CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-716

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-716 SUPPL # HFD # 520

Trade Name Hydase

Generic Name hyaluronidase injection

Applicant Name Prima Pharm, Inc.

Approval Date, If Known 10/25/05

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ NO ☐
Explain:

Investigation #2

IND # YES ☐ NO ☐
Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Lucious Lim
Title: Medical Officer
Date: 6/22/05

Name of Office/Division Director signing form: Wiley A. Chambers
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Wiley Chambers
11/7/2005 03:16:52 PM

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Anthony Dziabo, Prima Pharm	**From:** Lori Gorski, Project Manager
Fax: 858-259-8268	**Fax:** 301-827-2531
Phone: 858-259-0717	**Phone:** 301-827-2521
Pages: 6 (including cover page)	**Date:** June 23, 2005

Re: NDA 21-716 labeling comments for hyaluronidase

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Tony,

Attached is the Divisions draft labeling for Hydase. Please respond with an amendment to NDA 21-716 with a clean copy of the package insert and the changes to the carton and container. Please include a form FDA-356h with every submission.

Please contact me if you have questions.

Thanks,
Lori Gorski

NDA 21-716

Prima Pharm, Inc.

Attention: Anthony Dziabo
V.P. Regulatory Affairs
3443 Tripp Court
San Diego, California 92121

Submission date: January 12, 2005

1. The established name should be revised on the container and carton labeling to a font size that is at least half as large of that of the proprietary name and a prominence commensurate with the proprietary name, as stated in 21 CFR 201.10(g)(2).

2. The proposed established name "(hyaluronidase) ——— Solution" should be changed to "(hyaluronidase, injection)."

3. All carton and container labels should include the storage temperature in Fahrenheit. The labels should read, "Store at 2° to 8°C (36° to 46°F)."

4. Mock-up for the 26 x 1mL in a 2mL vial carton labeling should be provided.

6 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Administrative- 1

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/s/

Lori Gorski
6/23/05 03:23:02 PM
CSO

Lori Gorski
6/23/05 03:35:01 PM
CSO
label to sponsor

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
David Hussong Pkln 18B-08
DHHS/FDA/CDER/OPS/ONDC/HFD-805
Steve Langille

FROM:
Lori Gorski phone 301-827-2521

DHHS/FDA/CDER/ORM/DAAODP HFD-550

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 10, 2005		21-716	Amendment to NDA	June 7, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Hydase hyaluronidase injection	priority		June 17, 2005

NAME OF FIRM: Prima Pharm, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ **NEW PROTOCOL**
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE 2
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

XX Amendment to Original NDA submission

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Prima Pharm, Inc has submitted NDA 21-716 for Hydase (hyaluronidase injection) as an adjuvant to increase the absorption and dispersion of other injected drugs

This is the complete response to the micro comments forwarded from the review dated March 25, 2005. Steve Langille is the reviewer.

If you have any questions, please contact Lori Gorski, Project Manager at 7-2521.

Please cc GORSKIL RODRIGEUZLi and NGL on the DFS email when this review has been completed. Thanks

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) **XX Through Document Room** HAND

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/s/

Lori Gorski
6/10/05 09:27:13 AM
micro consult for NDA amendment

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-716

Prima Pharm, Inc.
Attention: Anthony Dziabo
V.P. Regulatory Affairs
3443 Tripp Court, Suite A
San Diego, California 92121

Dear Mr. Dziabo:

We acknowledge receipt on January 14, 2005, of your January 12, 2005, resubmission to your new drug application for Hydase (hyaluronidase injection).

We consider this a complete, class 2 response to our April 20, 2004, action letter. Therefore, the user fee goal date is July 14, 2005.

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Lori Gorski
4/5/05 10:20:18 AM
Lori Gorski has signed for Carmen DeBellas

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Anthony Dziabo, Prima Pharm	**From:** Lori Gorski, Project Manager
Fax: 858-259-8268	**Fax:** 301-827-2531
Phone: 858-259-0717	**Phone:** 301-827-2521
Pages: 3 (including cover page)	**Date:** March 29, 2005

Re: NDA 21-716 microbiologic reviewer requests and deficiencies for hyaluronidase

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Tony,

After review of the submission dated January 12, 2005, the following items have been identified as deficiencies by the micro reviewer for the Hydase. Please respond with an amendment(s) to NDA 21-716. Please include a form FDA-356h with every submission.

Please contact me if you would like an informal meeting or teleconference with the Division representatives to further discuss or request clarification regarding these issues.

Thanks,
Lori Gorski

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Administrative- 2

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/s/

Lori Gorski
3/29/05 11:11:08 AM
CSO

Lori Gorski
3/29/05 11:15:30 AM
CSO
comments sent to sponsor 3/29/05

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
David Hussong Pkln 18B-08
DHHS/FDA/CDER/OPS/ONDC/HFD-805
Steve Langille

FROM:
Lori Gorski phone 7-2521

DHHS/FDA/CDER/ORM/DAAODP HFD-550

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 18, 2005		21-716	Amendment to Original NDA submission	January 12, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Hydase hyaluronidase injection	priority		April 15, 2005

NAME OF FIRM: Prima Pharm, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ **NEW PROTOCOL**
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
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- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

XX Amendment to Original NDA submission

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

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- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Prima Pharm, Inc has submitted NDA 21-716 for Hydase (hyaluronidase injection) as an adjuvant to increase the absorption and dispersion of other injected drugs

This is the complete response to the AE letter sent April 21, 2004. Steve Langille is the reviewer.

If you have any questions, please contact Lori Gorski, Project Manager at 7-2521.

Please cc GORSKIL RODRIGEUZLi and NGL on the DFS email when this review has been completed. Thanks

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
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/s/

Lori Gorski
1/18/05 06:04:09 PM
consult to micro

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Janice Brown/Stephen Moore Pkln 14B-19
DHHS/FDA/CDER/OPS/ONDCII/HFD-510

FROM:
Lori Gorski phone 301-827-2521
DHHS/FDA/CDER/OND/DAAODP/ HFD-550

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 18, 2005		21-716	CMC Amendment to Orig NDA	January 12, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Hydase hyaluronidase injection	Priority		**April 15, 2005**

NAME OF FIRM: Prima Pharm

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
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- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

Amendment to Original NDA

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

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- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Prima Pharm, Inc has submitted NDA 21-716 for Hydase (hyaluronidase injection) as an adjuvant to increase the absorption and dispersion of other injected drugs

This is the complete response to the AE letter sent April 21, 2004. Janice Brown is the reviewer.

Please cc gorskiL and ngL on the DFS review.
Contact Lori Gorski if you have any questions at 301-827-2521.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND **DOCUMENT ROOM**
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Lori Gorski
1/18/05 06:12:03 PM
consult for viral clearance amendment

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Anthony Dziabo, Prima Pharm	**From:** Lori Gorski, Project Manager
Fax: 858-259-8268	**Fax:** 301-827-2531
Phone: 858-259-0717	**Phone:** 301-827-2521
Pages: 2 (including cover page)	**Date:** August 5, 2004

Re: NDA 21-716 reviewer requests and deficiencies for hyaluronidase

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Tony,

After review of the submission dated April 8, 2004, the following items have been identified as deficiencies by the reviewers for the Hydase application with regards to the viral clearance issues. Please respond with an amendment(s) to NDA 21-716. Please include a form FDA-356h with every submission.

Please contact me if you would like an informal meeting or teleconference with the Division representatives to further discuss or request clarification regarding these issues.

Thanks,
Lori Gorski

NDA 21-716

Prima Pharm, Inc.

Attention: Anthony Dziabo
V.P. Regulatory Affairs
3443 Tripp Court
San Diego, California 92121

Submission date: April 8, 2004

1. Numerical values for the log reduction and/or inactivation of model viruses for at least one additional step beside the [ ] step should be determined. Alternatively, values from published scientific literature (i.e., book or journal article) may be used. The information you provided for the [ ] steps was from unpublished sources and is therefore considered insufficient for this purpose. If published scientific literature is used then a table comparing the conditions used in the literature and your hyaluronidase process (e.g., type of intermediate, [ ], etc.) should be provided.

2. A description of the scale-down process used to perform the viral clearance of the [ ] step should be submitted. This should include the type of [ ] and sample storage conditions.

3. The results you reported for the viral clearance study for [ ] were derived from only a single test. Demonstration of an effective virus removal step should be performed using at least two independent studies.

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/s/

Lori Gorski
8/5/04 10:05:54 AM
CSO
faxed to sponsor 8-5-04

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Administrative- 3

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 20, 2004

FROM: William Boyd, M.D.
Clinical Team Leader
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

THROUGH: Wiley Chambers, MD
Deputy Division Director, HFD-550
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

THROUGH: Brian Harvey, M.D., Ph.D.
Acting Division Director, HFD-550
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

TO: Jonca Bull, M.D.
Office Director, HFD-550
Office of Drug Evaluation V

SUBJECT: Intradermal Injections of Hyaluronidase

The original test for the allergenicity of hyaluronidase was arbitrarily 10% of the proposed drug product. The product originally on the market was 15 units of hyaluronidase; therefore the test was 1.5 units. This testing was adequate to elicit allergic reactions in susceptible patients.

The next version of the product packaging was 30 units, and the recommended intradermal skin test became 3 units. This was written into the labeling of the hyaluronidase products. Later, products became packaged as 150 units or 1500 units per mL.

The Division initially suggested a volume of 0.1 mL for the convenience of administration; sponsors have preferred to utilize 0.02 mL of a 150 units/ml solution even though it is more difficult to withdraw and administer (i.e. requires a special size syringe).

This 0.02 mL volume for intradermal injection is acceptable. Historically, any amount of hyaluronidase $\geq$ 1.5 units will give a reaction if a patient is allergic.

