CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-859

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:	IND No.: Serial No.: 1	NDA No. **21-859**	DATE OF DOCUMENT **7/05/05**	
NAME OF DRUG **[Recombinant human hyaluronidaise] Hylenex™**	PRIORITY CONSIDERATION **P**		Date of informal/Formal Consult: 4/12/05	

NAME OF THE SPONSOR: [Halozyme Therapeutics]

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**

Background

This is a 505(b)(2) application for recombinant human hyaluronidaise (Hylenex™). The proposed indication for Hylenex™ is 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.

Dosing ranges from 50-300U (usually 150U) for use in hypodermoclyis and 75U for subcutaneous urography. Hylenex™ contains a recombinant human form of hyaluronidase (rHuPH20) as its sole active pharmaceutical ingredient. rHuPH20 has been shown to meet an in vitro test that has been correlated with in vivo data. The in vitro test is the United States Pharmacopeia Hyaluronidase for Injection assay for potency. This assay as applied to Hylenex™ has demonstrated unit to unit correlation to the USP hyaluronidase reference standard in an in

vivo analysis of enzyme activity as a spreading factor.

Hyaluronidase (previously marketed as Wydase®) was listed on the FDA Drug Shortage List until 5/04 when an ovine form (NDA 21-640-ISTA Pharm.) was approved. Subsequently a bovine form of hyaluronidaise was approved under NDA 21-665 from AMPHASTAR. The Hylenex™ formulation differs from the Wydase® formulation, and these recently approved products, in that it is of recombinant human origin and is preservative-free. This proposed formulation would provide an alternative to the existing supply and, being of recombinant human origin, would be potentially less antigenic than the animal extracts which are available.

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.

The recombinant human form of hyaluronidase differs in amino acid sequence, protein structure; carbohydrate analysis and the degree of enzyme activity from bovine derived hyaluronidase. The active ingredient in Hylenex™ is a highly purified preparation of recombinant human hyaluronidase, a protein enzyme. Hylenex is produced by genetically engineered Chinese Hamster Ovary (CHO) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). The purified hyaluronidase glycoprotein contains 447 amino acids with an approximate molecular weight of 61,000 Daltons.

Each vial contains 150 USP units of recombinant human hyaluronidase per mL with 8.5 mg sodium chloride, 1.78 mg sodium phosphate dibasic dihydrate, —— sodium hydroxide, 1.0 mg human serum albumin, 1.0 mg edetate disodium dihydrate, and 0.4 mg calcium chloride dihydrate. The ready for use solution is clear and colorless with an approximate pH of 7.4 and an osmolality of 290 to 350 mOsm.

Waiver Request

The current NDA submission contains no in vivo biopharmaceutic information. Halozyme Therapeutics is requesting a waiver of in vivo bioequivalence studies based on the fact that there are no existing stocks of Wydase® available for use as a comparator, that is a parenteral solution (i.e., bioavailability is self-evident), and that it meets a USP test for "potency".

The lack of a comparator is a problem it is not a valid reason for a waiver of in vivo biostudies cited under 21CFR320. The regulations do allow for the granting of a waiver through the use of an in vitro test if the test has been "...correlated with in vivo data..." (21 CFR 320.22(d)(3).) The USP "potency" test is a test of the enhancement of tryphan blue diffusion in the skin of nude mice, guinea pigs, or rabbits (see attachment). Under the conditions of the test, the Hylenex™ product was found to produce an "equivalent" degree of enhancement of tryphan blue diffusion in the skin of nude mice. As this test was developed with the Wydase® product, and was accepted by the USP as a measure of the drug's diffusion enhancement activity and as it is a solution intended for parenteral administration, the information submitted is acceptable as an in vitro demonstration of in vivo bioavailability.

Labeling

The current proposed package insert while providing information on the in vitro activity of the enzyme does not provide any information on the biologic fate of hylauronidaise. As it is a naturally occurring enzyme, and is of recombinant human origin, it is unlikely to be quantifiable in the traditional sense. The clinical pharmacology section of the label is appended following the in vitro test results.

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio-1

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
9/15/2005 10:29:56 AM
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Arzu Selen
9/19/2005 10:29:13 AM
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