary Disorders	Pollakiuria	2	0	2	0	0	0	0	2
Psychiatric Disorders	Mental Status Changes	2	0	2	2	0	0	2	0
Nervous System	Disorders Akinesia	2	0	2	1	0	0	0	1
Nervous System	Cerebrovascular Accident	2	0	2	2	0	0	0	0
Nervous System	Dizziness	2	0	1	1	0	0	1	0
Nervous System	Dysarthria	2	0	2	0	0	0	0	2
Nervous System	Intracranial Haemorrhage NOS	2	2	2	0	0	0	0	0
Nervous System	Neurological Disorder NOS	2	0	2	0	0	0	0	2
Nervous System	Paralysis NOS	2	0	2	0	0	0	0	2
Nervous System	Peripheral Neuropathy NOS	2	0	2	1	1	0	0	0
Nervous System	Stupor	2	0	2	0	0	0	0	2
Nervous System	Tremor	2	0	2	1	0	0	0	1
Nervous System	Trismus	2	0	2	0	0	0	0	2
Musculoskeletal And Connective Tissue	Back Pain	2	0	2	0	0	0	0	2
Investigations	Blood Pressure Decreased	2	0	2	1	0	0	0	1
Investigations	Computerised Tomogram Abnormal	2	0	2	1	0	0	0	1
Investigations	Intraocular Pressure Increased	2	0	2	2	0	0	0	0
Investigations	Oxygen Saturation Decreased	2	0	2	0	0	0	0	2
Investigations	Pupillary Light Reflex Tests Abnormal	2	0	2	1	0	0	0	1
Injury, Poisoning	Blister	2	0	2	2	0	0	0	2
Injury, Poisoning	Delayed Recovery From Anaesthesia	2	0	2	0	0	0	2	0
Injury, Poisoning	Medication Error	2	0	1	0	0	0	0	1
Infections And Infestation	Eye Infection Staphylococcal	2	0	2	2	0	0	0	0
Infections And Infestation	Infection NOS	2	0	2	2	0	0	0	1
Infections And Infestation	Meningitis	2	0	2	0	0	0	2	0
Infections And Infestation	Pharyngitis	2	0	2	0	0	0	0	2
Immune System Disorders	Anaphylactic Reaction	2	0	2	2	0	0	0	0
General Disorders	Condition Aggravated	2	0	2	1	0	0	0	1
General Disorders	Discomfort NOS	2	0	2	0	0	0	0	2
General Disorders	Injection Site Atrophy	2	0	2	0	0	0	0	2
General Disorders	Injection Site Hypersensitivity	2	0	2	0	0	0	0	2
General Disorders	Injection Site Pain	2	0	2	0	0	0	0	2
General Disorders	Tenderness NOS	2	0	2	2	0	0	0	0
Eye Disorders	Blindness Transient	2	0	2	0	0	0	0	2
Eye Disorders	Blindness Unilateral	2	0	2	0	0	0	0	2
Eye Disorders	Ocular Retrobulbar Haemorrhage	2	0	2	0	2	0	0	0

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SOC	PT	Total Events	Death	Serious	Hospitalized	Disabled	Congenital Anomalies	Life Threatening	Required Intervention
Eye Disorders	Optic Disc Haemorrhage	2	0	2	2	0	0	0	0
Eye Disorders	Optic Nerve Cupping	2	0	2	2	0	0	0	0
Eye Disorders	Optic Nerve Disorder NOS	2	0	2	2	0	0	0	0
Eye Disorders	Orbital Oedema	2	0	2	2	0	0	0	0
Eye Disorders	Parophthalmia	2	0	2	2	0	0	0	0
Eye Disorders	Pupil Fixed	2	0	2	0	0	0	0	2
Eye Disorders	Retinal Artery Occlusion	2	0	2	0	2	0	0	0
Eye Disorders	Retinal Artery Thrombosis	2	0	2	0	0	0	0	2
Eye Disorders	Retinal Exudates	2	0	2	0	2	0	0	0
Eye Disorders	Retinal Oedema	2	0	2	0	2	0	0	0
Eye Disorders	Retinal Vascular Disorder NOS	2	0	2	0	2	0	0	0
Eye Disorders	Uveitis NOS	2	0	2	1	0	0	0	2
Cardiac Disorders	Cyanosis NOS	2	0	2	2	0	0	0	0
Cardiac Disorders	Supraventricular Tachycardia	2	0	2	2	0	0	1	1

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.

