CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-665

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

EXCLUSIVITY SUMMARY FOR NDA # **21-665**

Trade Name **Amphadase**

Generic Name **hyaluronidase injection, USP, 150 IU/mL**

Applicant Name **Amphastar Pharmaceuticals, Inc.**

HFD # **550**

Approval Date If Known **October 26, 2004**

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 question about the submission.

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

YES / **X** / 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 / **X** /

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 /__X__/ NO /___ /

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

__5 years__

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

YES /___/ NO /__X__ /

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen 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 /__X__ /

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 /__X__/

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

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 NDA'S 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 /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ 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: _____

_____

Prepared By: Michael Puglisi

Project Manager

Concurrence By: William Boyd, M.D.
Clinical Team Leader

Wiley A. Chambers, M.D.
Deputy Office Director

Form OGD-011347 Revised 05/10/2004

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/s/

Wiley Chambers
11/15/04 05:23:43 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA #: 21-665

Stamp Date: July 7, 2003 Action Date: to be determined

HFD-550 Trade and generic names/dosage form: Amphadase (hyaluronidase injection, USP) 150 IU/mL

Applicant: Amphastar Pharmaceuticals, Inc. Therapeutic Class: 5

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 3

Indication #1:

An adjuvant to increase the absorption and dispersion of other injected drugs

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☐ ✓ No: Please check all that apply: ___Partial Waiver ___Deferred ✓ Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	kg____	mo.____	yr. 0	Tanner Stage____
Max____	kg____	mo.____	yr. 16	Tanner Stage____

Comments: Hyaluronidase was permitted in 1947 and efficacy was re-confirmed in 1970 in a DESI review for several indications, including for use in neonates for hypodermoclysis. More information is included in the Clinical review.

Indication #2:

For hypodermoclysis

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☐ ✓ No: Please check all that apply: ___Partial Waiver ___Deferred ✓ Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

tion D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg**____	**mo.**____	**yr.** 0	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.** 16	**Tanner Stage**____

Comments: Hyaluronidase was permitted in 1947 and efficacy was re-confirmed in 1970 in a DESI review for several indications, including for use in neonates for hypodermoclysis. More information is included in the Clinical review.

Indication #3:

An adjunct in subcutaneous urography for improving resorption of radiopaque agents

Is there a full waiver for this indication (check one)?

- ☐ ✓ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred __Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

tion A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ ✓ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

This page was completed by:

{See appended electronic signature page}

Michael Puglisi
Regulatory Project Manager

cc: NDA 21-665
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Division Director Summary of NDA 21-665

Review completed: August 26, 2004

Proposed Name: Amphadase (hyaluronidase injection)

Applicant: Amphastar Pharmaceuticals, Inc.
11570 Sixth Street
Rancho Cucamonga, CA 91730

I. Recommendations

A. Recommendation on Approvability

I concur with the Medical Officer Review recommendations for NDA 21-665 and recommend approval of NDA 21-665.

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

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

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Amphadase (hyaluronidase injection) 150 USP units/vial is a protein enzyme prepared from bovine testicular tissue. It is administered as an injection, but is not intended for intravenous use. The efficacy of hyaluronidase for the proposed indications (as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents) is supported by the USP monograph test for hyaluronidase units as a surrogate for hyaluronidase's effect in tissues. The safety and efficacy of hyaluronidase is supported by the DESI evaluation for use published in 1970. Additional safety information for this particular formulation is provided in the clinical safety study conducted by the applicant.

B. Efficacy

The efficacy is supported by the USP test for units of hyaluronidase and the DESI evaluations of hyaluronidase (mammalian origin) (DESI 6343, 6714, 7933) for use as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. There are no unresolved efficacy issues.

C. Safety

Hyaluronidase injection and hyaluronidase for injection have been safely marketed for over 50 years with millions of uses per year. The safety is supported by the literature and the safety study conducted by the applicant which demonstrates an allergic reaction level of less than 10%.

D. Chemistry/Manufacturing Review

I agree with the Chemistry/Manufacturing Review recommendation that the application be approved. The application includes information to support that the applicant is capable of producing a consistent drug product with a definable number of hyaluronidase units as described in the USP monograph.

E. Pharmacology/Toxicology Review

I concur with the Pharmacology/Toxicology conclusions concerning the adequacy of the DESI Review to support the safety and efficacy of the proposed indications.

F. Pediatrics

Clinical studies have been conducted in pediatric patients and included in the DESI review. Published studies include:

Schwartzman J and Levbarg M. Hyaluronidase: Further Evaluation in Pediatrics. The Journal of Pediatrics. 1950; 36: 79-86.

Britton RC, Habif DV. Clinical Uses of Hyaluronidase. Recent Advances in Surgery. 1952. 33(6): 917-942.

G. Trademark

DDMAC and DMETS were consulted with respect to the trademark, Amphadase and have no objections to the trademark.

H. Labeling

The revised labeling is consistent with the approved labeling for Vitrase (hyaluronidase for injection) and is considered acceptable.

I. Safety Update

A safety update was submitted on August 23, 2004. No new safety information has been identified. In addition, the Review Division is not aware of any new safety information which would affect the safety or efficacy of the drug product.

Wiley A. Chambers, MD
Deputy Division Director, HFD-550

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/s/

Wiley Chambers
8/26/04 02:46:44 PM
MEDICAL OFFICER

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/s/

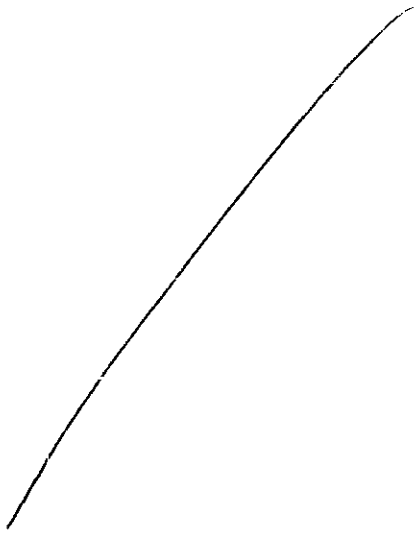
Wiley Chambers
8/26/04 02:56:08 PM
MEDICAL OFFICER

Memorandum to File

From:	**Zhou Chen**
Through:	**Josie Yang**
Date:	**August 23, 2004**
Re:	**Labeling Review for Amphadase NDA21-665**
Sponsor:	**Amphastar Pharmaceuticals, Inc.**

In this NDA submission, the nonclinical study-related sections of the proposed labeling are based on the labeling for Wydase, a DESI drug product [Federal Register Vol 35, No 185, p14800-14801 for hyaluronidase (Wydase, NDA 6-343)]. After several discussions within the review team, the following changes in the labeling are recommended.

1. In the "CLINICAL PHARMACOLOGY" section, two paragraphs [redacted] are removed. These [redacted] Amphadase for this NDA submission, and did not provide additional information on clinical pharmacology.



2. In the "PRECAUTIONS" section, the [redacted] was removed (see below). The study results were not from this NDA submission and were not informative.

3. The "Teratogenic Effects—Pregnancy Category" under the "Pregnancy" section will remain to be a "C". However, this section is revised as followings: "No adequate and well controlled animal studies have been conducted with Amphadase to determine reproductive effects. No adequate and well controlled studies have been conducted with Amphadase in pregnant women. Amphadase should be used during pregnancy only if clearly needed."

cc: list:

HFD-550/CSO/Puglisi
HFD-550/MO/Boyd
HFD-550/TL Pharm/YangJ
HFD-550/Pharm/ChenZh

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/s/

Zhou Chen
8/24/04 09:58:59 AM
PHARMACOLOGIST

Josie Yang
8/24/04 11:05:55 AM
PHARMACOLOGIST

CONSULTATION RESPONSE

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

DATE RECEIVED: August 11, 2004	**DESIRED COMPLETION DATE:** September 3, 2004 **PDUFA DATE:** October 26, 2005	**ODS CONSULT #:** 03-0204-1

TO: Brian Harvey, MD, PhD
Acting Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
HFD-550

THROUGH: Mike Puglisi
Project Manager
HFD-550

PRODUCT NAME: **Amphadase™** (Hyaluronidase Injection, USP) [Bovine] 150 USP Units/mL **NDA#:** 21-665	**NDA SPONSOR:** Amphastar Pharmaceuticals, Inc.

