CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-665

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 860/870/880) Tracking/Action Sheet for Formal/Informal Consults**

From: **E.Dennis Bashaw, Pharm.D.**			**To: DOCUMENT ROOM (LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 10/15/03	IND No.: Serial No.:	NDA No. **21-665**	DATE OF DOCUMENT **6/13/03**	
NAME OF DRUG **[Bovine hyaluronidaise] Amphadase**	PRIORITY CONSIDERATION **P**		Date of informal/Formal Consult: **8/04/03**	

NAME OF THE SPONSOR: [Amphastar Pharmaceuticals, Inc.]

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	X IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☐ OTHER *(SPECIFY BELOW)*: [ ]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☐ See comments below
☐Medical☐Chemist☐Pharm-Tox	☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ See submission cover letter
☐Micro☐Pharmacometrics☐Others		X OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)		[Original NDA Review]

REVIEW COMMENT(S)

X **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

Background

This is a 505(b)(2) application for Amphadase® (bovine hyaluronidase). The proposed indication for Amphadase® is as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis (subcutaneous administration of fluids); and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. Dosing ranges from up to 150U for use in hypodermoclyis to 75U for subcutaneous urography.

Hyaluronidase (previously marketed as Wydase®) is considered by the FDA to be a medically necessary drug product and is currently on FDA's list of drug shortages because it is no longer manufactured by Wyeth Laboratories. The Amphadase® formulation is similar to that of Wydase® in that they are both of bovine origin and contain thimerosal (0.1mg — This proposed formulation would provide a safe, consistent and reliable supply of this product as an alternative to the existing supply, which is provided by compounding of bovine hyaluronidase by individual pharmacies.

Drug Substance

Wydase®, the original Wyeth product (NDA 6-343) was approved in March 1950 and was subject to the Drug Efficacy Study Implementation or DESI review and was found to be effective for the indications in a FR notice published 9/23/70 (vol. 35, no. 185, pg. 14800-801. Wydase® itself was a purified form of hyaluronidase from bovine testicular protein, although exact comparisons are impossible to quantify due to the lack of Wydase® for comparison.

Like Wydase®, the active ingredient in Amphadase® is a preparation of highly purified bovine testicular protein enzyme hyaluronidase from BSE negative animals —. The exact chemical structure of the enzyme is still unknown. Hyaluronidase is a — , enzyme product capable of hydrolyzing mucopolysaccharides of the type of hyaluronic acid. It contains not less than — units of hyaluronidase activity per mg, calculated with reference to the dry substance. The molecular weight is estimated, by the sponsor, to be between —

The product is a sterile solution for parenteral use. It is packaged in 2ml glass vials, each containing 1mL of 150U/mL — Based upon a comparison of the Amphadase® and Wydase® package inserts, the two formulations appear to be quantitatively and qualitatively identical in formulation.

Waiver Request

The current NDA submission contains no in vivo biopharmaceutic information. Amphastar Pharmaceuticals is requesting a waiver of in vivo bioequivalence studies under the waiver provisions of 21CFR320.22(b)(1), in that this product is for parenteral use and is identical in both active and inactive ingredients to an already approved NDA. While it would be nice to have a definitive structure associated with this compound, no structure was ever elucidated for Wydase®, thus even if a structure was available for Amphadase® there would be no Wydase® available for comparison.

Recommendation

The sponsor has presented sufficient information in this NDA to substantiate their claim that their hyaluronidase of bovine origin is similar to that of the approved Wydase® product. As the Amphadase® injection is identical to the Wydase® Stabilized Solution formulation, in terms of both active and inactive ingredients, a waiver of in vivo biostudies is granted under the provisions of 21CFR320.22(b)(1).

SIGNATURE OF REVIEWER: _____	Date _____
SIGNATURE OF TEAM LEADER: _____	Date _____
CC.: HFD # [880]; TL: [Selen]; DD: [Lazor]	**Project Manager:** _____ **Date** _____

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

/s/

Dennis Bashaw
11/24/03 11:50:40 AM
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Arzu Selen
11/24/03 12:12:49 PM
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