7.1.5.5 Identifying common and drug-related adverse events

Refer to Section 7.1.5.4

7.1.5.6 Additional analyses and exploration

Not applicable.

7.1.6 Less Common Adverse Events

Refer to Section 7.1.5.4

7.1.7 Laboratory Findings

Laboratory testing was not performed during the development program.

7.1.8 Vital Signs

Vital signs were not assessed during the development program.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not performed during the development program.

7.1.10 Allergenicity

A Phase 1 safety study was performed to determine the allergenicity of HYLENEX recombinant in normal healthy volunteers. The results of the study were that 100% of the patients had a negative hypersensitivity response to HYLENEX recombinant.

7.1.11 Human Carcinogenicity

Not applicable. Hyaluronidase does not have positive genotoxicity or animal carcinogenicity findings to warrant investigation.

7.1.12 Special Safety Studies

No special safety studies were performed.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Not applicable. This is not a therapeutic class with known abuse potential or apparent withdrawal potential.

7.1.14 Human Reproduction and Pregnancy Data

There are adequate and well-controlled studies in third trimester pregnant women and in women trying to conceive. There are no reported malformations or other problems reported during pregnancy.

7.1.15 Assessment of Effect on Growth

The product has been well studied in pediatric patients including neonates. There are no reported problems with respect to growth.

7.1.16 Overdose Experience

Hyaluronidase is rapidly inactivated and broken down in the body. Systemic doses over 100 times the therapeutic dose have been given without adverse consequences.

7.1.17 Postmarketing Experience

HYLENEX recombinant has not yet been marketed or distributed. The FDA Spontaneous Reporting System's listing of adverse event reports for hyaluronidase of animal origin is presented in Section 7.1.5.4.

7.2 Adequacy of Patient Exposure and Safety Assessments

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

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Refer to Section 10.1.

7.2.1.1 Study type and design/patient enumeration

A Phase 1 clinical safety trial of HYLENEX recombinant to evaluate patient sensitivity to the HYLENEX recombinant injection was performed. The submitted clinical study report, clinical protocol, and literature reports related to this trial, R04-0851 were reviewed. This study was conducted in the United States under IND 66,888 and is evaluated in this Medical Officer's review.

Refer to Section 10.1 for additional details.

7.2.1.2 Demographics

Refer to Section 10.1 for details

7.2.1.3 Extent of exposure (dose/duration)

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

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

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

7.2.2.1 Other studies

Not applicable.

7.2.2.2 Postmarketing experience

Refer to Section 7.1.5.4 for a tabulation of the postmarketing adverse events for animal derived hyaluronidase from the spontaneous reporting system.

7.2.2.3 Literature

The applicant's literature search was complete, including important issues of safety and efficacy.

7.2.3 Adequacy of Overall Clinical Experience

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

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable. There was no special animal or in vitro testing performed.

7.2.5 Adequacy of Routine Clinical Testing

Not applicable.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Not applicable.

7.2.8 Assessment of Quality and Completeness of Data

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

7.2.9 Additional Submissions, Including Safety Update

The sponsor submitted the Safety Update Report on July 27, 2005.

No new safety issues had been identified since the submission of the clinical trial summary. The study is closed and there are no other ongoing studies with the product that would yield additional safety information.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Refer to Section 10.1

7.4 General Methodology

Refer to Section 10.1.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable. Data was not pooled across studies to estimate or compare incidence.

7.4.1.1 Pooled data vs. individual study data

Not applicable. Data was not pooled across studies to estimate or compare incidence.

7.4.1.2 Combining data

Not applicable. Data was not pooled across studies to estimate or compare incidence.

7.4.2 Explorations for Predictive Factors

The only predictive factor identified for a drug-related adverse event in other hyaluronidase products was a prior hypersensitivity reaction.

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.

7.4.3 Causality Determination

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.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

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.

8.2 Drug-Drug Interactions

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.

8.3 Special Populations

Gender effects have been investigated. No significant differences have been observed. Differences based on race have been proposed; however, the data in controlled studies has not supported any differences based on age, race or ethnicity.

8.4 Pediatrics

Hyaluronidase has been well studied in pediatric patients including neonates.