Cc:
NDA 21-665
NDA 21-640
NDA 21-716
NDA 21-593
ODEV/Dir/Bull
ODEV/ADRA/Rumble
HFD-550/Sup CSO/DeBellas
HFD-550/Div Dir/Harvey
HFD-550/Dep Div Dir/Chambers
HFD-550/CSO/Gorski
HFD-550/CSO/Puglisi
HFD-550/M.O./Harris
HFD-550/M.O./Lim

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/s/

William Boyd
4/20/04 11:46:42 AM
MEDICAL OFFICER

Wiley Chambers
4/20/04 11:50:58 AM
MEDICAL OFFICER

Brian Harvey
4/20/04 01:38:38 PM
MEDICAL OFFICER

Jonca Bull
4/20/04 03:50:53 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Stephen Moore Pkln 14B-19
DHHS/FDA/CDER/OPS/ONDCII/HFD-510
Janice Brown

FROM:
Lori Gorski phone 301-827-2521
DHHS/FDA/CDER/OND/DAAODP/ HFD-550

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 15, 2004		21-716	CMC Amendment to Orig NDA	April 8, 2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Hydase hyaluronidase injection	Priority		June 1, 2004

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

Amendment to Original NDA

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Prima Pharm submitted the original NDA on Oct 17, 2004. There was not adequate viral clearance data submitted in the original NDA. Per numerous requests to the sponsor for further viral clearance information, this amendment was submitted. An approvable letter was issued to the sponsor on April 20 with the deficiencies from the April 7, 2004 completed viral clearance review.

Please cc gorskiL and ngL on the DFS review.
Contact Lori Gorski if you have any questions at 301-827-2521.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND **DOCUMENT ROOM**
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Lori Gorski
4/15/04 01:53:26 PM
consult sent 4/15/04

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # **21-716** Supplement # SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: **Hydase**
Generic Name: **(hyaluronidase injection)**
Strengths:

Applicant: **Prima Pharm, Inc.**

Date of Application: **October 17, 2003**
Date of Receipt: **October 20, 2003**
Date clock started after UN:
Date of Filing Meeting: **December 4, 2003**
Filing Date: **December 19, 2003**
Action Goal Date (optional): User Fee Goal Date: **April 20, 2003**

Indication(s) requested: **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.**

Type of Original NDA: (b)(1) _____ (b)(2) __XX____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S _____ P __XX_____
Resubmission after withdrawal? __NO_____ Resubmission after refuse to file? ____No____
Chemical Classification: (1,2,3 etc.) ____3____
Other (orphan, OTC, etc.) ___No_____

User Fee Status: Paid ____XX____ Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

Form 3397 (User Fee Cover Sheet) submitted: **YES** NO
User Fee ID # ___4632_____
Clinical data? YES _____ **NO, Referenced to NDA # ___6-343___**

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES **NO**

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES **NO**

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES **NO**

Is the application affected by the Application Integrity Policy (AIP)? YES **NO**
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES **NO**

- Does the submission contain an accurate comprehensive index? **YES** NO
- Was form 356h included with an authorized signature? **YES** NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? **YES** NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? **N/A** YES NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? **N/A** YES NO
- Is it an electronic CTD? **N/A** YES NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- Patent information submitted on form FDA 3542a? **YES** NO
- Exclusivity requested? YES, _____years **NO**
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? N/A **YES** NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., *"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."* Applicant may not use wording such as "To the best of my knowledge . . . ."
- Financial Disclosure forms included with authorized signature? **N/A** YES NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? **YES** NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? **YES** NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: **IND 66,907**

- End-of-Phase 2 Meeting(s)? Date(s) _____ **NO**
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ **NO**
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **YES** NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? **YES** NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? **N/A** YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? **N/A** YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? **N/A** YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? **N/A** YES NO

Chemistry SEE CMC REVIEW

- Did applicant request categorical exclusion for environmental assessment? YES NO
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If a parenteral product, consulted to Microbiology Team (HFD-805)? **YES** NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and **NDA 6,343**

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). **New formulation**

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES **NO**

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES **NO**

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES **NO**

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

  _XX___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

  ____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

  ____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
  ____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES **NO**

  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES **NO**

  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug? **NO RLD available to compare to.**

    N/A YES NO

  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4): **No clinical studies in this application – only a skin sensitivity study.**

  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO

  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO

  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    IND # 66,907 NO

    OR

    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 4, 2003

BACKGROUND:
Hyaluronidase has been on the CDER drug shortage list for more than 2 years since the last US sponsor ceased manufacturing the product. This application will be a priority review in light of the drug shortage (6 month review clock).

The NDA is a 505b2 application which references the DESI notice of September 23, 1970.

ATTENDEES: see below

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Lucious Lim
Pharmacology:	Zhou Chen
Chemistry:	Li Rodriguez
Biopharmaceutical:	Dennis Bashaw (later assigned to Lei Zhang)
Microbiology, sterility:	Steve Langille
Viral clearance:	Stephen Moore
Regulatory Project Management:	Lori Gorski
Other Consults:	

Per reviewers, are all parts in English or English translation? **YES** NO
If no, explain:

CLINICAL **FILE __XX___** REFUSE TO FILE _____

- Clinical site inspection needed: YES **NO**
- Advisory Committee Meeting needed? YES, date if known _____ **NO**
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **N/A** YES NO

BIOPHARMACEUTICS **FILE _XX___** REFUSE TO FILE _____

- Waiver should be requested. YES NO

PHARMACOLOGY **FILE _XX___** REFUSE TO FILE _____

CHEMISTRY **FILE _XX___** REFUSE TO FILE _____

- Establishment(s) ready for inspection? **YES** NO

MICROBIOLOGY **FILE _XX___**

VIRAL CLEARANCE **FILE _XX___**

ELECTRONIC SUBMISSION: **N/A**

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

_XX___ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

_XX___ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues conveyed to applicant by Day 74.

Lori Marie Gorski
Regulatory Project Manager, HFD-550

See electronic signature page

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/s/

Lori Gorski
4/12/04 11:40:52 AM
CSO

Lori Gorski
4/12/04 11:42:47 AM
CSO

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 01/20/04 **DATE OF DOCUMENT:** 10/17/03	**DESIRED COMPLETION DATE:** 04/01/04	**ODS CONSULT #:** 04-0020

TO: Brian Harvey, M.D., Ph.D. (Acting)
Director, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products
HFD-550

THROUGH: Lori Gorski
Project Manager
HFD-550

PRODUCT NAME: **Hydase** (Hyaluronidase Injection, USP [Bovine]) 150 USP units/mL **NDA #:** 21-716	**NDA SPONSOR:** PrimaPharm, Inc.

SAFETY EVALUATOR: Jinhee L. Jahng, Pharm.D.

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, Hydase.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name, Hydase, acceptable from a promotional perspective.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 03/15/04

NDA #: 21-716

NAME OF DRUG: Hydase
(Hyaluronidase Injection, USP [Bovine])
150 USP units/mL

NDA HOLDER: PrimaPharm, Inc.

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550), for assessment of the proprietary name, "Hydase", regarding potential name confusion with other proprietary or established drug names. According to the Pharmacology/Toxicology review, Wydase, a DESI drug product, was withdrawn for reasons unrelated to safety and efficacy. Container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Hydase is a protein enzyme containing hyaluronidase 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. Hydase is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. Absorption and dispersion of other injected drugs may be enhanced by adding 150 units of hyaluronidase to the injection solution. For hypodermoclysis, 150 units of hyaluronidase is injected into the rubber tubing close to the needle after the start of clysis or subcutaneously before clysis for each 1000 milliliters or more of parenteral fluid to be administered. For subcutaneous urography, 75 units of hyaluronidase is injected subcutaneously over each scapula, followed by injection of the contrast medium at the same sites.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2,] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Hydase to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Hydase. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Hydase acceptable from a promotional perspective.

2. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Hydase. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

---

[1] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual dose*	Other**
Hydase	**Hyaluronidase Injection, USP [Bovine] 150 units/mL Single Use Vial**	**Inject 150 units subcutaneously prior to procedure.**	
Hydrea	Hydroxyurea Capsules 500 mg	For solid tumors and chronic myelocytic leukemia, 20 to 30 mg/kg/day administered as a single daily dose. A dose of 80 mg/kg every third day may be used for solid tumors.	LA
Zydone	Acetaminophen and Hydrocodone Bitartrate Tablets 400 mg/5 mg, 400 mg/7.5 mg, 400 mg/10 mg	1 to 2 tablets every 4 to 6 hours up to 8 per day.	LA
Wydase (not marketed)	Hyaluronidase Injection, USP [Bovine] 150 units/vial, 1500 units/vial	Inject 150 units subcutaneously prior to procedure.	SA/LA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
***Name pending approval. Not FOI releasable

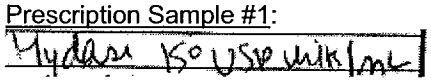
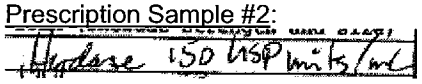
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Hydase were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Hydase with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Two prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Hydase (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the written orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Prescription Sample #1: 	Pharmacy Requisition Order 012B #2 Hydase 150 USP units/mL
Prescription Sample #2: 	

2. Results:

Two respondents from the written study interpreted the proposed name as the formerly U.S. marketed product Wydase. One respondent interpreted the proposed names as ——— a product pending approval. See Appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

In reviewing the proprietary name, Hydase, the primary concerns related to look-alike and sound-alike confusion with Hydrea, Zydone, ———[***], and Wydase.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Hydase could be confused with ——— and Wydase. Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. The remaining incorrect misinterpretations for the verbal and written prescription studies were phonetic/misspelled interpretations of "Hydase".

1. Hydrea and Hydase have potential for look-alike confusion. Hydrea is an antineoplastic agent available for oral use as capsules providing 500 mg of hydroxyurea. It is indicated for melanoma, resistant chronic myelocytic leukemia, and recurrent, metastatic, or inoperable carcinoma of the ovary. It is also concomitantly used with irradiation therapy in the local control of primary squamous cell carcinomas of the head and neck, excluding the lip. Hydrea and Hydase share the same beginning ("Hyd-") and the remaining letters can resemble each other if not precisely scripted (see page 6). Additionally, the two names each have six letters. Hydrea is available as a 500 mg capsule and stored at room temperature; Hydase will be available as a 150 units/mL single use vial and refrigerated. Both medications are given once daily. In a 50 kg patient, Hydrea's dosage range is 1000 mg to 1500 mg, administered as a single dose. The 1500 mg dose can be confused with Hydase's 150 unit dose, as post-marketing experience has shown medication errors occurring as a result of a numerical similarity in strengths. A patient inadvertently receiving Hydrea instead of Hydase may be subject to bone

[***] Pending approval proprietary and confidential information that should not be released to the public.

marrow depression, gastrointestinal symptoms, and dermatological reactions. Hydrea is genotoxic and should be avoided in males and females contemplating conception. On the contrary, inadvertent administration of Hydase may subject the patient to local edema or urticaria, erythema, chills, nausea, vomiting, dizziness, tachycardia, and hypotension. Although Hydrea will only be used during surgical procedures, the potential for a dispensing error with Hydase still exists in the inpatient hospital setting due to similar product characteristics.