SAFETY EVALUATOR: Kimberly Culley, RPh

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Amphadase. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name, associated labels and labeling must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

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

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

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

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: August 18, 2004

NDA# 21-665

NAME OF DRUG: **Amphadase** (Hyaluronidase Injection, USP) [Bovine]
150 USP Units/mL

NDA HOLDER: Amphastar Pharmaceuticals, 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 a final assessment of the proprietary name, Amphadase, in regard to potential name confusion with other proprietary or established drug names. The carton label, container label and insert labeling were provided for review and comment. This name was previously reviewed and found acceptable by DMETS on October 03, 2003 (DMETS Consult 03-0204).

PRODUCT INFORMATION

Amphadase is purified bovine testicular hyaluronidase, which is a protein enzyme that modifies the permeability of the connective tissue through hydrolysis of hyaluronic acid. The modification in permeability is due to the temporary decrease in viscosity of the cellular cement, which will promote diffusion of injected fluids, localized transudates and exudates to facilitate absorption. Amphadase 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 50 to 300 units of hyaluronidase to the injection solution. The standard dose is 150 USP units. For hypodermoclysis, use of 150 USP is recommended to facilitate absorption of 1000 mL or more of solution. For small volumes (up to 200 mL), Amphadase may also be utilized. However, for infants and children less than 3 years of age, the volume of a single clysis should be limited to 200 mL with the daily dosage for a premature infant to not exceed 25mL/kg of body weight. In subcutaneous urography, 75 USP units will be injected over each scapula that will be followed by the contrast medium. Amphadase will be supplied as 150 USP units of hyaluronidase per mL, packaged in - vials.

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 Amphadase 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]. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Amphadase. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Error Prevention Staff with representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical skill, 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 Amphadase acceptable from a promotional perspective.

2. The Expert Panel identified the two additional proprietary names of Amphotericin and Vancenase AQ that were thought to have the potential for confusion with Amphadase. These products with the available dosage forms and usual dosage are listed in table 1 (see page 4).

3. Independent review identified the further two names of Amidate and Alphaderm, which are listed in table 1 with their available dosage forms and usual dosage (see page 4).

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[1] MICROMEDEX Integrated Index, 2004, 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 98-04, and the electronic online version of the FDA Orange Book.
[4] WWW location http://tess2.uspto.gov/bin/gate.exe?f=searchstr&state=m2pu5u.1.1

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

Proper Name*	Established Name(s) and Strength(s)	How Supplied	Other**
Amphadase	Hyaluronidase Injection USP, 150 USP Units/mL	Absorption and dispersion of injection drugs: 50 - 300 USP units (standard dose - 150 USP units) Hydrocortisone: 150 USP units for 1000 mL Ringer's solution Subcutaneous Urography: 75 USP units	
Amidate	Etomidate Injection, 2mg/mL	For induction of anesthesia: Adults and children (> 10 years of age) 0.2 to 0.6 mg/kg. Usual dose is 0.3 mg/kg, injected over 30 to 60 seconds. Can be used for concomitant anesthesia, smaller increments may be given to adults during short operative procedures to supplement subpotent anesthetic agents.	SA
Amphotericin	Amphotericin B Desoxycholate, Powder for Injection 50 mg Amphotericin B, lipid based, Powder for Injection 50 mg, 100 mg (cholesteryl) 50 mg (liposomal) Suspension for Injection 100 mg/20 mL	Desocycholate: Varies by infection and ranges from 0.5 – 1.5 mg/kg/day. Lipid Based: Cholesteryl: 3 to 4 mg/kg/day prepared as a 0.6 mg/ml (range, 0.16 to 0.83 mg/ml) infusion delivered at a rate of 1 mg/kg/hr Liposomal: 3 to 5 mg/kg/day prepared as a 1 to 2 mg/ml infusion delivered initially over 120 minutes Suspension: 5 mg/kg/day prepared as a 1 mg/ml infusion and delivered at a rate of 2.5 mg/kg/hour	LA
Alphaderm	Hydrocortisone (1%) and Urea (10%) Cream	Apply a small amount to the affected area, two to four times per day	LA
Vancenase AQ® (Beconase AQ®)	Beclomethasone Dipropionate, Monohydrate 42 mcg per spray	One to two nasal inhalations in each nostril twice daily	SA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

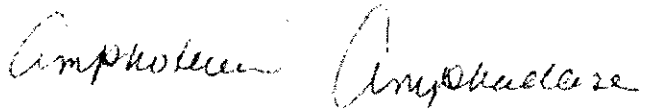
As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine 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 Amphadase were captured by the Expert Panel (EPD).

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Amphadase, the primary concerns related to look-alike and sound-alike confusion with Amphotericin and Vancenase. Similarly, through independent review, two additional drug names, Amidate and Alphaderm were also determined to have potential for confusion with Amphadase. Upon further review of the names gathered from EPD, independent analysis and POCA, the name of Alphaderm was not reviewed further due to a lack of convincing look-alike/sound-alike similarities with Amphadase. In addition, Alphaderm is no longer marketed in the US and no generic is on the market for this product. Although there is another drug product named Carmol HC which contains the same active ingredients, these products are not cross-referenced in standard pharmaceutical sources. In addition, Alphaderm and Alphadase do not share overlapping product characteristics such as the formulation, product strength, indication for use, and frequency of administration.

1. Amidate may sound like Amphadase. Amidate contains etomidate for injection, which is indicated for induction of general anesthesia. Etomidate is intravenously administered with standard dosing of 0.2 to 0.6 mg/kg for adults and children greater than 10 years of age. The usual dose is 0.3 mg/kg injected over 30 to 60 seconds. Amidate is available as 2 mg/mL, packaged in 20 mL Abbojects, and 10 and 20 mL ampules. The verbal similarities result from the shared leading letters "Am" in conjunction with the auditory correlation of "date" and "dase" in speech. This is compounded by the three syllable count shared by both names. Although their route of administration and dosing frequency could be considered congruent, their context of use should help to prevent name confusion. Amidate is a specialized product used in the induction of anesthesia and will primarily be used by anesthesiologists, which contrasts the use of Amphadase for increased absorption of injected drugs, hypodermoclysis and adjunct to urography that will be used by nurses and physicians. Normally doses of Amidate and Amidase will not overlap. Doses of Amidate will generally range in less than 50 mg (0.6 mg/kg for a 53 kilogram person) whereas Amphadase doses will usually range between 75-100 units. Due to differing characteristics, DMETS believes the potential for error to be minimal.

2. Amphotericin may look like Amphadase when scripted. Amphotericin is indicated for the treatment of fungal infections and Leishmaniasis. The drug products are available as Amphotericin B Desoxycholate and Amphoterin B, lipid based. Amphotericin B Desoxycholate is dosed in ranges from 0.5 to 1.5 mg/kg/day. This is typically administered for four to twelve weeks. Amphoterin B, lipid based is dosed at 3 to 5 mg/kg/day. The visual similarities of this name pair result from the shared leading "Amph" (see below).



However, the names can be distinguished by the final characters "icin" and "ase"; in addition to the noticeable difference in length (twelve letters compared with nine). Although both products are injectables and can have potential overlapping dosing (amphotericin desoycholate dosages range from 26.5-79.5 mg and lipid based from 159-265 mg for a 53 kilogram patient compared with Amphadase ranging between 75-100 units), the basic characteristics differ. For example, they contrast in the following ways: infusion method

(slow intravenous push compared with injecting under the skin), indication (fungal infection compared with increased absorption of injected drugs, hypodermoclysis and adjunct to urography), strength (50 mg or 100 mg compared with 150 USP units), and duration of therapy (weeks compared with one occurrence). Furthermore, amphotericin is a drug product that is closely monitored due to the deleterious side effects and subsequent required monitoring of dosage and renal function. Henceforth, DMETS concludes the possibility for confusion is lessened as the product characteristics differ, the visual similarity is low and the nature of amphotericin monitoring.