8.5 Advisory Committee Meeting

Not applicable. No Advisory Committee Meeting will be held regarding this application.

8.6 Literature Review

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

8.7 Postmarketing Risk Management Plan

Not applicable. The agency has not requested a postmarketing risk management plan nor has the applicant submitted a postmarketing risk management plan. Routine monitoring of adverse events is recommended.

8.8 Other Relevant Materials

Comments have been received from DDMAC and have been incorporated in the labeling review as appropriate.

9 OVERALL ASSESSMENT

9.1 Conclusions

NDA 21-859 is supported from a clinical perspective with the labeling identified in this review by the USP monograph test for hyaluronidase, 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 of the DESI report was published in the Federal Register on September 23, 1970 (35 FR 14800-1).

9.2 Recommendation on Regulatory Action

The application is recommended for approval with the labeling changes listed in this review.

9.3 Recommendation on Postmarketing Actions

No postmarketing risk management activities are recommended.

9.3.1 Risk Management Activity

No postmarketing risk management activity is recommended.

9.3.2 Required Phase 4 Commitments

Not applicable. No required Phase 4 commitments are applicable.

9.3.3 Other Phase 4 Requests

Not applicable. No Phase 4 requests will be made.

9.4 Labeling Review

The reviewer's additions are noted by underline and deletions by

HYLENEX™ recombinant (hyaluronidase human injection)

Reviewer's Comments:

The trade name has been revised to read "HYLENEX™ recombinant" and the established name has been corrected to read "(hyaluronidase human injection)" here and throughout the label.

Rx Only

DESCRIPTION

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

HYLENEX recombinant (hyaluronidase human injection) is supplied as a sterile, clear, colorless, nonpreserved, ready for use solution. Each mL contains 150 USP units of recombinant human hyaluronidase per mL with 8.5 mg sodium chloride, 1.8 mg sodium phosphate dibasic dihydrate, 4.2 mg sodium hydroxide, 1.0 mg human serum albumin, 1.0 mg edetate disodium dihydrate, and 0.4 mg calcium chloride dihydrate.

HYLENEX recombinant has an approximate pH of 7.4 and an osmolality of 290 to 350 mOsm.

Reviewer's Comments:

The DESCRIPTION section has been edited to conform to current hyaluronidase labels.

The first sentence of the DESCRIPTION section has been revised removing the word _____ because it is promotional in tone.

[

]

CLINICAL PHARMACOLOGY

Hyaluronidase is a spreading or diffusing substance which modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid, a polysaccharide found in the intercellular ground substance of connective tissue, and of certain specialized tissues, such as the umbilical cord and vitreous humor. Hyaluronic acid is also present in the capsules of type A and C hemolytic streptococci. Hyaluronidase hydrolyzes hyaluronic acid by splitting the glucosaminidic bond between C₁ of an N-acetylglucosamine moiety and C₄ of a glucuronic acid

moiety. 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 albumin-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 hyaluronidase preparations may result in the formation of neutralizing antibodies. The reconstitution of the dermal barrier removed by intradermal injection of hyaluronidase (20, 2, 0.2, 0.02, and 0.002 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.

Reviewer's Comment:

The second paragraph and the third sentence of the third paragraph have been added to the CLINICAL PHARMACOLOGY section to be consistent with current hyaluronidase labels.

INDICATIONS AND USAGE

HYLENEX recombinant 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.

CONTRAINDICATION

Hypersensitivity to hyaluronidase or any other ingredient in the formulation is a contraindication to the use of this product.

Reviewer's Comment:

The CONTRAINDICATIONS section has been revised to be consistent with current hyaluronidase labels.

WARNINGS

Discontinue HYLENEX recombinant (hyaluronidase human 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.

Reviewer's Comment:

The WARNINGS section has been revised to be consistent with the current hyaluronidase labels.

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.

Reviewer's Comment:

The PRECAUTIONS, General subsection has been revised to conform to the current hyaluronidase labels.

Laboratory Tests

A preliminary skin test for hypersensitivity to HYLENEX recombinant can be performed. The skin test is made by an intradermal injection of approximately 0.02 mL (3 Units) of a 150 Unit/mL solution. (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.

Reviewer's Comment:

The Agency does not agree with the sponsor's inclusion of an Immunogenicity subsection. This information is included in the CONTRAINDICATION section.