Hydase
Hydrea

2. Zydone and Hydase have look-alike characteristics. Zydone, a narcotic analgesic combination consisting of hydrocodone bitartrate and acetaminophen, is indicated for relief of moderate to moderately severe pain. Zydone and Hydase have six letters and share similar orthographic characteristics. The "Z-" in Zydone and the "H-" in Hydase resemble each other when scripted, as do the letters "-as-" vs. "-on-". This similarity in script, in combination with the overlapping letters "-yd-" and "-e", increase the likelihood for one name to be confused with the other (see below). However, Zydone is an oral tablet typically given multiple times daily whereas Hydase is an injectable given once prior to a procedure. In addition, Hydase and Zydone differ in respects to dosage form (injection vs. tablet), route of administration (subcutaneous vs. oral), dosage schedule (once daily vs. multiple times daily), strength, and storage conditions (refrigerated vs. room temperature). Despite some orthographic similarities, the likelihood for confusion between the two drug names is minimized because of the differences mentioned above.

Hydase Zydone

3. ——— *** was identified to have sound and look-alike potential with Hydase. ——— is a drug product currently marketed in the United Kingdom by CP Pharmaceuticals, Ltd. and is being reviewed at the division level for approval in the United States. ——— appears in the United States Patent and Trademark Office database. Although Hyalase is kept at room temperature, and Hydase is refrigerated, the two products share the same active ingredient, indication, dosage form, dosage route, and administration schedule. ——— and Hydase can look similar as demonstrated in the DMETS prescription studies. ——— and Hydase ——— The remaining letters, "-al-" vs. "-d", resemble each other when scripted, especially if the "-a-" is written in close proximity to the "-d-" as written in the writing sample below. ——— has three syllables as opposed to the two in Hydase, however, ——— could potentially be misinterpreted for ——— if the second syllable "-a-" is deemphasized. Although, the outcome of confusion between these two drugs is not likely to result in patient harm, DMETS discourages the use of proprietary names that may result in medication errors due to their similar appearance or sound.

*** Pending approval proprietary and confidential information that should not be released to the public.

Hydase

4. Wydase and Hydase look and sound similar when written. Wydase is a prescription product no longer marketed in the United States. According to the Pharmacology/Toxicology review, Wydase, a DESI drug product, was withdrawn for reasons unrelated to safety and efficacy. The sponsor indicated that Hydase is equivalent to Wydase with the same active ingredient, inactive ingredients, dosage form, strength, route of administration, and indication. Wydase and Hydase can look similar as demonstrated in the DMETS prescription studies. Wydase and Hydase share five of six letters in each respective name. The "W-" can resemble the "H-" as demonstrated below. Wydase and Hydase each have two syllables and have rhyming characteristics. Despite the phonetic, orthographic, and product similarities the two names share, the information that Wydase is no longer marketed in the United States minimizes the potential for confusion and error between Wydase and Hydase.

Wydase Hydase

WYDASE
HYDASE

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name, Hydase. In reviewing the proprietary name, the primary concerns related to look-alike confusion with ——— , which is listed in the United States Patent and Trademark Office database, and the currently marketed product, Hydrea.

A. Hydrea and Hydase have potential for look-alike confusion. Hydrea is an antineoplastic agent available for oral use as capsules providing 500 mg of hydroxyurea. It is indicated for melanoma, resistant chronic myelocytic leukemia, and recurrent, metastatic, or inoperable carcinoma of the ovary. It is also concomitantly used with irradiation therapy in the local control of primary squamous cell carcinomas of the head and neck, excluding the lip. Hydrea and Hydase share the same beginning ("Hyd-") and the remaining letters can resemble each other if not precisely scripted (see page 8). Additionally, the two names each have six letters. Hydrea is available as a 500 mg capsule and stored at room temperature; Hydase will be available as a 150 units/mL single use vial and refrigerated. Both medications are given once daily. In a 50 kg patient, Hydrea's dosage range is 1000 mg to 1500 mg, administered as a single dose. The 1500 mg dose can be confused with Hydase's 150 unit dose, as post-marketing experience has shown medication errors occurring as a result of a numerical similarity in strengths. A patient inadvertently receiving Hydrea instead of Hydase may be subject to bone marrow depression, gastrointestinal symptoms, and dermatological reactions. Hydrea is genotoxic and should be avoided in males and females contemplating conception. On the contrary, inadvertent administration of Hydase may subject the patient to local edema or urticaria, erythema, chills, nausea, vomiting, dizziness, tachycardia, and hypotension. Although Hydrea will only be used

during surgical procedures, the potential for a dispensing error with Hydase still exists in the inpatient hospital setting due to similar product characteristics.

Hydase
Hyalua

B. In the review of the container labels, carton and insert labeling of Hydase, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

1. GENERAL COMMENTS

   a. DMETS does not recommend the use of the abbreviation "U" or "u" for the term, Unit. The abbreviation "U" has been misinterpreted to mean, "cc" and the number "0 and 4". Please use the word "unit" on all labels and labeling.

   b. DMETS recommends the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products consult with the CDER Labeling and Nomenclature Committee (LNC) to determine the proper designation of the established name.

   [ ] DMETS also questions the proper presentation of the dosage formulation in the established name. The sponsor should revise the presentation of the established name on all labels and labeling based on the LNC recommendation.

   c. The active ingredient, hyaluronidase, is present, but the established name and dosage form is missing from the label and labeling provided by the sponsor. Please revise per 21 CFR 21.57(a).

   d. The sponsor uses —— Solution" to describe its product. DMETS questions the meaning and use of this terminology and asks for further clarification.

2. CONTAINER LABEL

   a. See GENERAL COMMENTS.

   b. If the drug product is anything other than oral, a route of administration must be present 21 CFR 201.100(b) (3). DMETS recommends the route of administration statement to appear directly above and replace the statement "Not recommended for IV use".

   c. [ ]

indication for this product.

d. The inactive ingredients are not present on the carton labeling. Per 21 CFR 210.100(b)(5), injectable products need quantitative and qualitative inactive ingredients listed. Please revise.

e. The "1 mL" net quantity statement should be relocated away from the expression of concentration or strength.

3. CARTON LABELING

See GENERAL and CONTAINER LABEL comments.

4. INSERT LABELING

See GENERAL COMMENTS.

IV. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name, Hydase.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. DDMAC finds the proprietary name, Hydase, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Jinhee L. Jahng, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

\ Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Administrative- 4

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/s/

Alina Mahmud
4/2/04 04:19:59 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
4/2/04 04:42:58 PM
DRUG SAFETY OFFICE REVIEWER

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Anthony Dziabo, Prima Pharm	**From:** Lori Gorski, Project Manager
Fax: 858-259-8268	**Fax:** 301-827-2531
Phone: 858-259-0717	**Phone:** 301-827-2521
Pages: 2 (including cover page)	**Date:** March 4, 2004

Re: NDA 21-716 reviewer requests and deficiencies for hyaluronidase

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Tony,

The following items have been identified as deficiencies by the reviewers for the Hydase application. Please respond as soon as possible with an amendment(s) to NDA 21-716.

Please contact me if you have questions.

Thanks,
Lori Gorski

NDA 21-716

Prima Pharm, Inc.

Attention: Anthony Dziabo
V.P. Regulatory Affairs
3443 Tripp Court
San Diego, California 92121

Dear Mr. Dziabo:

The following items are issues that require a response to your application.

Unless otherwise specified, all items should be formally submitted though the document room. Also include a form FDA-356h with every submission.

Administrative

1. If available, please provide an electronic copy of the proposed package insert. This can be sent to me (Lori Gorski) via e-mail or through overnight mail addressed directly to me as a "Desk Copy".

2. Provide a Form FDA 3542a - Patent Information Submitted with the Filing of an NDA available at http://forms.psc.gov/forms/FDA/fda.html.

3. In a number of places in your application you state "This application has been submitted under section 505(b)1 of the act...", specifically sections V, VI, VII and VIII. This statement should be corrected to reflect that this application has been submitted under section 505(b)2 of the Act.

4. Under 21 CFR 314.50(d)(5)(vi)(*b*), you are required to update your NDA by submitting all new safety information you now have regarding your new drug.

PK

1. The pharmacokinetic section of the NDA is inadequate. At a minimum the submitted information should be sufficient to both describe the product and its methods of use and either establish its bioavailability or provide sufficient information to allow the Agency to waive the requirement of in vivo bioavailability testing. You may wish to consider a waiver request for your product.

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

/s/

Lori Gorski
3/4/04 01:23:38 PM
CSO

Lori Gorski
3/4/04 01:27:27 PM
CSO
sent to sponsor 3/4/04

Department Of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE: January 30, 2004

FROM: Renan A. Bonnel, Pharm.D., MPH
Postmarketing Safety Evaluator
Division of Drug Risk Evaluation, HFD-430
Office of Drug Safety

THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation, HFD-430
Office of Drug Safety

TO: Brian Harvey M.D., Ph.D., Acting Director
Division of Antiinflammatory, Analgesics and Ophthalmic Drug Products, HFD-550

SUBJECT: ODS Postmarketing Safety Review - (PID #: D030714)
Drug: Hyaluronidase (NDA #: —— 21-640, 21-665,21-716)
Adverse Events: Post-Marketing Safety Review

Confidential: contains IMS data; not to be used outside of the FDA without clearance from IMS.

INTRODUCTION/EXECUTIVE SUMMARY

In response to a written consult from Lori Gorski, Project Manager from the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (DAAODP), we reviewed postmarketing adverse event reports in association with hyaluronidase products. Hyaluronidase products are unavailable in the US since 2002 due to manufacturing issues and the new drug applications for hyaluronidase products are currently being reviewed by DAAODP.

The AERS search resulted in a total of 210 unduplicated adverse event cases reported with hyaluronidase. The majority of the reports were domestic (188) and were received from health care professionals. Five cases were excluded from further analysis. The Wydase® brand name was indicated as the suspect agent in most of the reports.