3. Vancenase may sound like Amphadase. The Vancenase product line has been discontinued from the US market, but Beconase AQ is currently still available. Both products contain beclomethasone as 0.042 mg per spray, therefore practitioners may substitute. Beclomethasone as a metered spray pump is used for the treatment of seasonal rhinitis and hay fever symptoms. The usual dose for adults and children over 6 years of age is one to two nasal inhalations (42 micrograms for each inhalation) into each nostril twice daily. The verbal similarity is due to the identical ending of "ase" and the fact that both names are composed of three syllables. The concluding letters "n" and "m" of the first syllable are also similar in speech. However, the products share no overlapping characteristics. They differ in dosage form/administration route (nasal inhaler compared with injectable), strength (microgram actuations compared with units of injection), duration of therapy (seasonal compared with single use), and dose (42 micrograms compared with 150 USP units). Due to the differences in the drug products, DMETS believes the possibility for confusion to be low.

4. — different hyaluronidase proprietary names have been proposed. One is approved (Vitrase®) — each sharing the same indication as Amphadase. After review of these products names, there were no concerns found in regard to look-alike and sound-alike potential with Amphadase.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

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

A. GENERAL COMMENT

DMETS recommends the Division of the 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 has questioned if the bovine source of the soluble enzyme product should be part of the established name or follow the presentation of the established name. The sponsor should revise the presentation of the established name on all labels and labeling based on LNC recommendation.

B. CONTAINER LABEL

C. CARTON LABEL

D. INSERT LABELING

1. General Comment

2. Description Section

   Please include the

3. Overdosage Section

4. Dosage and Administration Section

   a. Adsorption and Dispersion of Injected Drugs

      i. Please consider the inclusion of this statement

      ii. Please consider the inclusion of this statement

   b. Hypodermoclysis

      i. There is no specifically stated recommended dose or the maximum daily dose of hyaluronidase to be administered in neonates, infants, or children. Revise accordingly.

c. Subcutaneous Urography

i. —— . Currently, the labeling representation is "prone. 75 U of Amphadase."

5. How Supplied

Please clarify the vial size. Currently, the labeling list "150 USP units of hyaluronidase per mL in a 2 mL glass vial", —

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name, Amphadase. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

B. 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.

C. DDMAC finds the proprietary name Amphadase 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 301-827-2102.

Kim Culley, RPh
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise Toyer, PharmD
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Kimberly Culley
9/1/04 11:08:04 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/1/04 12:02:38 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-665

Amphastar Pharmaceuticals, Inc.
Attention: Stephen A. Campbell, Esq.
Senior Vice President, Regulatory Affairs
11570 Sixth Street
Rancho Cucamonga, CA 91730

Dear Mr. Campbell:

We acknowledge receipt on April 26, 2004, of your April 23, 2004, resubmission to your new drug application for Amphadase (hyaluronidase injection, USP) 150 IU/mL.

We consider this a complete, class 2 response to our January 7, 2004, action letter. Therefore, the user fee goal date is October 26, 2004.

If you have any questions, call Michael Puglisi, 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/

Michael Puglisi
5/21/04 02:47:09 PM
for Carmen DeBellas

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 & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-665

Amphastar Pharmaceuticals, Inc.
Attention: Stephen A. Campbell, Esq.
Senior Vice President, Regulatory Affairs
11570 Sixth Street
Rancho Cucamonga, CA 91730

Dear Mr. Campbell:

Please refer to the meeting between representatives of your firm and FDA on February 11, 2004. The purpose of the meeting was to discuss the clinical requirements concerning your product.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Michael Puglisi, 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

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	February 11, 2004
SCHEDULED START TIME:	3:00 pm
START TIME:	3:08 pm
END TIME:	3:40 pm
LOCATION:	9201 Corporate Boulevard
APPLICATION (DRUG):	NDA 21-665 Amphadase (hyaluronidase injection, USP) 150 IU/mL
SPONSOR:	Amphastar Pharmaceuticals, Inc.
TYPE OF MEETING:	Guidance
MEETING CHAIR:	Wiley A. Chambers, MD
MEETING RECORDER:	Michael Puglisi

FDA PARTICIPANTS:
Wiley Chambers/ Deputy Division Director
Jonca Bull/ Director, Office of Drug Evaluation V
Brian Harvey/ Acting Division Director
Terri Rumble/ Associate Director for Regulatory Affairs
Sandra Kweder/ Deputy Director, Office of New Drugs
Jane Axelrad/ Director, Office of Regulatory Policy
Elizabeth Dickinson/ Attorney, Office of Chief Counsel
Carol Drew/ Regulatory Counsel
Ginny Beakes/ Regulatory Counsel
Warren Rumble/ CDER Ombudsman
Dennis Bashaw/ Pharmacokinetics Team Leader
William Boyd/ Clinical Team Leader
Jennifer Harris/ Medical Officer
Lucious Lim/ Medical Officer
Carmen DeBellas/ Chief Project Manager
Mike Puglisi/ Project Manager
Lori Gorski/ Project Manager
Raphael Rodriguez/ Project Manager
David Lin/ Acting Director, DNDC III
Linda Ng/ Chemistry Team Leader

Libaniel Rodriguez/ Chemist
Stephen Moore/ Chemist
Jouhayna Saliba/ CDER Drug Shortage

INDUSTRY PARTICIPANTS:
Stephen A. Campbell/ Senior V.P., Regulatory Affairs
Tony Marrs/ Director, Product Development
Jack Zhang/ President and CEO
Rong Zhou/ Vice President, Quality Assurance
Diane Gerst/ Vice President, Scientific Affairs
Selina Su/ Senior Manager, Technical Development

MEETING OBJECTIVE:
To discuss the Agency's requirement for a clinical safety study of Amphadase (hyaluronidase injection).

QUESTION FOR DISCUSSION:
Why was a clinical deficiency listed in the action letter after discussion with the Division suggested that a clinical study would not be necessary?

Agency Response: *Until December 2003, it was the Division's belief that it would be able to rely on the DESI notice for hyaluronidase to substitute for safety and efficacy of Amphastar's intended application. Following a series of discussions in the Center for Drug Evaluation and Research on how best to handle a number of different products which had not been and could not be fully characterized, the expectations for establishing safety and efficacy were clarified to the Division.*

The inability to fully characterize Amphastar's hyaluronidase coupled with the inability to fully characterize the products studied to support the DESI notice left a gap between the safety and efficacy data in the DESI notice and Amphastar's product.

To bridge that gap, the following is believed to be necessary to link clinical efficacy and safety directly to the proposed drug product. Since the USP test is a direct measure of the substrate, HA (hyaluronic acid), being broken down in the body and the drug product being administered locally, the USP test is an appropriate surrogate for clinical efficacy. The labeled amount of hyaluronidase is expressed in the drug product packaging in USP units utilizing this assay.

The inability to completely characterize hyaluronidase leads to an inability to verify that the allergic reaction rate of the product proposed for marketing is less than the allergic reaction rate for a less purified product (10% incidence in the general population).[1] *For hyaluronidase products without human exposure or when a change in the source or manufacturing process occurs, the potential for immunogenicity is recommended to be evaluated using either a dosing regimen as indicated for the proposed indications of hyaluronidase or a skin test utilizing an intradermal injection of approximately 0.1 mL (15 U) of a 150 USP Unit/mL in at least 30*

[1] Schwartzman J, Levbarg M. Hyaluronidase: Further Evaluation in Pediatrics. J Pediat. 1950; 36: 79-86.

healthy subjects. Thirty subjects in this case are only acceptable if there are no allergic reactions observed in the thirty subjects. If an allergic reaction is noted, additional subjects would need to be evaluated to assure that the 95% confidence interval of the event rate is less than 10%. Because there is a chance of a reaction occurring, however unlikely, we strongly recommend that the study be conducted in more than 30 individuals. The table below identifies the number of positive reactions which could occur in a given set of subjects, yet still maintaining an adverse reaction rate of less than 10%:

Number tested	*Maximum number of reactions*
30 subjects	*No reactions*
31 or more subjects	*1 reaction or less*
50 or more subjects	*2 reactions or less*
67 or more subjects	*3 reactions or less*
83 or more subjects	*4 reactions or less*
98 or more subjects	*5 reactions or less*
169 or more subjects	*10 reactions or less*
236 or more subjects	*15 reactions or less*
300 or more subjects	*20 reactions or less*

Allergic reactions, if they occur, would be expected local to the site of administration within 20 minutes of administration of the drug product.

The requirement for this clinical safety study will also apply to any post-approval drug substance source changes.

ACTION ITEMS:
The Sponsor will submit an IND application with a clinical protocol for the requested safety study. The Division will provide comment on that protocol as soon as possible after its submission.