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The sponsor has omitted the Laboratory Tests subsection. The Laboratory Tests subsection should be included.

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.

Reviewer's Comment:

The Drug Interactions subsection has been divided into two paragraphs.

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.

Reviewer's Comments:

The Carcinogenesis, Mutagenesis, Impairment of Fertility subsection has been revised to conform to the current hyaluronidase labels.

Pregnancy

Teratogenic Effects—Pregnancy Category C

No adequate and well controlled animal studies have been conducted with HYLENEX recombinant to determine reproductive effects. No adequate and well controlled studies have been conducted with HYLENEX recombinant in pregnant women. HYLENEX recombinant should be used during pregnancy only if clearly needed.

Reviewer's Comment:

The labeling recommendations from the Pharmacology Toxicology review have been incorporated in the Pregnancy subsection to be consistent with other hyaluronidase labels.

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

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hyaluronidase has an effect on the later growth, development, and functional maturation of the infant.

Reviewer's Comment:

The PRECAUTIONS, Labor and Delivery subsection has been revised to be consistent with other hyaluronidase labels.

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.

Reviewer's Comment:

The PRECAUTIONS, Nursing Mothers subsection has been revised to be consistent with other hyaluronidase labels.

Pediatric Use

Hyaluronidase may be added to small volumes of solution (up to 200 mL), such as a small clysis for infants or solutions of drugs for subcutaneous injection. The potential for chemical or physical incompatibilities should be kept in mind (See "Dosage and Administration".)

For infants and children less than 3 years old, the volume of a single clysis should be limited to 200 mL; and in premature infants or during the neonatal period, the daily dosage should not exceed 25 mL/kg of body weight; the rate of administration should not be greater than 2 mL per minute. For older patients, the rate and volume of administration should not exceed those employed for intravenous infusion.

During hypodermoclysis, special care must be taken in pediatric patients to avoid over hydration by controlling the rate and total volume of the clysis. (See "**DOSAGE and ADMINISTRATION**, Hypodermoclysis")

Reviewer's Comments:

The Pediatric Use subsection has been revised to be consistent with other hyaluronidase labels.

*The Agency does not agree with the sponsor's inclusion of the second and third sentences in the third paragraph. These sentences have been deleted because this information is included in the **WARNINGS and PRECAUTIONS** sections.*

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

Reviewer's Comment:

*In the sponsor's submission, the Geriatric Use subsection was placed in the **DOSAGE AND ADMINISTRATION** section. It has been moved to the correct section, **PRECAUTIONS**.*

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 or angioedema) have been reported in less than 0.1% of patients receiving hyaluronidase. Anaphylactic-like reactions following retrobulbar block or intravenous injections have occurred, rarely.

Reviewer's Comment:

The ADVERSE REACTIONS section has been revised to be consistent with other hyaluronidase labels.

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.

Reviewer's Comment:

The OVERDOSAGE section has been revised to be consistent with other hyaluronidase labels.

DOSAGE AND ADMINISTRATION

HYLENEX recombinant (hyaluronidase human 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 U, most typically 150 U hyaluronidase, to the injection solution.

It is recommended that appropriate references be consulted regarding physical or chemical incompatibilities before adding HYLENEX recombinant 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 HYLENEX recombinant into rubber tubing close to needle.

An alternate method is to inject HYLENEX recombinant 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 the same precautions for restoring fluid and electrolyte balance as in intravenous injections. The dose, the rate of injection, and the type of solution (saline, glucose, 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.

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HYLENEX recombinant 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 HYLENEX recombinant 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.

Reviewer's Comment:

*The **DOSAGE AND ADMINISTRATION** section has been revised to be consistent with other hyaluronidase labels.*

HOW SUPPLIED

HYLENEX recombinant (hyaluronidase human injection) is supplied sterile as 150 USP units of nonpreserved recombinant human hyaluronidase per mL in a single-use 2 mL glass vial with a gray rubber stopper and aluminum flip-off seal.

1 mL Single Dose Vial available in boxes of 1 (NDC 60977-319-02)

1 mL Single Dose Vial available in boxes of 10 (NDC 60977-319-01)

Not Recommended for IV Use.

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

DO NOT FREEZE.