Of the remaining 205 cases, there were 73 females, 41 males, and unknown gender in 91 of the cases. The ages of the patients ranged from 10-days old to 91 years old (n=103) with a median age of 67. Fifty two reports were medically serious resulting in hospitalization (27), disability (11), life-threatening (5), interventions (8) and one death. The cause of death was reported as unspecified infectious complications following pustulosis that was thought to be associated with mercurothiolate in hyaluronidase.

Possibly due to the use of the products for retrobulbar or peribulbar anesthesia, the largest number of cases (68) reported ocular related adverse events. The severity of adverse events varied from pain, swelling, corneal burn, retrobulbar hemorrhage, retinal hemorrhage, retinal artery occlusion, endophtalmitis, tonic pupil, temporary contralareal amaurosis to permanent loss of vision. . Two patients required corneal transplants due to corneal burns and one patient experienced permanent loss of eye sight from endophtalmitis. A small number of patients developed cardiac arrest, generalized seizures, pulmonary edema and respiratory arrest following a combination of lidocaine-bupivacaine-hyaluronidase for ophthalmic surgery. The causal role of hyaluronidase in the reports was unclear. Concomitant use of local anesthetics agents (e.g., lidocaine and bupivacaine), block technique, and accidental injection into subarchnoid or subdural space were considered to be contributory to most adverse events per reporters.

The presence of local anesthetic agents in the injection mixture might have contributed to other adverse reactions, such as localized reactions, allergic reactions and dose-related systemic reactions involving cardiovascular, CNS and respiratory systems.

Overall, our review of the postmarketing adverse event reports indicated that most of the adverse events were eye related. The events occurred following the injection of hyaluronidase and local anesthetics for retrobulbar or peribulbar anesthesia. These adverse events are not addressed in the labeling but often affect vision including eye pain, swelling, corneal edema and burn, temporary loss of vision, or retinal hemorrhages. Allergic skin reactions are consistent with current hyaluronidase labeling. Systemic adverse events including seizures, respiratory edema and arrest could be attributed to the concomitant use of hyaluronidase and local anesthetics and/or inadvertent injection into the subarchnoid or subdural spaces. Although the exact causal role of hyaluronidase alone cannot be determined, it is prudent to include these ocular and systemic adverse events under the adverse reactions section of the labeling, since hyaluronidase is routinely mixed with local anesthetics for ocular use. We will continue to monitor the safety of the drug closely.

DRUG INFORMATION/LABELING [1,15]

Hyaluronidase is an enzyme that reversibly depolymerises hyaluronic acid, a component of the ground substance or tissue cement surrounding cells, thereby temporally reducing its viscosity and promoting diffusion of injected fluids or of localized transudates or exudates, thus facilitating their absorption. It is indicated as an adjunct 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.

According to medical literature, hyaluronidase is used in conjunction with a mixture of bupivacaine and lidocaine for peribulbar anesthesia during ophthalmic surgery [2-13].

Wydase® (Wyeth-Ayerst) was the only hyaluronidase product in the US. It was approved by FDA in 1950s but Wydase® was discontinued in the US on Jan 7, 2002 due to manufacturing concerns. No other hyaluronidase products are currently available in the US.

The Wydase® hyaluronidase product in the US was a preparation of highly purified bovine testicular hyaluronidase. The product was presented in 1ml and 10 ml lypholized or stabilized solutions. Each milliliter contained 150 USP (TR) units of Hyaluronidase for Injection BP (bovine testicular). The ready to use Wydase solution contained thiomerosal (mercury derivative).

Rare allergic reactions (urticaria, angioedema), anaphylactic-like reactions following retrobulbar block or intravenous injections and a report of cardiac fibrillation are listed under the Adverse Reactions section of the revised Wydase® product labeling in October 2000.

Local anesthetic agents (e.g., lidocaine, bupivacaine) may cause localized reactions, allergic reactions and dose-related systemic reactions involving cardiovascular (e.g., bradycardia, hypotension, cardiac arrest), CNS and respiratory systems (e.g., confusion, convulsion, respiratory arrest). Systemic adverse events with local anesthetics are generally dose-related and may result from overdose, rapid absorption from injection site and unintentional intravascular injection.

DAAODP is currently reviewing 4 NDA's for hyaluronidase. Some NDAs rely on the safety profile from DESI notice but no human data.

DRUG USE[16]

The IMS Health, National Sales Perspectives™ (Retail and Non-Retail-Combined) projected sales of approximately [redacted] vials or (EA-eaches) of Wydase from 1998 through 2002 from the manufacturer to the various channels of distribution. These channels included retail outlets (chain, independent, mass merchandisers, food stores, mail order and long-term care pharmacies) and non-retail outlets (hospitals, HMOs, clinics, non-federal and federal facilities, home health care and miscellaneous). The amount of products purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume that facilities purchase drugs in quantities reflective of actual patient use.

Additionally, [redacted] database showed a total [redacted] discharges associated with Wydase in a sample of over [redacted] acute, short-stay hospitals from 2001 through 3Q2003. This is only to say that a patient was billed for Wydase during their hospital stay. Data are available with a lag time of approximately six months. The [redacted] network is a large hospital drug utilization and financial database and the information is available from over [redacted] acute care facilities and includes approximately [redacted] inpatient records. The hospitals that contribute information to this database are a select sample of both [redacted] and U.S. institutions, and do not necessarily represent all hospitals in the U.S. The [redacted] data show some use of Wydase although it declined in 2002 - probably due to the manufacturing problems.

PRODUCT INFORMATION FROM UNITED KINGDOM [14]

Upon our request, on December 22, 2003, The Office of Drug Safety received the following postmarketing safety information on hyaluronidase products in the UK upon request. The only licensed hyaluronidase product in the UK is Hyalase®. It is indicated to enhance permeation of subcutaneous or intramuscular injections, local anaesthetics and subcutaneous infusions and to promote resorption of excess fluids and blood in the tissues. The product is presented in a 1ml ampule; each ampule contains 1500 international units of Hyaluronidase for Injection BP (ovine).

The Undesirable Effects section of the Summary of Product Characteristics (SPC) lists the following possible side effects: "Edema has been reported in association with hypodermoclysis. Severe allergic reactions including anaphylaxis have been reported rarely. Local irritation, infection, bleeding and bruising occur rarely."

In the UK, healthcare professionals report suspected ADRs under a voluntary scheme, however pharmaceutical companies are obliged to report ADR reports by law. Adverse Drug Reaction Online Information Tracking (ADROIT) database for cumulative suspected adverse drug reaction (ADR) reports associated with the drug substance hyaluronidase was searched

Cumulatively since 1967, they have received 42 reports involving 60 suspected adverse drug reactions for hyaluronidase products. The majority of these suspected ADRs (41) have been associated with Hyalase® (the only single constituent product), but the others were associated with multiple constituent products that are no longer licensed. The majority of the reactions reported have been allergic reactions (including 6 anaphylactoid/anaphylactic reactions and 5 reports angiodema/face oedema) or application/injection site reactions. There was one case of cardiac failure with a fatal outcome and one case of syncope.

SELECTION OF CASE SERIES

DAAODP requested a safety summary of all adverse events in FDA's AERS database associated with brand name hyaluronidase products. We used "Wydase" brand name in this evaluation if it appeared as such, otherwise "hyaluronidase" was used.

On December 29, 2003, the AERS search of all adverse events reports associated with hyaluronidase, Wydase®, Hyalase®, and Hyalase® resulted in a total of 210 cases. The majority of the reports indicated Wydase® brand name as the suspect agent. Five cases were excluded from further analysis due to following reasons: a) reaction unevaluable, b) no adverse event, and c) hyaluronidase is not a suspect agent (3 cases). The remaining 205 cases reported adverse events in which hyaluronidase was listed as a suspect or a co-suspect agent.

Counts of most frequently reported Preferred Terms (PT) in AERS reports were:

PT Terms	% of total
Drug Ineffective	28.6
Conjunctivitis	9.8
Dermatitis	9.8
Injection site reaction	8.9
Apnea	6.4
Hypertension	6.4
Eye disorder	5.9
Face edema	5.5
Pain	4.7
Vomiting	4.7
Blindness	4.2
Hypersensitivity	3.8

The majority of the reports was domestic (188) and received from health care professionals. The cases involved 73 females, 41 males, and the gender was unknown in 91 cases. The majority of the reports were received by the FDA from 1991 to 1999. Retrobulbar anesthesia during ophthalmic surgery was the indication for hyaluronidase in most reports. The ages of the patients ranged from 10-day old infant to 91 years old (n=103) with a median age of 67. Fifty two (52) reports were medically serious that indicated hospitalization (22), disability (14), life-threatening (6), or interventions needed (10). There was one death which was possibly related to infectious complication of pustulosis per reporter.

REVIEW OF CASES BY BODY SYSTEM

1. Application site reactions (18)

Eighteen patients experienced application site reactions after receiving injection of Wydase®. The application site reactions occurred locally in the areas of hyalurionidase injections. The adverse events included pain, aggravation of back pain, severe back pain, local necrosis, scarring, swelling, injection site hives, erythema, skin sloughing, and trismus/pain. Sixteen of the patients received hyaluronidase by epidural, subcutaneous or intradermal injection with

combination of corticosteroids and/or local anesthetics for various indications including treatment of back pain, hypodermoclysis, sclerotherapy, allergy testing and diagnostic radiology. Fourteen cases were non-serious. Three patients required interventions for local necrosis and pain, one patient required hospitalization due to complications of epidural catheter and severe pain.

Dechallenge and rechallenge information were available in 2 patients. One patient received Wydase® with lidocaine for retrobulbar block during eye surgery and developed erythema, severe swelling and itching around the injection site. Lidocaine rechallenge was negative. The reporter suspected that the reaction was secondary to Wydase®. The second patient received allergy skin testing for Wydase, lidocaine and bupivacaine for pre-cataract surgery. Skin tests for lidocaine and bupivacaine were negative and **skin test for Wydase® was positive.**

Reviewer comment: Application site reactions including pain, scarring, swellings, erythema, skin sloughing, and necrosis occurred with ocular, intradermal and subcutenous administration of hyaluronidase and local anesthetics. These adverse events are not listed in the hyaluronidase labeling. One case had positive skin testing for Wydase and reporter's opinion that Wydase was the suspect drug.