Minutes Prepared by: Michael Puglisi
Project Manager

Concurrence by: Wiley A. Chambers, M.D.
Deputy Division Director

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/s/

Wiley Chambers
2/27/04 09:05:51 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-665

Amphastar Pharmaceuticals, Inc.
Attention: Stephen A. Campbell, Esq.
Senior Vice President, Regulatory Affairs
11570 Sixth Street
Rancho Cucamonga, CA 91730

Dear Mr. Campbell:

Please refer to the meeting between representatives of your firm and FDA on February 11, 2004. The purpose of the meeting was to discuss the clinical requirements concerning your product. The first part of our meeting was followed by a discussion of your draft clinical protocol.

The official minutes of that discussion are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Michael Puglisi, 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

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 11, 2004
APPROXIMATE START TIME: 3:40 pm
APPROXIMATE END TIME: 4:00 pm
LOCATION: 9201 Corporate Boulevard

APPLICATION (DRUG): NDA 21-665
Amphadase (hyaluronidase injection, USP)
150 IU/mL

SPONSOR: Amphastar Pharmaceuticals, Inc.

TYPE OF MEETING: Guidance

MEETING CHAIR: Wiley A. Chambers, MD

MEETING RECORDER: Michael Puglisi

FDA PARTICIPANTS:
Wiley Chambers/ Deputy Division Director
Brian Harvey/ Acting Division Director
William Boyd/ Clinical Team Leader
Jennifer Harris/ Medical Officer
Lucious Lim/ Medical Officer
Mike Puglisi/ Project Manager
Lori Gorski/ Project Manager
Linda Ng/ Chemistry Team Leader
Libaniel Rodriguez/ Chemist

INDUSTRY PARTICIPANTS:
Stephen A. Campbell/ Senior V.P., Regulatory Affairs
Tony Marrs/ Director, Product Development

MEETING OBJECTIVE:
To discuss the Sponsor's planned clinical protocol for the requested safety study for Amphadase (hyaluronidase injection).

ISSUES DISCUSSED:

- *It is acceptable to have a positive control, but there is no requirement for a positive control.*
- *The protocol should be designed to show that with a 95% confidence interval, the allergic reaction rate is less than 10%.*
- *0.02 mL injections may be acceptable.*
- *For the purposes of this protocol, the agency is interested in information concerning allergenicity, not necessarily immunogenicity since it is already known that the product is immunogenic.*
- *There is no need to exclude pregnant women from the study. There has been widespread use of these products in fertility procedures with no evidence of safety problems. There is not expected to be any contraindication statement in the product's labeling concerning pregnancy.*
- *There is no requirement for three injection sites per patient. If any one of the three sites is positive, it would be considered a positive reaction.*
- *A 50 patient study would require that there are no more than 2 positive reactions for study success.*
- *Although unlikely considering the duration of the trial, any interim data analysis would require statistical adjustment.*
- *Patients should be monitored for at least 20 minutes post-injection. 10 minutes is not an acceptable monitoring period.*
- *Investigator information must be included with the IND submission.*
- *The IND can cross-reference the NDA submission.*
- *The Sponsor may request a waiver of the 30 day IND waiting period.*

ACTION ITEMS:

The Sponsor will submit an IND application with a clinical protocol for the requested safety study. The Division will provide comment on that protocol as soon as possible after its submission.

Minutes Prepared by: Michael Puglisi
Project Manager

Concurrence by: William Boyd, M.D.
Clinical Team Leader

Wiley A. Chambers, M.D.
Deputy Division Director

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/s/

Wiley Chambers
3/5/04 02:52:48 PM

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 #: 21593, 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.

. 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).

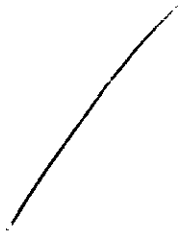
Rare allergic reactions (urticaria, angioedema), anaphylactic-like reactions following retrobulbar block or intravenous injections and a report of cardiac fibrillation are listed under the Adverse Reactions section of the revised Wydase® product labeling in October 2000.

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 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 — vials or (EA-eaches) of Wydase from 1998 through 2002 from the manufacturer to the various channels of distribution. These channels included



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. <u>Respiratory (8)</u>

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, We will continue to monitor the safety of the drug closely.

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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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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

Memorandum on Clinical Recommendations for Hyaluronidase Drug Products

Date: January 15, 2004

From: Wiley A. Chambers, MD
Deputy Director, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products, HFD-550

Through: Brian Harvey, MD, PhD _____
Acting Division Director, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products, and Deputy Director, Office of Drug Evaluation V

Through: Jonca Bull, MD _____
Director, Office of Drug Evaluation V

Background
The hyaluronidases are a family of β, 1-4 endoglucosaminidases that depolymerize hyaluronic acid (HA) and chondroitin sulfate. The drug products are partially purified preparations usually sourced from mammalian testicular tissue. The family of hyaluronidase products has never been fully characterized. After multiple discussions within the Center for Drug Evaluation and Research, the following recommendations have been established.

Efficacy
Sodium hyaluronidase is always administered and acts with a co-administered product. The co-administered product is another drug product, when hyaluronidase is used as an adjuvant to increase the absorption and dispersion of other injected drugs; the co-administered product is parental fluid in hypodermoclysis; the co-administered product is a radiopaque product when hyaluronidase is used as an adjunct in subcutaneous urography for improving resorption of radiopaque agents.

The action of hyaluronidase to cause the hydrolysis of hyaluronic acid, a viscous mucopolysaccharide which seems to bind water in the interstitial tissues and act as a physical barrier to the invasion of foreign substances that has been known since the 1940's.[1]
Clinical efficacy of hyaluronidase is based on the ability to break down (depolymerize) HA in the body, thereby allowing the co-administered product to flow into the tissue.

The drug product hyaluronidase was named hyaluronidase (versus the original name of "spreading factor of Duran-Reynals") because it breaks down hyaluronic acid (HA). The USP assay for the potency of hyaluronidase for injection is a direct in vitro measurement of the ability to depolymerize HA. Standardized HA is used in the test. The action to depolymerize HA and act as a spreading agent, along with the correlation to the USP test has been demonstrated or described in multiple clinical study publications which include:

[1] JAMA, September 20, 1949. Volume 135, No. 3, p. 160-161. Submitted to NDA 6-343.

1. Hechter, O et al. The Clinical Use of Hyaluronidase in Hypodermoclysis. J Pediatrics. 1947; 30(6):645-656. (submitted to NDA 6-343)
2. Cella LJ, Means JA. Clinical Significance of Hyaluronidase. Marquette M Review. 1947; 13:14-18. (submitted to NDA 6-343)
3. Hyaluronidase (The Spreading Factor) in Hypodermoclysis. JAMA, 1947; 135(5):289. (submitted to NDA 6-343)
4. The Biologic Significance of Hyaluronidase. JAMA, 1947; 135(3): 160-161. (submitted to NDA 6-343)
5. Hechter O, Dopkeen SK, Yudell MH. The Clinical Use of Hyaluronidase in Hypodermoclysis. J Pediatrics, 1947; 30(6): 645-656. (submitted to NDA 6-343)
6. Hechter O. Reconstitution of the Dermal Barrier to Fluid Diffusion Following administration of Hyaluronidase. Proc Soc Exp Biol Med. 1948; 67: 343-344. (submitted to NDA 6-343).

Hyaluronidase is administered to the local site where the product is expected to act.[2] There are no issues of distribution or bioavailability because of the local administration. The expected pharmacologic action is immediate (within a minute) of contact. The potency of the product is determined using a controlled amount of substrate. Since the USP test is a direct measure of the substrate, HA being broken down in the body and the drug product being administered locally, the test is an appropriate surrogate for clinical efficacy. The standardization of the test provides an acceptable mechanism for determining the efficacy of the drug product. The labeled amount of hyaluronidase is expressed in the drug product packaging in USP units utilizing this assay.

Safety

Hyaluronidase injection and hyaluronidase for injection have been safely used and marketed for over 50 years with millions of uses per year. The safety of different formulations and sources of hyaluronidase is described in the literature from the 1940s through 2003 (including cattle, sheep, horse, rabbit, human, recombinant human). Additionally, a review of adverse events for hyaluronidase products from different formulations and different sources has demonstrated very few adverse events. In the case of products with their own clinical studies or marketing history, evaluations of the clinical studies and the adverse events from the marketing history of that particular product have demonstrated similar results.