Marketed by: Baxter Healthcare Corporation
Deerfield, IL 60015 USA
Manufactured for: Halozyme Therapeutics, Inc.
San Diego, CA 92121
By Baxter Pharmaceutical Solutions LLC
Bloomington, IN 47403

HYLENEX recombinant is a trademark of Baxter International, Inc. or its subsidiaries.

For Product Inquiry 1 800 ANA DRUG (1-800-262-3784)

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Reviewer's Comment:

*The **HOW SUPPLIED** section has been revised to clarify the proper use of HYLENEX recombinant.*

No Medication Guide or Patient Package Insert has been proposed or is necessary for this product.

9.5 Comments to Applicant

No comments pertaining to specific deficiencies.

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10 APPENDICES

10.1 Review of Individual Study Reports

Safety Trial R04-0851 - Evaluation of Sensitivity to HYLENEX™ recombinant (hyaluronidase human injection)

Objective: To evaluate the sensitivity of subjects to HYLENEX™ recombinant (hyaluronidase human injection);
To determine that less than 10% of patients tested will have a positive reaction to HYLENEX™ recombinant.

Study Design: A prospective, single-masked, single center controlled trial.

Test Drug Schedule: The test product, HYLENEX recombinant was administered intradermally to subjects at 0.1 mL (15U) in the volar forearm. The control 0.1 mL of 0.9% Sodium Chloride Injection, USP was administered intradermally to subjects in the contralateral forearm.

Principal Investigator: Rachel A. Bittker, MD
PRACS Dermatology, LLC
15222-B Avenue of Science
San Diego, CA 92128

Study Design:

This study was a single blind, single-center, open-label, placebo-controlled clinical study intended to evaluate patient sensitivity to a single injection of HYLENEX™ recombinant.

One hundred healthy volunteers of either gender, ranging in age from 18 to 85 years of age, were enrolled in the study. Subjects were pre-screened for eligibility using the inclusion and exclusion criteria determined appropriate for this study. All eligible subjects were asked to sign informed consent forms prior to enrollment in the study.

Enrolled subjects had blood drawn and the serum retained for analysis in those cases that exhibited a positive reaction to HYLENEX™ recombinant. Subjects were given 0.1 mL (15U) of test solution intradermally in the volar forearm. In the contra-lateral forearm, they were injected with 0.1 mL of 0.9% sodium chloride injection USP. All subjects were monitored for at least 30 minutes post injection to identify those subjects exhibiting a positive reaction at the injection site. The monitor was blinded to the forearm that receives the test article and control article. A positive reaction consisted of a wheal with pseudopods appearing within five minutes post injection, and persisting for at least 20 minutes with localized itching. Transient vasodilation at the test site, i.e., erythema, was not considered a positive reaction.

Subjects exhibiting a positive reaction were monitored until the reaction subsided (generally within 30 minutes). They were followed-up by telephone, or an office visit, 24 hours post injection. All subjects were to return to the test facility approximately 48 hours post injection for a second evaluation. A final follow-up was done for all subjects by telephone 30 days post injection. All subjects were asked to observe the test sites daily for 30 days following the injection. The duration of the study was 31 days (the day of injection, plus 30 days after). Subjects were not permitted to participate in another clinical study during that time.

Inclusion Criteria:

All of the following criteria must have been met for the subject to be eligible for participation:

- 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
- 4) Women of childbearing potential willing and able to use an acceptable method of birth control (e.g. barrier methods used with a spermicidal agent, hormonal methods, IUD, surgical sterilization, abstinence) during the study.
 - a. Women will not be considered of childbearing potential if one of the following is documented in the medical history
 - i. Postmenopausal with an absence of menses for at least one year
 - ii. Bilateral oophorectomy with or without a hysterectomy and an absence of bleeding for at least 6 months
 - iii. Total hysterectomy

Exclusion Criteria:

If any of the following exclusion criteria were met, the subject was NOT eligible for participation:

- 1) Subjects who are pregnant or lactating
- 2) Subjects who have had hyaluronidase treatment or testing within the last 3 months
- 3) Subjects who were treated with chemotherapy agents or systemic corticosteroids within the past 3 months, or who will be treated with them during the study
- 4) Subjects who were treated with topical corticosteroids near the sites of injection within 7 days of enrollment, or who will be treated with them during the study
- 5) Subjects who were treated with immunosuppressive drugs within the past 3 months, or who will be treated with them during the study
- 6) Subjects who have used oral antihistamines within 14 days of study conduct, or who will use them during the study
- 7) Subjects who have used topical antihistamines near the sites of injection within 7 days of study conduct, or who will use them during the study
- 8) Subjects who have used β -blockers within 14 days of study conduct, or who will use them during the study
- 9) Subjects with a history of autoimmune disorder (including systemic lupus erythematosus, rheumatoid arthritis, thyroid disorders, etc)

- 10) Subjects with a current disease state that can effect immune response (e.g., flu, cancer, HIV)
- 11) Subjects with diabetes or heart disease
- 12) Subjects who have infected/inflamed skin or skin disease in the area of the injection
- 13) Subjects who have skin imperfections such as moles and tattoos at the sites of injection
- 14) Subjects with known sensitivity to hyaluronidase
- 15) Subjects with known allergy to proteins
- 16) Subjects with severe allergies manifested by a history of anaphylaxis
- 17) Subjects who are allergic to bee or vespid (yellow jackets, hornets, and wasps) venom
- 18) Subjects who are allergic to Chinese hamster proteins
- 19) Subjects who have participated in any clinical testing involving unapproved investigational drugs or devices, including other studies being conducted at PRACS, within 30 days prior to enrollment
- 20) Subjects that have a medical condition that, in the opinion of the investigator, might significantly affect their ability to safely participate in the study or affect the conduct of the study. Examples might include: active asthma, epilepsy, cancer, etc.

Subject Disposition and Demographics

Table 7.2.1.2 – 1 HYLENEX™ Study R04-0851	
	Treatment group
	Test Product & Negative Control
Age (years)	
Mean ± SD	37.27 ± 3.51
Range	18 – 70
Groups	
<18	0%
18-40	62%
40-64	35%
65-75	3%
>75	0%
Sex	
Male	25
Female	75
Race	
Caucasian	79
Black/African American	12
Asian	4
Asian/Hawaiian/Pacific Islander	3
American Indian / Alaskan Native	2

Criteria for Evaluation

The injection sites were evaluated for the presence of a wheal with pseudopods and itching. A positive response required the presence of all three reactions occurring within five minutes post injection and with persistence for at least 20 minutes.

Skin Test Evaluations

Injection sites were evaluated by the Investigator, Rachel A. Bittker, M.D., who was blinded to the rotation schedule. Assessments were done approximately each minute for the first five (5) minutes after injection. If a reaction consistent with a positive response developed at an injection site during that time, it was reassessed approximately twenty (20) minutes following the onset of the reaction. All injection sites for all subjects were reassessed approximately thirty (30) minutes following the injection. Subjects exhibiting a positive response were to be followed-up by telephone or visit, 24 hours post injection. All subjects returned to the testing facility approximately 48 hours post injection and test sites were again assessed. Additionally, subjects were instructed to observe the test sites daily for 30 days following the injection. The Investigator was to be notified immediately if any new reaction or systemic effect was experienced. Final follow-up was performed by telephone 30 days post injection for all subjects.

Skin Test Results

100% of the subjects exhibited a negative response. Common reactions consisted of stinging, itching, erythema, the presence of a wheal and ecchymosis. More appearances of ecchymosis were observed for the test sites at the 48 hour time point that were injected with HYLENEX™ recombinant than the test sites injected with the control (65 versus 26 instances).

No statistical analysis was performed due to the 100% negative response result.

Safety Results

The frequency of adverse events was recorded. The 95% confidence interval for allergic reaction is less than 3%.

HYLENEX™ Study R04-0851	
Body System / Adverse Event	Reported Incidence by Treatment Group
	HYLENEX™ : Test Article
	0.9% NaCl Injection : Negative Control
	Patient Count N=100
Aural Disorders	
Ear Ache	1(1%)
Respiratory Disorders	
Sore throat	3(3%)
Post Nasal Drip	1(1%)
Respiratory Tract Infections	
Flu	1(1%)
Strep. Throat	1(1%)
Joint Disorder	
Swollen knee	1(1%)
Headaches	
Headache	1(1%)
Migraine	1(1%)
Skin Appendage Condition	
Acne	1(1%)

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10.2 Line-by-Line Labeling Review

Refer to Section 9.4.

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/s/

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