2. <u>Cardiovascular (11)</u>

There were 11 reports involving cardiovascular system following concomitant Wydase use with local anesthetics for retrobulbar anesthesia. There were 6 females, 4 males, and one was unknown. The patients' ages ranged from 40 to 82 years old with a median of 66. The majority of the reports lacked clinical information to determine the causal role of Wydase. The events were hypertension (2), hypertension/papilledema (1), hypotension with and w/o apnea (5), heart block (1), cardiac fibrillation (1), and cardiac arrest (1). Four patients required hospitalization. Eight patients reported recovery. The most detailed case was a literature report of apnea, hypertension leading to cardiac arrest after Wydase injection for retrobulbar anesthesia. The summary of the case is as follows:

> A 58-year old diabetic male (#ISR 4209546-2, US, 2003, 15-day/**literature**) received hyaluronidase, lidocaine and bupivacaine for retrobulbar anesthesia and developed **unresponsiveness, apnea, and cardiac arrest** within 30 seconds of the injection. The patient received ventilatory support for 24 hours and extubated. The cardiac, neurological exams, including cardiac enzymes, and MRI were normal. The reporter indicated that the event was the severe complication of retrobulbar anesthesia. Local anesthetics and hyaluronidase are considered as suspect agents.

Reviewer comment: One case of "cardiac fibrillation" is mentioned under the Adverse Reactions section of the hyaluronidase labeling. Because concomitant local anesthetics can have cardiac manifestations including bradycardia,

hypotension and collapse, the causal role of hyaluronidase alone could not be established.

3. **Central Nervous system (14)**

There were 14 reports involving central nervous system with Wydase use. Twelve patients received the drug for ocular surgery and two patients received for intraarticular or intradermal use. The adverse events included seizures (5), meningitis (1), sixth nerve palsy (1), foot drop (1), confusion (1), unconsciousness (1), paresthesia (1) and cranial nerve deficit (3).

Five patients developed of **foot drop, unresponsiveness, confusion, paresthesia and** one developed **sixth nerve palsy**. Wydase was used in combination with local anesthetics for epidural and interspinal or retrobulbar block. The reports lacked further clinical information to determine causality.

Three patients (44M, 58M, and 79M) received Wydase with local anesthetics and developed **cranial nerve deficit** manifested by stupor, unconsciousness, fixed and dilated pupils. The patients recovered 2 hours later. The reporter indicated that the patient's course was consistent with accidental injection into subarchnoid space causing brain stem anesthesia.

One patient (63 years old, literature) developed a case of **nosocomial meningitis** following combination of bupivacaine, etidocaine and hyaluronidase for peribulbar anesthesia. The patient presented with high fever, headache, and CSF leukocytosis. The CSF cultures were positive for methicillin sensitive S.Hemolyticus. MRI was negative. The event was thought to be due to inadvertent injection into subdural or subarchnoid space. The patient recovered.

Five patients (10M, 64M, 70M, 82M, unknown) reported seizure disorders. Four were **grand mal seizures** and one was **focal seizure** following Wydase use. Two of the cases lacked clinical information. The third case was a 10- year old male who developed clonic and tonic seizure in all extremities following intradermal hyaluronidase and lidocaine intradermal injection for sutures placement for leg laceration. The blood glucose was normal. EKG was not conclusive of a seizure disorder. The patient was hospitalized and recovered. The remaining two cases (82M,64M) were from the same reporter and published in the literature. These two patients developed grand mal seizure and apnea lasting forty seconds to one minute following hyaluronidase injection in combination with local anesthetics for retrobulbar anesthesia. The patients required respiratory support. MRI was negative for new neurological abnormalities. The reporter stated the event was a severe neurological complication of retrobulbar local anesthetic injection.

Reviewer comment: Cranial nerve deficit, nosocomial meningitis, seizures were likely associated with inadvertent injection of hyaluronidase with local

anesthetics into subarchnoid or subdural space leading to neurological complications. The causal role of hyaluronidase alone could not be established.

4. Gastrointestinal (5)

Five (65M, 77F, 80F, unknown-2) patients experienced nausea and vomiting after receiving Wydase® in combination with lidocaine and/or bupivacaine for retrobulbar anesthesia. The onset of events was immediate in three cases and 5-8 hours in two cases. Three patients received the same lot numbers of Wydase® (# 4900601) in the same medical facility. Lots were analyzed and the reporter was told that the syringes contained "lidocaine, bupivacaine, PCP and Darvon". The investigation was ongoing at the time of the report for possible contamination or adulteration with other CNS agents. Two of the five cases required outpatient treatments.

Reviewer comment: Nausea and vomiting occurred following the combination use of Wydase and local anesthetics. The causal role of Wydase could not be established.

5. General (3)

Three patients (64M, 67 F, 69 F) reported generalized pustular erythema/fever, myalgias/ fever/mental status change, and generalized macular rash following unknown dose of hyaluronidase injection. The route of administration was intraarticular or retrobulbar injection in two cases and unknown in the third patient.

One patient (foreign report) received concomitant systemic corticosteroids, antibiotics, acetycysteine, and hyaluronidase for pulmonary infection and developed pustular erythema/pustulosis. Pustulosis was thought to be due to mercurothiolate in hyaluronidase. He died from unspecified infectious complications.

The second patient (domestic) developed myalgias, chills, fever and mental status changes following the second dose of hyaluronidase intra-articular injection to knee. She was hospitalized and received systemic antibiotics with no results. All cultures, CTscan, ANA/ANCA results were negative. The final outcome was unknown.

The third patient (domestic) developed a red, itchy, macular "measle-like"rash over her entire body following Wydase injection. Concomitant medications were unknown. Two previous Wydase injections were given without problems. The patient recovered after 6 weeks.

Systemic reactions including erythema, urticaria, chills, nausea, vomiting, dizziness, tachycardia, and hypotension could occur with hyaluronidase administration and are listed under the "Overdose Section" of the labeling.

Reviewer comment: Generalized skin reactions with and without constitutional symptoms were temporally related to Wydase and local anesthetic administration.

6. **Immune system (23)**

There were 23 immune system reports temporally associated with Wydase use. The ages of the patients ranged from 35 to 79 years old (n=17) with a median age of 56 years old. The severity of reactions manifested as orbital edema, angioneurotic edema, throat swelling, erythema, heaving, apnea/hypotension, facial swelling, dyspnea, and pruritic rash. Five patients had a history of drug allergy (3), asthma (1), and allergic rhinitis (1). Five patients reported positive skin testing for Wydase. Eleven patients had serious outcomes including hospitalizations (6) and five required systemic treatments (6). Eleven patients reported recovery. The outcomes were unknown in 12 patients. Additional summary of the cases follows:

- 4- allergic or hypersensitivity reactions manifested as rash and swelling. One patient had a history of asthma.
- 10- facial edema and /or orbital edema with or without rash. Two had drug allergies (TCN, sulfa) and/or allergic rhinitis.
- 8- allergic reaction with cardiac or respiratory involvement- diaphoresis, tachycardia, dyspnea, SOB, swelling. One had a drug allergy (PCN).
- 1- unspecified allergic reaction

Two serious allergic reactions are summarized below:

> 1. A 35 year-old diabetic female (ISR# 858882, US, 1991) experienced flushing of eight hours duration after Wydase, lidocaine and bupivacaine administration during cataract surgery. She underwent the same procedure 14 days later and developed flushing, dry cough, chest tightness, and inspiratory strider with the same mixture of agents. She was intubated, hospitalized, received systemic steroids and recovered.
>
> 2. A 70-year old female (ISR# 3825945-2, foreign, 2001) developed facial edema, neck swelling, and dysphagia after receiving Wydase, lidocaine, bupivacaine during cataract extraction. The patient had a history of penicillin allergy. She was hospitalized and treated with systemic steroids, adrenaline and antihistamines. Skin testing results were pending. The patient recovered.

Adverse Reactions section of the labeling mentions rare allergic reactions (urticaria, angioedema) and anaphylactic-like reactions following retrobulbar block or intravenous injections of hyaluronidase.

Reviewer's comments: Hyaluronidase is a protein enzyme and allergic reactions have occurred and are listed in the product labeling. Skin testing for Wydase was positive in five cases of allergic reactions that confirmed the role of Wydase.

7. **Ocular (68)**

There are 68 reports of ocular adverse events following hyaluronidase injection for retrobulbar anesthesia. Most reports indicated Wydase® brand name as a suspect agent. The drug was routinely mixed with lidocaine, bupivacaine and/or epinephrine prior to surgery. Ocular use of hyaluronidase is not approved by the FDA. The adverse events included pain, swelling, corneal edema, iris depigmentation, corneal lesion, corneal burn, conjunctivitis, retrobulbar hemorrhage, retinal hemorrhage, retinal artery occlusion, endophtalmitis, tonic pupil, contralareal amaurosis, loss of vision, papillary disorder, infection, " toxic eye" (nonallergic, direct toxic reaction to chemical or substance impurity), and increased ocular pressure/macular edema.

Nineteen patients reported serious outcomes including 6 hospitalizations and 13 disabilities. Two of the patients required corneal transplants due to injury and one had a permanent loss of eye sight.

We evaluated all reports in 3 groups: 1) Cluster of reports consist of 46 cases from 8 different medical facilities and reporters 2) Literature reports of serious complications, and 3) The remaining cases.

1) There were 8 clusters of reports with a total of 46 cases. Each cluster was received from the one reporter from the same medical facility and reported a similar adverse event. We summarized each cluster as follows:

- Five foreign cases (57M, 66F, 67F, 73M, 91M) of **corneal edema and depigmentation of iris** following hyaluronidase (unspecified brand name) use during cataract surgery and vitrectomy from the same local health unit. Multiple medications including tropicamide, cyclopentolate, adrenaline, phenylephrine and ringer lactate solutions, and ropivacaine were suspect medications. The reports did not provide clinical information to assess the causal role of hyaluronidase.

- Twenty domestic reports of **conjunctivitis and lid swelling** following Wydase® administration during ophthalmic surgery. The age and the gender of the patients were not reported. The lot number was identified as 4930692. No information on sterility or cultures was provided. However, it was noted that the concentration of bicarbonate was recently increased 5 fold to prepare the "eye block" solution. The reporter ascertained that the reaction was not caused by Wydase.