The benefit to risk ratio is supported by conclusions reached during the DESI evaluation with the expectation that the allergic reaction rate would not exceed an incidence of 10% in the general population. The indicated uses 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 radiopaque agents. The most frequently reported adverse experiences have been a lack of effectiveness of the co-administered product. It is not possible to determine whether that lack of effect is due to the hyaluronidase or the co-administered drug product. The next most common events are local injection site reactions. Hyaluronidase has also been reported to enhance the adverse events associated with co-administered drug products.

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[2] Swinyard EA, Pathak MA. Surface-Acting Drugs. In: Goodman AG, Gilman LS, Rall TW, Murad F eds. The Pharmacological Basis of Therapeutics. Seventh Edition, MacMillan Publishing Company 1985.

In addition to the years of marketing experience and studies in the United States, ten (10) years of foreign post-marketing information exists for a product marketed in the United Kingdom. The reported safety profile is consistent with the current labeling of the approved Wydase product.

The inability to completely characterize hyaluronidase leads to an inability to verify that the allergic reaction rate of the product proposed for marketing is less than the allergic reaction rate for a less purified product (10% incidence in the general population).[3] For hyaluronidase products without human exposure or when a change in the source or manufacturing process occurs, the potential for immunogenicity is recommended to be evaluated using either a dosing regimen as indicated for the proposed indications of hyaluronidase or a skin test utilizing an intradermal injection of approximately 0.1 mL (15 U) of a 150 USP Unit/mL in at least 30 healthy subjects. Thirty subjects, in this case are only acceptable, if there are no allergic reactions observed in the thirty subjects. If an allergic reaction is noted, additional subjects would need to be evaluated to assure that the 95% confidence interval of the event rate is less than 10%. Because there is a chance of a reaction occurring, even if unlikely, it is highly recommended that the study be conducted in more than 30 individuals. The table below identifies the number of positive reactions which could occur in a given set of subjects, yet still maintaining an adverse reaction rate of less than 10%:

Number tested	Maximum number of reactions
30 subjects	No reactions
31 or more subjects	1 reaction or less
50 or more subjects	2 reactions or less
67 or more subjects	3 reactions or less
83 or more subjects	4 reactions or less
98 or more subjects	5 reactions or less
169 or more subjects	10 reactions or less
236 or more subjects	15 reactions or less
300 or more subjects	20 reactions or less

Allergic reactions, if they occur, would be expected to occur local to the site of administration within 20 minutes of administration of the drug product.

Summary:

While the extensive literature available for hyaluronidase products establishes a good base for safety and efficacy of hyaluronidase drug products, the following additional tests are considered clinically necessary anytime the source or manufacturing process changes because the drug product cannot be fully characterized:

1. Efficacy should be confirmed by a determination of potency utilizing the USP monograph test for hyaluronidase.
2. Safety should be confirmed by the monitored administration of the drug product in its proposed final form to individual subjects in a manner that establishes that the 95% confidence interval of the expected allergic reaction rate is less 10%.

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[3] Schwartzman J, Levbarg M. Hyaluronidase: Further Evaluation in Pediatrics. J Pediat. 1950; 36: 79-86.

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/s/

Wiley Chambers
1/26/04 08:31:36 AM
MEDICAL OFFICER

Brian Harvey
1/26/04 10:06:52 AM
MEDICAL OFFICER

Jonca Bull
1/27/04 01:18:30 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-665

Amphastar Pharmaceuticals, Inc.
Attention: Stephen A. Campbell, Esq.
Senior Vice President, Regulatory Affairs
11570 Sixth Street
Rancho Cucamonga, CA 91730

Dear Mr. Campbell:

Please refer to your new drug application (NDA) dated June 6, 2003, received July 7, 2003, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Amphadase (hyaluronidase injection, USP) 150 IU/mL.

We acknowledge receipt of your submissions dated September 9, October 28, November 7 and 24, and December 4, 2003.

We also acknowledge receipt of your submission dated December 18, 2003. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b).

The not approvable deficiencies are summarized as follows:

CLINICAL

The clinical section is deficient. Clinical study information for safety of your proposed drug is needed to provide assurance of the low potential for significant allergic reactions in patients for the proposed indications.

To address this deficiency, we recommend that the level of immunogenicity be evaluated in a clinical trial of a representative population of patients using a skin test by means of an intradermal injection of approximately 0.1 mL (15 U) of a 150 USP Units/mL to determine if the level is <10%. Further studies may be needed and we recommend that the study designs addressing these regulatory safety concerns be discussed with the Division.

CHEMISTRY, MANUFACTURING AND CONTROLS

Drug Substance:

The methods to be used in, and the facilities and controls used for the manufacture, processing, packaging and holding of the drug substance are inadequate to preserve its identity, strength, quality, purity, potency and stability. Specifically:

1. Regarding the source and quality of the raw material:
   a) Provide the name and address of the abattoirs where the testes are collected.
   b) Describe what kinds of animals are processed at the abattoir(s).
   c) Clarify if the room/area for processing the bovine testes is a dedicated area.
   d) Clarify what the veterinary requirements — are to certify an area as non-infected.
   e) Describe what tests are conducted to verify that the cattle are BSE free.

2. Regarding the tests for the drug substance:
   a) Submit acceptance criteria and the analytical procedure for impurities in the drug substance.
   b) Establish the analytical procedure and acceptance criteria to account for the —
      — portion of the drug substance.

Drug Product:

The methods to be used in, and the facilities and controls used for the manufacture, processing, packaging and holding of the drug product are inadequate to preserve its identity, strength, quality, purity, potency and stability. Specifically:

4. Regarding the tests for the drug product.
   a) Include the analytical method and acceptance criteria for hyaluronidase content and impurities in the drug product specification for stability studies.
   b) Include the analytical procedure and acceptance criteria for content uniformity regarding activity in the drug product specification.
   c) Propose either one specific or two non-specific identification tests for the drug product specification.

5. Regarding the delivery of product to the patient.
   a) Provide fill volume data for more than one batch of drug product to support the claim that ~ mL is deliverable by syringe from ~ mL of product.
   b) Provide a description of the syringe(s) to be used with the product.
   c) Provide data to support the compatibility of the drug product with the syringe, i.e., 150 USP units of product transferred to the syringe is the same amount leaving the syringe.

The totality of the following issues makes it difficult to determine the quality of the drug product. These issues need to be resolved before the application can be approved:

Drug Substance:

6. Regarding the tests for the drug substance.
   a) Establish a range in mg hyaluronidase/mg protein for the acceptance criterion for Hyaluronidase Content.
   b) The drug substance is described as ' '. Clarify whether

7. Provide analysis data for the drug substance.

8. Acceptance criteria for tests should be based on actual long-term stability data. Tighten the criteria appropriately and submit the revised specification and stability protocol.

9. Submit data to support compatibility of the drug substance with the container/closure system.

10. The stability data do not support the proposed retest period. Revise the retest period or submit updated stability data.

11. Conduct and submit the results of the stress studies according to the ICH Q5C guidance.

Drug Product:

12. . Amend your application accordingly.

13. Acceptance criteria for tests should be based on actual long-term stability data. Tighten appropriately and submit the revised specification and stability protocol.

14. Submit compatibility studies of the drug product with the container/closure system to ensure that the solution is

15. The stability data do not support the proposed expiry period. Revise the expiry period or submit updated stability data.

16. Conduct and submit results for stress studies of the drug product according to the ICH Q5C guidance.

Inspections of the manufacturing facilities for this application are ongoing. We remind you that the facilities, controls for the manufacturing, processing packing and holding of the drug substance and drug product must be in compliance with current good manufacturing practice regulations as described in 21 CFR 210 and 211.

LABELING

We will continue to work with you on the proposed labeling once you have adequately addressed the deficiencies noted above.

In addition, please be advised that on December 3, 2003, the Pediatric Research Equity Act of 2003 (PREA) was signed into law. We will work with you to determine the applicability of this new law with regard to your NDA submission.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Michael Puglisi, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Jonca C. Bull, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Jonca Bull
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Office Director Memorandum
Office of Drug Evaluation V
Office of New Drugs

NDA 21-665

Date: January 6, 2004

Sponsor: Amphastar Pharmaceuticals, Inc

Drug Product: hyaluronidase injection USP, 150 IU/mL

Pharmacologic Category: proteolytic enzyme

Proposed Tradename: Amphadase

Proposed Indication: As an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radioapaque agents.

Background

NDA 21-665 for hyaluronidase solution 150 IU/mL, a bovine testes derived proteolytic enzyme, was submitted as a 505(b(2) application based on literature and the agency's prior finding of safety and efficacy for the proposed indications approved under the Drug Efficacy and Safety (DESI) review published in the Federal Register September 23, 1970. There is a long history dating to the 1940's of marketing of this drug product. Hyaluronidase ceased to be marketed due to a business decision by Wyeth Pharmaceuticals in 2002 to stop manufacture. Wyeth's NDA 06-343 was the last remaining marketed NDA approved under the DESI notice. Because of this, the product is currently under drug shortage.

There are unresolved concerns discussed below by the Agency due to the biological sourcing and the adequacy of the submitted data to meet current scientific standards. Also, a Citizen's Petition has been submitted by the current NDA owner (Baxter Healthcare Corporation) of the last marketed NDA (Wyeth 06-343) for this product.

Clinical Deficiencies

No clinical studies have been submitted by the sponsor. Therefore, there is no clinical data in this submission which provides adequate assurance of low allergic potential of this product for safety issues of hypersensitivity. A consult by the Division of Pulmonary Drug Products recommends for hyaluronidase products without clinical or postmarketing data the following:

> 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.

Chemistry and Manufacturing

This application contains multiple manufacturing deficiencies due to unresolved Agency information requests to the sponsor responding satisfactorily to drug substance composition, drug substance specification, drug substance stability, drug product specification, and stability regulatory concerns. The viral clearance review found that the sponsor has not satisfactorily determined the viral clearance capability of the hyaluronidase manufacturing process.

Conclusion of Office Review of Action Package

The Office is in concurrence with the findings of the Pulmonary consultation and Chemistry reviews that the sponsor has failed to provide adequate evidence for regulatory approval for demonstration of safety for the proposed indications. Therefore, under 21CFR section 314.125, a non-approval action is deemed appropriate given the significance of these regulatory issues to patient safety and the proposed marketing of this product. The drug shortage concerns do not override the compelling public health need for the sponsor to address the clinical and manufacturing deficiencies prior to marketing approval.

Respectfully submitted,

Jonca C. Bull, MD
Director, Office of Drug Evaluation V
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Jonca Bull
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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: Stephen Campbell, Esq.	**From:** Mike Puglisi, Project Manager
Fax: 909-980-8296	**Fax:** 301-827-2531
Phone:	**Phone:** 301-827-2522
Pages: 2 (including cover page)	**Date:** October 23, 2003

Re: Microbiology Deficiency for NDA 21-665 for Amphadase

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

• **Comments:**

Mr. Campbell-

Here's a comment from our Microbiology reviewer concerning NDA 21-665 for Amphadase. Please respond in an amendment to your NDA. Please let me know if you have any questions about this comment. Thanks.

-Mike

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-665

FILING REVIEW LETTER

Amphastar Pharmaceuticals, Inc.
Attention: Stephen A. Campbell, Esq.
Senior Vice President, Regulatory Affairs
11570 Sixth Street
Rancho Cucamonga, CA 91730

Dear Mr. Campbell:

Please refer to your June 6, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Amphadase (hyaluronidase 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 September 5, 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. stability of the drug substance,
    d. specification of the drug product,
    e. manufacture of the drug product, and
    f. stability of the drug product.

2. Full information regarding the facilities to be inspected has not been provided.

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.

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

If you have any questions, call Michael Puglisi, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Linda L. Ng, Ph.D.
Chemistry Team Leader for the
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Linda Ng
9/12/03 05:16:44 PM

CONSULTATION RESPONSE

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

DATE RECEIVED: 07/17/03 **DATE OF DOCUMENT:** 06/06/03	**DESIRED COMPLETION DATE:** 10/07/03	**ODS CONSULT #:** 03-0204

TO: Lee Simon, M.D.
Director, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products
HFD-550

THROUGH: Mike Puglisi
Project Manager
HFD-550

PRODUCT NAME: **Amphadase** (Hyaluronidase Injection, USP [Bovine]) 150 USP units/mL **NDA #:** 21-665	**NDA SPONSOR:** Amphastar Pharmaceuticals, Inc.

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

SUMMARY: In response to a consult from the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Amphadase" to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proposed proprietary name, Amphadase. This name and its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the name Amphadase 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: August 29, 2003

NDA #: 21-665

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

NDA HOLDER: Amphastar Pharmaceuticals, Inc.

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 "Amphadase", regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Amphadase is a protein enzyme containing hyaluronidase which hydrolyzes intercellular ground substance. According to the sponsor, Amphadase is bioequivalent to the reference listed drug, Wydase Stabilized Solution, which is currently a discontinued drug. Amphadase 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. Doses of 50 to 1500 units have been used as an aid in the resolution of hematomas, transudates, and edema. Amphadase will be supplied as 150 USP units of hyaluronidase per mL in a 1 mL vial.

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

[1] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/database within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, 2003, Facts and Comparisons, St. Louis, MO.
[3] The Drug Product Reference File [DPR], the DMETS database of proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

which sound alike or look alike to "Amphadase" 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 trademark electronic search system (TESS) was conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential 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

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Amphadase. Potential concerns regarding drug marketing and promotion related to the proposed names 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. The Expert Panel identified three proprietary names that were thought to have the potential for confusion with Amphadase. Additionally, the established name Alteplase was also identified. These products are listed in Table 1 (see below), along with the dosage forms available and usual FDA-approved dosage.

2. DDMAC did not have concerns with Amphadase in regard to promotional claims.

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

Product Name	Dosage form(s); Established name	Usual adult dose*	Other**
Amphadase	Hyaluronidase Injection, USP [Bovine] 150 USP units/mL	150 units added to the injection solution	
Activase	Alteplase, Recombinant Injection 50 mg, 100 mg	Acute Myocardial Infarction: The recommended total dose is based upon patient weight, not to exceed 100 mg. Acute Ischemic Stroke: The recommended total dose is 0.9 mg/kg (not to exceed 90 mg total dose). Pulmonary Embolism: The recommended dose is 100 mg administered by intravenous infusion over 2 hours.	SA
Ceredase	Alglucerase Injection 80 units/mL	Initial dosage may be as little as 2.5 units/kg of body weight 3 times a week up to as much as 60 units/kg administered as frequently as once a week or as infrequently as every 4 weeks.	SA
Amphotec	Amphotericin B Cholesteryl Sulfate Complex for Injection 50 mg, 100 mg	3 to 4 mg/kg/day intravenously (doses up to 7.5 mg/kg/day may be administered).	SA/LA

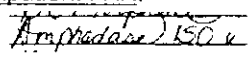
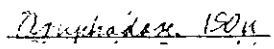
*Frequently used, not all-inclusive
**LA (look-alike), SA (sound-alike)

[4] WWW location http://www.uspto.gov/main/trademarks.htm
[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Amphadase with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 127 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Two inpatient orders were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Amphadase (see below). 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 inpatient order was 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.

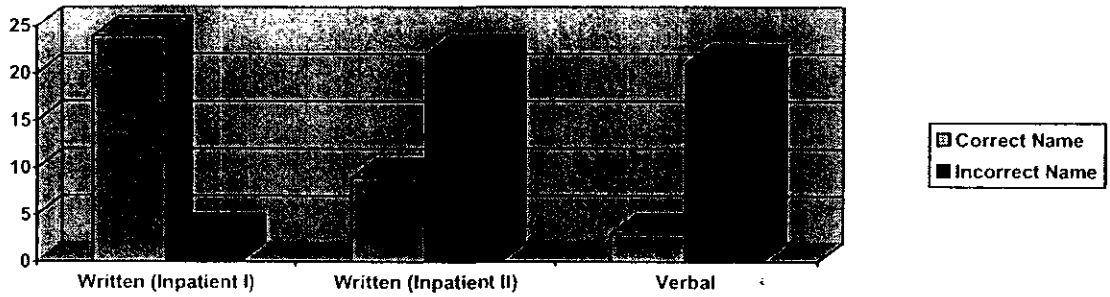
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Inpatient I RX: 	Amphadase 150 units SC prior to clysis.
Inpatient II RX: 	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient I	41	27 (66%)	24 (89%)	3 (11%)
Written Inpatient II	43	31 (70%)	9 (29%)	22 (71%)
Verbal	43	24 (56%)	3 (12%)	21 (88%)
Total	127	82 (64%)	36 (44%)	46 (56%)



Among the first written inpatient prescriptions, 3 of 27 (11%) participants interpreted the name incorrectly. The incorrect interpretations from the prescriptions included Amphase, Aphadase, and Ampradase. None of the interpretations are similar to a currently marketed drug product.