- Four domestic reports (47M, 89F, 90F, unknown) of **corneal burns/lens clouding** with Wydase use. The drug was administered concomitantly

with other anesthetics and epinephrine for peribulbar anesthesia. **Two of the patients required corneal transplantation.**

- Six domestic reports (54M, 69F, 73M, 3 unknown) of **papillary disorder and/or "tonic pupil"** following Wydase use during cataract surgery. Wydase was the primary suspect agent in the reports. Other anesthetic agents were used concomitantly. The onset of event was unknown but the pupil abnormality was noted six weeks post-op in 3 cases.

- Three domestic cases (unknown age and gender) of **prolonged blurred vision and drooping eye lids** after receiving Wydase, bupivacaine, and lidocaine concurrently. The patients had drooping eye lids, blurred vision and experienced difficulty recovering from anesthesia. The recovery was about 20 hours in one patient and unknown in other cases. Lot numbers were not reported.

- Three domestic cases (64 F, 69F, 78F) from the same reporter and the same facility where the patients experienced **excruciating pain** one day following Wydase, bupivacaine and normal saline use for peribulbar anesthesia. Lot numbers were not reported. All patients required pain medications and subsequently recovered.

- Three domestic cases (68 M, 70 F, 82 M) of **progressive loss of vision** and disability after receiving hyaluronidase and lidocaine injection during cataract surgery. All three patients received the same lot but no product analysis was reported. The patients had significant underlying cardiac history including h/o carotidaterectomy, abdominal aneurysm, CAD, HTN, and arrhythmias that might have contributed to event. The final clinical outcomes were unknown.

- Two domestic reports (45F, 84 F) of **severe head and eye pain with nausea and vomiting** following Wydase injection. The patients were hospitalized and recovered after receiving treatment with antiemetics, systemic prednisone, topical steroids/ antibiotics, pain medication and IV fluids and recovered. CT scan was negative for both patients.

2) Literature reported events included retinopathy, retinal hemorrhage, temporary contralateral amaurosis, temporary bilateral amaurosis, and sight-threatening acute orbital swelling/optic nerve dysfunction following Wydase and local anesthetics use for retrobulbar or peribulbar anesthesia. The causal role of Wydase was unclear due to injection mixture with local anesthetics. The narratives of the literature reports are as follows:

1. A 70- year-old female (ISR # 3361157-7, Foreign, 1999, 15-day, Literature) with controlled chronic open-angle glaucoma (COAG)(treated previously with bilateral trabeculoctemies w/o adverse events) received tropicamide 1%, phenylephrine 10% for

pre-op mydriasis, and proxymethacaine and 0.5%, lidocaine 2%, bupivacaine 0.75% and hyaluronidase 500 units for peribulbar anesthesia. Approximately 12 hours after surgery, she experienced a **painful, swollen right orbit, low-grade fever, increased intraocular pressure and decreased visual acuity**. CT scan was negative for hematoma but confirmed soft tissue swelling and gas bubble within the muscle cone. Blood cultures were negative. CBC was normal, except for a slight eosinophilia of 0.6 x 10 09/L (normal 0.1-0.4 x 10 E09/L). She was treated with systemic corticosteroids and antibiotics with improvement. The patient required second local anesthetic infiltration **(rechallenge)** with lidocaine/bupivacaine and hyaluronidase and experienced more severe localized allergy reaction with lid swelling and tenderness onto the cheek with decreased visual acuity. Subsequently, she recovered and the authors suspected a delayed allergic reaction to lidocaine or hyaluronidase. No skin testing was performed.

2. A 76-year-old male (ISR 3239758-6, Foreign, 1999, 15-day, Literature) with bilateral primary open angle glaucoma was admitted for trabeculectomy procedure in his left eye. The patient had a history of high blood pressure, angina pectoris, a myocardial infarction and hypothyroidism and an abdominal aneurysm. The patient received 2% lidocaine, 0.5% bupivacaine and hyaluronidase for peribulbar anesthesia. Two minutes later, he experienced **bilateral amareusis**. The vision returned to normal thirty minutes later. CT scan was unremarkable. The authors commented the bilateral amaurosis was due to intraconal diffusion of the anesthetic solution, which then spread by way of the subdural space or subarchnoid space, or both, of the ipsilateral optic nerve to the chiasm and the contralateral optic nerve.

3. A 67-year-old female (ISR 3435994-6, Foreign, 2000, 15-day/ literature) with a history of chronic open angle glaucoma presented with progressive vision loss and cataracts in both eyes. The patient received xylocaine, bupivacaine and hyaluronidase as retrobulbar anesthesia for cataract extraction in the right eye. After the procedure she experienced blindness in the left eye **(contralateral amaurosis)**. Over the next 12 hours, the patient's vision returned to 20/40 OS. Seven months later, the patient underwent uncomplicated cataract extraction of the left eye. The authors postulated that the patient experienced an optic nerve subarchnoid injection as a result of the retrobulbar anesthesia.

4. A 53-year-old female (ISR# 3133866-6, US, 1998, 15-day/literature) underwent for cataract extraction of the left eye. She received bupivacaine, mepivacaine, and 150-U hyaluronidase for peribulbar anesthesia and developed **global perforation, retinal hemorrhage and loss of vision.** The optic nerve and the macula was healthy. Thirty hours post-op, visual acuity improved and she recovered.

5. A 46-year old male (ISR # 4118031-8, Foreign, 2003, Literature) received retrobulbar injection of lidocaine, hyaluronidase and adrenaline for pterygium excision. The patient complained of reduced vision in the operated eye one day later. Fundoscopy showed patches of retinal whitening, disc swelling, tortuous veins and **intraretinal hemorrhage**. Angiogram showed peripheral arteriolar occlusion and hypoperfusion to the optic disc. Vision improved gradually to 20/20 within two months, however the relative adherent papillary defect and visual feels defect persisted.

3) The remaining reports (17 cases) included endophthalmitis (6), retinal arterial occlusion (1), inflammation/swollen eye (4), pain (1), unspecified reaction in the eye (1), unspecified hemorrhage, edema and bruising (3), and unspecified anterior chamber reaction (1). Although, Wydase was reported as a suspect agent, the drug was routinely administered in combination with local anesthetics and the reports lacked detailed clinical information to assess the causal role of Wydase. Cases of

endophthalmitis did not provide sufficient information on bacterial cultures or sterility tests to identify the etiology of infection. One patient reported S.Epidermis growth in vitreous humor and lost permanent sight of one eye. Three patients required hospitalization. Although all events occurred following Wydase use, the causal role of the drug could not be determined.

Reviewer's comments: Ocular events constituted the largest number of adverse events reports for hyaluronidase in AERS database. The occurrence of serious adverse events including severe eye pain, orbital swelling, decrease visual acuity, temporary loss of vision, corneal burn, and retinal hemorrhages were temporally related to hyaluronidase and local anesthetic mixture. In all cases, hyaluronidase was routinely mixed with local anesthetics and administered for retrobulbar or peribulbar anesthesia and causal role of hyaluronidase alone could not be established. Ocular use of hyaluronidase is not mentioned in product labeling.

8. Respiratory (8)

There were eight reports involving respiratory systems following Wydase injection for ocular (7) and nasal surgery (1). Wydase was administered concomitantly with local anesthetics. The reactions included rhinitis (1), acute pulmonary edema (2), and respiratory arrest (5). Seven patients required hospitalization. All eight patients recovered. Respiratory arrest and pulmonary edema were thought to be due a complication from subarchnoid injection of hyaluronidase and local anesthetics during retrobulbar anesthesia. Hyaluronidase may have played a role to promote the spreading of the anesthetic into the brainstem and respiratory center per reporter. Three literature cases are summarized below:

1. A 55-year old female (ISR # 3682461-9, US, 2001, 15-day, Literature) experienced dizziness, loss of consciousness and seizure following Wydase, lidocaine and bupivacaine injection during keratoplasty. After 30 minutes of artificial ventilation, the patient began to awaken and was tachypneic with respiratory rate of 25/min. The BP was125/80 and the HR was 80/min. Blood gases revealed pH of 7.25, PaO_2 of 58 mm Hg, $PaCO_2$ of 40 mm Hg, base deficit of 6 and bicarbonate of 19. A chest x-ray revealed a **pulmonary edema**. EKG showed no evidence of myocardial infarction. She received diuretics and was discharged two days later without complications. Hyaluronidase injection into subarchnoid space was thought to be the possible cause of pulmonary edema.

2. A 72-year diabetic female (ISR# 1917642-5, foreign, 1997, 15-day, Literature) developed tingling sensation, difficulty of breathing, nausea, restlessness, diaphoresis, dry cough, cyanosis, and tachycardia one hour after injection of hyaluronidase, mepivacaine, and bupivacaine for retrobulbar anesthesia. There were no changes on EKG. Congestive heart failure, MI, PE and allergic reaction were ruled out. A chest X-ray revealed **pulmonary edema.** The patient was diagnosed with neurogenic pulmonary edema (NPE). She received diuretics and recovered promptly. The central spread of local anesthetics and hyaluronidase and partial trigeminal block are thought to be the possible cause of NPE.

3. A 62-year old male (ISR# 531442, US, 1989, 15-day, Literature) in good health received lidocaine, bupivacaine and hyaluronidase for retrobulbar anesthesia. Five

minutes later, the patient became obtunded, developed hypertension, irregular breathing, episodes of apnea, **respirator arrest,** and a total of ophthalmoplegia. Following cardiopulmonary support, the patient recovered. Five days later, he had an uneventful cataract extraction with the same anesthetic mixture. This was reported as a complication of direct injection of anesthetic into subarchnoid space leading to respiratory depression

Reviewer's comments: Acute pulmonary edema and respiratory arrest following ocular use of hyaluronidase and local anesthetics have occurred. Literature reports postulated that inadvertent injection of hyaluronidase and local anesthetics into subarchnoid space may have resulted in serious pulmonary adverse events. Hyaluronidase may have played an indirect role to promote the spreading of the anesthetic into the brainstem and respiratory center causing respiratory arrest and pulmonary edema. The causal role of hyaluronidase alone could not be established.