In the second written inpatient prescriptions, 22 of 31 (71%) participants interpreted the name incorrectly. The incorrect interpretations from the prescriptions included Amphadose (17 occurrences), Aniphadase (two occurrences), Amphredase, and Aniphadose (two occurrences). None of the interpretations are similar to a currently marketed drug product.

Among the verbal prescription study participants for Amphadase, 21 of 24 (88%) participants interpreted the name incorrectly. Some of the incorrect interpretations were misspelled/phonetic variations of "Amphadase". The incorrect responses included Ephidase, Amphidase (seven occurrences), Anphadase (two occurrences), Afadase, Anfidase (two occurrences), Effigel, Amfadase, Amfidase, Aphadase, Amphodase, Acidase, Antedase, and Amphydase.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, the primary concerns related to look-alike, sound-alike confusion with Amphadase are Activase and its established name Alteplase, Ceredase, and Amphotec.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Amphadase could be confused with any of the aforementioned names. The majority of incorrect interpretations were misspelled/phonetic variations of the proposed name, Amphadase. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size.

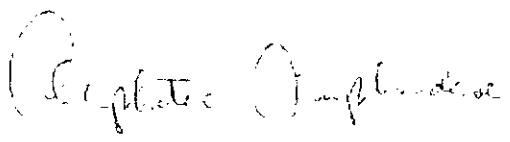
1. Activase and Amphadase have the potential for sound-alike confusion. Activase is a thrombolytic agent also known as tissue-type plasminogen activator. Activase is available in injection form. Depending on the indication, Activase is typically administered at doses not exceeding 100 mg and a bolus dose precedes an infusion dose. Both Activase and Amphadase begin with the letter "A-" and share the suffix "-ase". Although Activase and Amphadase both have three syllables and rhyming characteristics, when pronounced, the two product names can be differentiated because of the prefix "Acti-" in Activase and "Ampha-" in Amphadase. Amphadase is stored in the refrigerator, whereas Activase can be stored at room temperature or in the refrigerator. Activase and Amphadase share a common route of

administration (injection) and storage conditions (refrigeration), but differences in their dosage schedules, strengths, and phonetic characteristics minimize the potential for an error to take place between the two drug products.

2. Alteplase and Amphadase have potential for sound-alike confusion. Alteplase is the established name for Activase (discussed above). Both Alteplase and Amphadase begin with the letter "A-" and share the suffix "-ase". They also have three syllables and share rhyming characteristics, but when pronounced, the names can be differentiated from one another because of the "Alte-" in Alteplase and the "Ampha-" in Amphadase. Alteplase and Amphadase share a common route of administration (injection) and mode of storage (refrigeration), but differences in their dosage schedules, strengths, and phonetic characteristics minimize the potential for an error to take place between the two drug products.

3. Ceredase and Amphadase have potential for sound-alike confusion. Ceredase is an enzyme used for replacement therapy in Type 1 Gaucher's disease and available in injection form. The administration of Ceredase is usually repeated every 2 weeks, but it may be given as often as every other day or as infrequently as every 4 weeks depending on response. The suffixes, "-edase" in Ceredase and "-adase" in Amphadase can sound similar. However, the prefix "Cere-" in Ceredase and the "Ampha-" in Amphadase can be differentiated from one another. Although the two names share rhyming characteristics, storage conditions (refrigeration required), and the same number of syllables, they sound distinct from one another. Additionally, Ceredase and Amphadase do not have overlapping dosage schedules or strengths. Therefore, DMETS believes that the likelihood for a dispensing error with Ceredase and Amphadase is minimal given the differences between the products.

4. Amphotec and Amphadase have potential for sound-alike and look-alike confusion. Amphotec is a lipid-form of amphotericin B indicated for the treatment of invasive aspergillosis in patients where renal impairment or unacceptable toxicity precludes the use of Amphotericin B deoxycholate in effective doses, and in patients with invasive aspergillosis where prior amphotericin B deoxycholate has failed. Amphadase is given intravenously once daily. Amphotec and Amphadase both have three syllables and share similar prefixes, "Ampho-" vs. "Ampha-". However, Amphotec has eight letters whereas Amphadase has nine letters and the suffix "-tec" in Amphotec and "-dase" in Amphadase distinguishes the two names from each other (see writing sample below) orthographically and phonetically. Amphotec, if pronounced as AMPHO-TEK, sounds different than AMPHA-DASE. Amphotec and Amphadase share a dosage form (injection), but vary in dosage schedules. Amphotec is available in two strengths, whereas Amphadase is available in one strength. Given the differences between Amphotec and Amphadase and the lack of convincing sound-alike and look-alike potential, the likelihood for confusion between these two products is minimal.



III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In addition, DMETS has reviewed the container label, carton and insert labeling and has identified several areas of possible improvement which may minimize potential user error.

A. GENERAL COMMENTS

1.

2. 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 has questioned if the mammalian source of the soluble enzyme product should be part of the established name or follow the presentation of the established name. DMETS also questioned 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.

B. CONTAINER LABEL

C. CARTON LABELING

D. PACKAGE INSERT LABELING

1. See comments A1 and A2.

2. Precautions Section

2. Dosage and Administration Section

a. The Absorption and Dispersion of Injected Drugs Subsection

The first two sentences of the subsection reads: "Absorption and dispersion of other injected drugs may be enhanced by adding

i.

ii.

iii.

b. Hypodermoclysis Subsection

i. The subsection does not specifically state the recommended dose or the maximum daily dose of hyaluronidase to be administered in neonates, infants, or children. Revise accordingly.

ii. Please clarify "For older patients, the rate and volume of administration should not exceed those employed for intravenous infusion'

iii

3. How Supplied

c. Insert does not contain information about a 2 mL vial, though there is mention of a 2 mL vial on the carton label. Please clarify the use of the 2 mL vial.

IV. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Amphadase. This name and its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. DMETS recommends the labeling revision as 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.
3. DDMAC finds the proprietary name, Amphadase, 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

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/s/

Jinhee Jahng
10/3/03 03:46:32 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
10/3/03 03:48:35 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/3/03 03:58:10 PM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
10/3/03 04:08:22 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-665

Amphastar Pharmaceuticals, Inc.
Attention: Stephen A. Campbell, Esq.
Senior Vice President, Regulatory Affairs
11570 Sixth Street
Rancho Cucamonga, CA 91730

Dear Mr. Campbell:

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

You were notified in our letter dated June 27, 2003, that your application was not accepted for filing due to non-payment of fees. This is to notify you that the Agency has received all fees owed and your application has been accepted as of July 7, 2003.

The review priority classification for this application is priority (P).

Unless we notify you within 60 days of the fee receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 5, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 7, 2004.

Under 21 CFR 314.102(c), you may request an informal conference 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. All communications concerning this NDA should be addressed 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 Michael Puglisi, 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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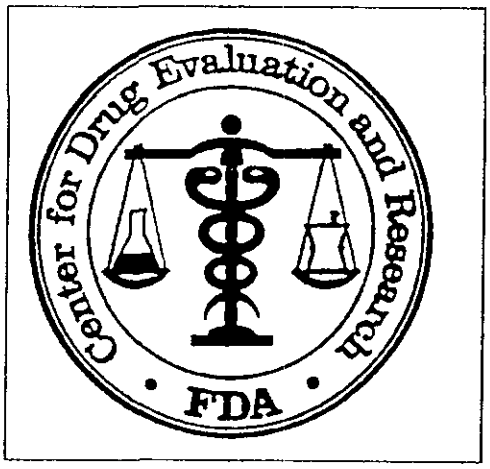
/s/

Michael Puglisi
8/1/03 09:16:54 AM
for Carmen DeBellas

FACSIMILE TRANSMISSION
RECORD



From: Libaniel Rodriguez. Ph.D.
Review Chemist

Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products
HFD-550

Phone 301-827-2069
Fax 301-827-2531

Date: July 10, 2003

To:

Name: Stephen A. Campbell
Company: Amphastar Pharmaceuticals Inc.
City: Rancho Cucamonga State:CA
Phone #: 909 980 9484 ext 2019

FAX #: 626 459 5592

Number of Pages (INCLUDING COVER PAGE): 2

Please telephone (301) 827-2069MMEDIATELY if re-transmission is necessary.

If you have any question about this information request, please call me.

Libaniel Rodriguez

July 10, 2003

NDA 21-665 Amphadase (hyaluronidase injection USP, 150 USP unist/mL, 1 mL)

CMC COMMENTS

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information as an amendment to the submission.

DRUG PRODUCT

1. Please establish analytical procedures and acceptance criteria for the specification of the following:

   For drug substance: — hyaluronidase content, and impurities.

   For drug product: Osmolality. — hyaluronidase content and impurities.

2. The manufacturing process should be capable of removal or inactivation of adventitious agents. The results of a validation study to demonstrate the inactivation of potential viral contamination from the testes material should be provided. The validation should be performed at the laboratory scale. The log reduction of model viruses for the various steps and overall process should be reported in tabular form.

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/s/

Libaniel Rodriguez
7/21/03 02:02:51 PM
CHEMIST
IR

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-665

Amphastar Pharmaceuticals, Inc.
Attention: Stephen A. Campbell, Esq.
Sr. Vice President, Regulatory Affairs
11570 Sixth Street
Rancho Cucamonga, CA 91370

Dear Mr. Campbell:

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 Drug Product: Amphadase (hyaluronidase for injection)

Date of Application: June 6, 2003

Date of Receipt: June 13, 2003

Our Reference Number: NDA 21-665

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Checks sent by a courier should be addressed to:

Food and Drug Administration (360909)
Mellon Client Service Center, Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number are on the enclosed check.

The receipt date for this submission (which begins the review for filability) will be the date the review division is notified that payment has been received by the bank.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed 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 Michael Puglisi or Lori Gorski, Project Managers, 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
6/27/03 03:27:55 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-665

Amphastar Pharmaceuticals, Inc.
Attention: Stephen A. Campbell, Esq.
Senior Vice President, Regulatory Affairs
11570 Sixth Street
Rancho Cucamonga, CA 91730

Dear Mr. Campbell:

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 Drug Product: Amphadase (hyaluronidase injection, USP) 150 IU/mL

Review Priority Classification: Priority (P)

Date of Application: June 6, 2003

Date of Receipt: June 13, 2003

Our Reference Number: NDA 21-665

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 August 12, 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. 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 Michael Puglisi, 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/

Michael Puglisi
6/24/03 04:09:00 PM
for Carmen DeBellas

February 4, 2003

Amphastar Pharmaceuticals

Hyaluronidase Guidance Teleconference Meeting Minutes

FDA Attendees: Wiley Chambers, Lee Simon, Jennifer Harris, Lucious Lim, Matt Feinsod, Linda Ng, Bryan Riley, Mike Puglisi, Lori Gorski, Raphael Rodriguez

Amphastar Attendees: Stephen Campbell, Selina Su, Rong Zhou, Tony Marrs

Amphastar Pharmaceuticals has requested a guidance meeting to discuss the possibility of submitting an application for Hyaluronidase Injection.

Amphastar identified the source of Hyaluronidase as bovine material to be obtained from

For Amphastar's product to be submitted under an ANDA, the product would need to be bioequivalent to Wydase. Since no Wydase is available for comparison or characterization, an ANDA is not an option.

Amphastar's product could be submitted under a 505(b)(1) or 505 (b)(2) application. The safety and efficacy of Hyaluronidase had been established through the FDA's evaluation of the National Academy of Sciences-National Research Council, Drug Efficacy Study Group's (DESI) reports for Hyaluronidase.

A submission which referenced the DESI notice would afford the Amphastar product the indications listed in the notice ("Hyaluronidase is effective for enhancing the absorption and dispersion of other injected drugs; for hypodermoclsis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents").

Because the availability of Hyaluronidase is considered a medical necessity, and there is currently a drug shortage due to the lack of manufacturing of this drug product, the sponsor could anticipate a Priority Review for the submission.

Expiry for the Amphastar product would depend on the Chemistry data presented in the NDA submission (at least on 1 year data would be expected).

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/s/

Wiley Chambers
1/23/04 03:58:39 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-665		
Drug: Amphadase (hyaluronidase injection)	**Applicant: Amphastar Pharmaceuticals, Inc.**	
RPM: Michael Puglisi	**HFD-550**	**Phone # 301-827-2522**

Application Type: ( ) 505(b)(1) **(X) 505(b)(2)** (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) *If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.* **(X) Confirmed and/or corrected**	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): **N/A – DESI Reference**

❖ Application Classifications:	
• Review priority	() Standard **(X) Priority**
• Chem class (NDAs only)	**Type 1**
• Other (e.g., orphan, OTC)	**N/A**
❖ User Fee Goal Dates	**October 26, 2004**
❖ Special programs (indicate all that apply)	**(X) None** Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	**(X) Paid** **UF ID number - 4572**
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes **(X) No**

• This application is on the AIP	( ) Yes **(X) No**
• Exception for review (Center Director's memo)	**N/A**
• OC clearance for approval	**N/A**
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	**(X) Verified**
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	**(X) Verified**
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified **21 CFR 314.50(i)(1)** **(X) (ii)** ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	**(X) N/A (no paragraph IV certification)** ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	**Exclusivity Summary Complete** **No remaining exclusivity to bar approval**
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X) No**

Actions	
• Proposed action	**(X) AP** ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	**Not Approvable – 1/7/04**
• Status of advertising (approvals only)	**(X) Materials requested in AP letter** ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(X) Yes** ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**(X) None** ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	**N/A**
• Most recent applicant-proposed labeling	**X - submitted 8/12/04**
• Original applicant-proposed labeling	**X - submitted 6/6/03**
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	**DDMAC- 1/29/04** **DMETS- 10/3/03, 9/1/04**
• Other relevant labeling (e.g.. most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	**N/A**
• Applicant proposed	**X – submitted 8/12/04**
• Reviews	**DDMAC- 1/29/04** **DMETS- 10/3/03, 9/1/04**
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	**N/A**
• Documentation of discussions and/or agreements relating to post-marketing commitments	**N/A**
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	**X**
❖ Memoranda and Telecons	**X**
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	**N/A**
• Pre-NDA meeting (indicate date)	**February 4, 2003**
• Pre-Approval Safety Conference (indicate date; approvals only)	**N/A**
• Other **Post-NA Action/Clinical Guidance Meeting**	**February 11, 2004**
❖ Advisory Committee Meeting **N/A**	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	**9/23/70 DESI Notice**
❖ Postmarketing Safety Review	**1/30/04**
❖ Office Director's Memo	**1/6/04**
Deputy Division Director's Memo	**1/15/04, 8/26/04**
❖ Clinical Team Leader's Memo	**4/20/04**

Summary Review	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	**8/26/04**
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	**12/8/03, 12/9/03, 8/16/04, 8/19/04**
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	**N/A**
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	**In 8/26/04 Dep.Director's Review**
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	**N/A**
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	**X**
❖ Demographic Worksheet *(NME approvals only)*	**N/A**
❖ Statistical review(s) *(indicate date for each review)*	**N/A**
❖ Biopharmaceutical review(s) *(indicate date for each review)*	**11/24/03**
❖ Pulmonary Review	**12/29/03**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	**N/A**
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	**N/A**
• Bioequivalence studies	**N/A**
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	**12/16/03, 8/20/04, 9/20/04, 10/8/04**
Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	**12/16/03**
• Review & FONSI *(indicate date of review)*	**N/A**
• Review & Environmental Impact Statement *(indicate date of each review)*	**N/A**
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	**11/21/03**
❖ Viral Clearance Reviews	**12/19/03, 7/19/04**
❖ Facilities inspection (provide EER report)	**Date completed: 7/20/04** **(X) Acceptable** ( ) Withhold recommendation
❖ Methods validation	( ) Completed **(X) Requested** ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**11/17/03**
❖ Nonclinical inspection review summary	**N/A**
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	**N/A**
❖ CAC/ECAC report	**N/A**