9. **Others:**

Lack of effect (54)

Fifty-four cases reported lack of drug efficacy and unsatisfactory numbing effect after receiving Wydase use with local anesthetics for peribulbar or retrobulbar anesthesia. There were seven lots numbers of Wydase brand name (4940162, 4970413, 4920559, 4920002, 4930484, 4920342, and 4960621) that were involved in 28 cases, but they met product specifications after the analysis. The product information was unknown in the remaining 26 cases.

Reviewer's comments: The information on individual ingredients in the injection mixture and an information on administration technique of anesthesia were unavailable to determine the reasons of unsatisfactory numbing during ocular surgery.

Overdose/ Medication Error (1)

One patient received 1500 units of hyaluronidase rectally instead of 150 units for unknown indication. The patient was hospitalized and the adverse event or outcome was unknown.

DISCUSSION/CONCLUSION

We reviewed 205 unduplicated reports with hyaluronidase use in AERS. The majority of the reports indicated the Wydase® brand name as the suspect or co-suspect agent while used concomitantly with local anesthetics.

The cases involved 73 females, 41 males, and unknown gender in 91 of the cases. The ages of the patients ranged from 10-days old to 91 years old with a median age of 67 (n=103). Fifty-two patients reported serious outcomes including hospitalization, disability, life-threatening, interventions and one death. The cause of death was

unspecified infectious complications following pustulosis that was thought to be related to mercurothiolate in hyaluronidase.

In most cases, the causal role of hyaluronidase could not be established. Concomitant use of local anesthetics agents (lidocaine and bupivacaine), and potential mishandling of the block technique resulting in accidental injection of the mixture into subarchnoid or subdural spaces might have contributed to most of the adverse events.

The largest number of reports was ocular adverse events including severe eye pain, orbital swelling, decreased visual acuity, temporary loss of vision, corneal burn, and retinal hemorrhages following off-label use of hyaluronidase in combination of local anesthetics for retrobulbar or peribulbar anesthesia. Other serious and potentially life-threatening adverse events included generalized seizures, pulmonary edema, respiratory arrest and one report of cardiac arrest following lidocaine-bupivacaine-hyaluronidase combination for ophthalmic surgery.

The important confounding factor in the reports was the presence of local anesthetic agents in the injection mixture that can cause localized reactions, allergic reactions and dose-related systemic reactions involving cardiovascular CNS and respiratory systems.

In conclusion, our review of the postmarketing adverse event reports indicated that most of the events were eye related and possibly due to the combination use of hyaluronidase and local anesthetics for retrobulbar or peribulbar anesthesia. These adverse events are not addressed in the labeling, but often affects vision including eye pain, swelling, corneal edema and burn, temporary loss of vision, or retinal hemorrhages. Allergic skin reactions are consistent with current labeling. Systemic adverse events including seizures, respiratory edema and arrest are concerning and might be attributable to the concomitant use of local anesthetics injection into subarchnoid or subdural spaces. Although we could not establish the exact causal role of hyaluronidase alone, it is prudent to include these ocular and systemic adverse events under the adverse reactions section of the labeling since hyaluronidase is routinely used with local anesthetics for ocular surgery. We will continue to monitor the safety of the drug closely.

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3. Elk R et al. Pulmonary Edema following retrobulbar anesthesia. J Cataract Refract Surg. March 1988, 14: 216-217.
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Signed on 1/30/2004

Renan A. Bonnel, Pharm.D., MPH
Safety Evaluator

Concur,

Signed on 1/30/2004

Min Chu Chen, RPh, MS
Associate Director, Division of Drug Risk Evaluation

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/s/

Renan Bonnel
1/30/04 04:11:08 PM
DRUG SAFETY OFFICE REVIEWER

Min Chen
1/30/04 04:20:10 PM
DRUG SAFETY OFFICE REVIEWER
Min Chen for Mark Avigan

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Sammie Beam Pkln rm. 6-34
DHHS/FDA/CDER/ODS/HFD-420

FROM:
Lori Gorski phone 827-2521
DHHS/FDA/CDER/OND/DAAODP/ HFD-550

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 15, 2004		21-716	Original NDA	October 17, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Hydase (hyaluronidase injection)	PRIORITY	Protyolitic enzyme	April 1, 2004 or sooner

NAME OF FIRM: Prima Pharma

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE 2
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

XX Original NDA name request

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

PrimaPharm has submitted an NDA for Hydase (hyaluronidase for injection). Please provide a tradename consult for Hydase for this application. PLEASE NOTE - This drug is used ONLY during surgical procedures and not ever administered via a prescription to the patient.

A paper copy of this request including the package insert (annotated), carton & container labels will follow in inter-office mail.

This application is a PRIORITY review - please process promptly. Please respond by April 1, 2004.

If you have any questions, please contact Lori Gorski, Project Manager at 7-2521. Thanks Sammie.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) **XX Through Interoffice Mail** HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Lori Gorski
1/15/04 09:58:05 AM
Sammie - labeling and packaging to follow in interoffice mail.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-716

FILING REVIEW LETTER

Prima Pharm, Inc.
Attention: Anthony Dziabo
V.P. Regulatory Affairs
3443 Tripp Court
San Diego, Califonia 92121

Dear Mr. Dziabo:

Please refer to your October 17, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ——— (hyaluronidase for injection).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on December 19, 2003, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance and drug product are inadequate to preserve its identity, strength, quality, purity, and stability. Specifically, there is deficient or missing information with respect to the:

    a. characterization of the drug substance,
    b. specification of the drug substance,
    c. specification of the drug product, and
    d. manufacture of the drug product.

2. In regard to the viral clearance studies, the overall log reduction and/or inactivation for the various model viruses should be determined for your process. In addition to the information you presented for the viral retention C

3. The pharmacokinetic section of the NDA is inadequate. At a minimum the submitted information should be sufficient to both describe the product and its methods of use and either establish its bioavailability or provide sufficient information to allow the Agency to waive the requirement of in vivo bioavailability testing. You may wish to consider a waiver request for your product.

4. The clinical section is deficient. Please clearly identify and provide complete information on the clinical use of your specific formulation in the packaging configuration that you intend to market.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Wiley Chambers
12/29/03 03:30:45 PM

MEMORANDUM

Date: December 24, 2003

To: Brian Harvey, M.D., Ph.D.
Deputy Director, Office of Drug Evaluation V, HFD-105
Acting Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products, HFD-550

Lori M. Gorski
Project Manager, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products, HFD-550

From: Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products, HFD-570

Through: Badrul A. Chowdhury, M.D., Ph.D.
Director, Division of Pulmonary and Allergy Drug Products, HFD-570

Subject: Medical officer consultation regarding clinical data necessary to support the safety of hyaluronidase products

Materials: Citizen Petition, Baxter Healthcare Corporation
FDA Docket 2003P-0494, 10/27/03
Draft Clinical Review of Citizen's Petition
W. A. Chambers, MD, 11/18/03
Clinical Team Leader Memorandum, Hyaluronidase NDAs
W. Boyd, M.D., 12/19/03

1. EXECUTIVE SUMMARY

The Office of Drug Evaluation V (ODE V) and the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (DAAODP) have consulted the Division of Pulmonary and Allergy Drug Products (DPADP) on safety issues related to hypersensitivity reactions to hyaluronidase.

Although the hyaluronidase applications reference the DESI notices, support for safety from clinical data for the specific product should be provided for products with no marketing history anywhere in the world. If the product is approved in other countries, support for safety should include postmarketing data for the specific product from those countries. Additional clinical data addressing the immunogenicity of the product is also recommended.

If the product has been marketed for a long period and where a reasonable amount of clinical data exist, a small open label clinical study of 100 to 200 patients is recommended to address immunogenicity. If the foreign postmarketing data are robust, they may be adequate to support safety, and a clinical study may not be necessary. Skin tests and samples for in vitro evaluations of hyaluronidase-specific IgE are recommended prior to and after administration of the product. The latter recommendation is based on the assumption that such in vitro tests of hyaluronidase-specific IgE already exist or can be easily developed. Skin tests would be preferable, because it may be immunologically very difficult to test for all epitopes of this varied protein mix in an in vitro assay. Furthermore, information gathered from skin tests would be more practical to apply in a clinical setting.

For products that have no clinical or postmarketing data, the amount of additional clinical data required to assess safety and immunogenicity will be greater. In this circumstance, it may be necessary to conduct an open-label study large enough to rule out a frequency of serious immediate hypersensitivity reactions of 0.5 to 1.0%. All patients should be skin tested prior to administration of the product and serum should be drawn at baseline prior to treatment and frozen. The frequency of immediate hypersensitivity reactions should be assessed and patients who have immediate hypersensitivity reactions should be re-skin tested at a reasonable time after the reaction, perhaps within 1 to 2 months. We recommend that serum samples also be drawn at the same time and paired with the baseline serum samples to be assayed for hyaluronidase-specific IgE using in vitro assays.

Spontaneous reports of immediate hypersensitivity reactions to the product should be monitored in the post-approval period, regardless of the amount of existing clinical and postmarketing data at the time of approval. We recommend that in the post-approval period, the applicant perform skin testing and in vitro testing of a defined number of patients who have immediate hypersensitivity reactions to the product.

2. BACKGROUND

The Office of Drug Evaluation V (ODE V) and the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (DAAODP) have consulted the Division of Pulmonary and Allergy Drug Products (DPADP) on safety issues related to hypersensitivity reactions to hyaluronidase. DAAOPD currently has four NDAs for hyaluronidase submitted under Section 505(b)(2) of the FD&C Act that reference DESI notices for hyaluronidase. ODE V and DAAODP would like to know what types of clinical data would be necessary to support drug safety for this group of products.

Hyaluronidases are a group of enzymes that depolymerize hyaluronic acid and chondroitin sulfate. The hyaluronidase enzymes have "spreading factor" activity, and increase the ability of toxins or drugs to diffuse through tissue by breaking down hyaluronic acid, a component of the extracellular matrix. [1] Hyaluronidases are produced by pathogenic bacteria such as Streptococci, and are found in a variety of toxic venoms. The enzymes are also produced by various mammalian tissues. Hyaluronidase drug products are mammalian in origin, and generally are derived from bovine or ovine testicular tissue.

Hyaluronidase products have been marketed for more than 50 years, with millions of uses per year. There have been NDAs for ten hyaluronidase products in the past and each of the applicants were permitted to market their products. The most recently marketed approved product, Wydase® (NDA 06-343), was originally marketed by Wyeth. The NDA is now held by Baxter Healthcare Corporation. Marketing of Wydase® was discontinued in 2000, but Baxter Healthcare Corporation is currently working to resume production. The Agency recently determined that the Wydase® product was not withdrawn from sale for reasons of safety or effectiveness and announced that this determination will allow the Agency to approved abbreviated new drug applications (ANDAs) for hyaluronidase for injection [68 FR 62810, November 6, 2003].

Approved indications for Wydase® include 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 radioopaque agents. The safety and effectiveness of the product was supported by DESI evaluations (DESI 6343, 6714, 7933). Currently, the most frequent use of hyaluronidase is in ophthalmic surgery as an adjunct to use of locally injected anesthetic agents. There is also some use of hyaluronidase in neonates to help speed the absorption of extravasated intravenous fluids.

The originally marketed product had a rate of anaphylaxis that was fairly high, on the order of 10% or so. The older products were less pure than the recently marketed product. As the purity of the product improved, there was a decrease in the frequency of anaphylaxis to less than 1%. Some large published studies have reported a frequency of reported immediate hypersensitivity reactions of less than 0.1%.

A search of AERS with AERS DataMart reveals 189 adverse events reports for Wydase® over the last 30 years. Among these 189 reports there are two reports for anaphylactic or anaphylactoid reactions. The clinical review of [redacted] notes that the

most common postmarketing report in the AERS database for hyaluronidase is "drug ineffective," followed by injection site reaction NOS, face edema, dermatitis NOS, and conjunctivitis.

One of the four NDAs for hyaluronidase that the Agency currently has in house includes clinical data. The other three rely on the safety profile from the DESI notices and have no clinical data. The NDA with the clinical data is [redacted] This product was approved in UK in 1993 and has been marketed by CP Pharmaceuticals, Ltd. for 10 years. The product is also approved in Australia, Hong Kong, Israel, Kenya, Korea, Kuwait, New Zealand, Singapore, and Sri Lanka. There have been [redacted] ampules sold between 1993 and 1998. In the UK postmarketing database for [redacted] there are seven AE reports for [redacted] for the period from November 1, 1993, to October 2, 2002. None of these AE reports were for anaphylaxis.

3. SPECIFIC QUESTIONS

ODE V and DAAODP's questions and DPADP's responses follow below.

What clinical data would be necessary to support drug safety for this type of product?

In our opinion, although these applications reference the DESI notices, support for safety from clinical data for the specific product should be provided for products with no marketing history anywhere in the world. The clinical data should be specific for the product that is proposed for marketing, as each hyaluronidase product is likely to be different in terms of origin, purity, and other CMC characteristics and therefore may be different in the potential for immunologic sensitization and immediate hypersensitivity reactions. If the product is approved in other countries, support for safety should include postmarketing data for the specific product from those countries. Additional clinical data addressing the immunogenicity of the product are also recommended.

With those products with a large volume of real world experience, would skin testing be adequate to address the issues of allergic reactions/immunogenicity?

The label for the Wydase® product recommended that patients have skin testing prior to receiving treatment. The proposed label for the [redacted] product recommends a preliminary intradermal skin test with 0.02 mL of the undiluted product to evaluate possible hypersensitivity to hyaluronidase. Skin testing and in vitro tests of hyaluronidase-specific IgE have been reported to be positive in individuals who have had immediate hypersensitivity reactions to hyaluronidase.[1,2] The sensitivity, specificity, and positive and negative predictive values of these tests are not known, however.

Skin testing would be an important part of plan to assess the immunogenicity of these products. In the circumstance of a product that has been marketed for a long period and where a reasonable amount of postmarketing data exist, a small clinical study that evaluates immunogenicity may be sufficient to demonstrate that the product is not highly likely to be associated with immediate hypersensitivity reactions. If the foreign postmarketing data are robust, they may be adequate to support the safety of the drug,

and a clinical study may not be necessary. If the postmarketing data are not robust, an open label study of 100 to 200 patients exposed to the drug for the proposed indications may be able to supply the necessary safety information. Patients could have skin tests prior to receiving the drug, as recommended in the labeling for the previously approved product, and could have repeat skin at an appropriate time after administration of the product, perhaps within one to two months. Serum samples could also be drawn prior to administration at the same time to assess the production of hyaluronidase-specific IgE using in vitro techniques such as ELISA, RAST, or IgE-immunoblotting. The recommendation for in vitro tests of hyaluronidase-specific IgE is based on the assumption that such tests already exist or can be easily developed. These data would be valuable in assessing the value and usefulness of these tests in identifying those who may be at risk for an immediate hypersensitivity reaction to the product. Skin testing would be preferable, because it may be immunologically very difficult to test for all epitopes of this varied protein mix in an in vitro assay. Furthermore, information gathered from skin tests would be more practical to apply in a clinical setting.

Consideration should be given to asking to applicant to monitor spontaneous reports of immediate hypersensitivity reactions to the product in the post-approval period. We also recommend that the applicant perform skin testing and in vitro testing of a defined number of patients in the post-approval period who have immediate hypersensitivity reactions to the product. Such information would further define the benefit of these tests.

In products which have no marketing experience/no human data, what types of clinical trial designs would you propose to demonstrate drug safety?

The amount of additional clinical data required to assess safety and immunogenicity will be greater for these products than for products that have existing data. In this circumstance, it may be necessary to conduct an open-label study large enough to rule out a frequency of serious immediate hypersensitivity reactions of 0.5 to 1.0%. We would recommend that all patients should be skin tested prior to administration of the product and that serum should be drawn at baseline prior to treatment and frozen. The frequency of immediate hypersensitivity reactions should be assessed and patients who have immediate hypersensitivity reactions should be re-skin tested at a reasonable time after the reaction, perhaps within 1 to 2 months. We would recommend that serum samples should also be drawn at the same time and paired with the baseline serum samples and assayed for hyaluronidase-specific IgE using in vitro assays.

We would recommend that spontaneous reports of immediate hypersensitivity reactions to these products in the post-approval period should also be monitored. As we recommended for hyaluronidase products that have clinical data, consideration should be given to skin testing and in vitro testing of a defined number of patients in the post-approval period who have immediate hypersensitivity reactions to the product.

4. REFERENCES

1. Szepfalusi Z, et. al. Eur J Pediatr. 1997; 156(3): 199-203.
2. Agarwal A, et. al. Anaesthesia. 2003; 58(8): 814-815.

Reviewed by:

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

Badrul Chowdhury, M.D., Ph.D.
Director, Division of Pulmonary and Allergy Drug Products

cc: Division File, NDAs 06-343, ___ 21-640, 21-665, 21-716
HFD-105/Harvey/Deputy Office Director
HFD-550/Gorski/Project Manager
HFD-105/Bull/Office Director
HFD-550/Chambers/Deputy Division Director
HFD-550/Boyd/Medical Team Leader
HFD-102/Meyer/Office Director
HFD-570/Chowdhury/Division Director
HFD-570/Sullivan/Deputy Division Director
HFD-570/Gilbert-McClain/Medical Team Leader
HFD-570/Barnes/CPMS
HFD-570/Lee/Medical Reviewer

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/s/

Charles Lee
12/29/03 10:00:31 AM
MEDICAL OFFICER

Badrul Chowdhury
12/29/03 10:30:59 AM
MEDICAL OFFICER
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Renan Bonnel, Pkln rm. 15B-18
DHHS/FDA/CDER/ODS/DDRE/HFD-430

FROM:
Lori Gorski phone 7-2521
DHHS/FDA/CDER/OND/DAAODP/HFD-550

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
December 24, 2003		21-593 21-640 21,665 21-716	Original NDA submissions	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Hyaluronidase ——— inj			ASAP

NAME OF FIRM: various

REASON FOR REQUEST

I. GENERAL

- ☐ **NEW PROTOCOL**
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE 2
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

XX Original NDA Submission

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

HFD-550 currently has 4 NDA's for hyaluronidase submitted under 505(b)2 which reference a DESI notice for hyaluronidase. Some of these NDAs have human clinical data; some rely on the safety profile from the DESI notice and have no human data.

Please provide a safety summary of the adverse events reports found on the hyaluronidase both domestically and internationally. If possible, please identify what brand name product is the cause of the AE.

If you have any questions or need additional information, please contact Lori Gorski, Project Manager at 7-2521.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
LM Gorski, Project Manager	**e-mail**
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Lori Gorski
12/24/03 10:32:24 AM
Renan - We are working on a number of
very short timelines here in the Division &
the Office. Anything you could do to move
this along as quickly as possible is appreciated.
Thanks, Lori

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Stephen Moore Pkln 14B-19
DHHS/FDA/CDER/OPS/ONDCII/HFD-510

FROM:
Lori Gorski phone 7-2521
DHHS/FDA/CDER/ORM/DAAODP HFD-550

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
October 30, 2003		21-716	Original NDA submission	October 17, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Hydase hyaluronidase injection	priority		**Filing mtg 12/4/03**

NAME OF FIRM: Prima Pharm, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ **NEW PROTOCOL**
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE 2
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

XX Original NDA submission

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Prima Pharm, Inc has submitted NDA 21-716 for Hydase (hyaluronidase injection) as an adjuvant to increase the absorption and dispersion of other injected drugs

The NDA is a 505b2 application which references the DESI notice of September 23, 1970.

This product uses bovine raw material source.

Please let me know who the assigned reviewer will be. If you have any questions, please contact Lori Gorski, Project Manager at 7-2521.

Please cc GORSKIL RODRIGEUZLi and NGL on the DFS email when this review has been completed. Thanks

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) **XX Through Document Room** **HAND**

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/s/

Lori Gorski
10/30/03 03:37:36 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-716

Prima Pharm, Inc.
Attention: Anthony Dziabo
V.P. Regulatory Affairs
3443 Tripp Court
San Diego, Califonia 92121

Dear Mr. Dziabo:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Product:	Hydase (hyaluronidase injection)
Review Priority Classification:	Priority (P)
Date of Application:	October 17, 2003
Date of Receipt:	October 20, 2003
Our Reference Number:	NDA 21-716

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 19, 2003, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Also include a FORM FDA 356h with every submission. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, call Lori M. Gorski, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center For Drug Evaluation And Research

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

/s/

Lori Gorski
10/31/03 10:30:33 AM
Lori Gorski has signed for Carmen DeBellas