

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:NDA 21174**

**ADMINISTRATIVE DOCUMENTS**

NDA No. 21-174

PATENT INFORMATION UNDER SECTION 505(b)

A drug substance of gemtuzumab zogamicin (CMA-676) is covered by U.S. Patent 4,970,198, normal expiration date November 30, 2007.

A drug substance of gemtuzumab zogamicin (CMA-676) is covered by U.S. Patent 5,079,233, normal expiration date January 7, 2009.

A drug substance of gemtuzumab zogamicin (CMA-676) is covered by U.S. Patent 5,585,089, normal expiration date December 17, 2013.

A drug substance of gemtuzumab zogamicin (CMA-676) is covered by U.S. Patent 5,606,040, normal expiration date February 25, 2014.

A drug substance of gemtuzumab zogamicin (CMA-676) is covered by U.S. Patent 5,693,762, normal expiration date December 2, 2014.

A drug substance of gemtuzumab zogamicin (CMA-676) is covered by U.S. Patent 5,739,116, normal expiration date April 14, 2015.

A drug substance of gemtuzumab zogamicin (CMA-676) is covered by U.S. Patent 5,767,285 normal expiration date June 16, 2015.

The composition and formulation of gemtuzumab zogamicin (CMA-676) are covered by U.S. Patent 5,773,001, normal expiration date June 30, 2015.

The use of gemtuzumab zogamicin (CMA-676) for inhibiting or eliminating acute myeloid leukemia is covered by U.S. Patent 5,773,001, normal expiration date June 30, 2015.

An application for extension under the terms of the Drug Price Competition and Patent Term Restoration Act of 1984 will be filed upon approval of the NDA. Patent Information will be updated upon issuance of a certificate of patent term extension. American Cyanamid Company, a wholly-owned subsidiary of the parent company of applicant is the owner of these patents, except for U.S. Patent 5,585,089 and U.S. Patent 5,693,762 which are licensed to the parent company of applicant by the owner. In the opinion of applicant and to the best of applicant's knowledge, there is no other U.S. patent which claims the drug for which applicant has sought approval or which claims the use of the drug for which applicant has sought approval.

WYETH-AYERST LABORATORIES

By:   
Elizabeth M. Barnhard  
Senior Patent Attorney

Patent/Exclusivity Information

- |    |   |  |
|----|---|--|
| 1) | Active ingredient(s)  | gemtuzumab zogamicin (CMA-676)   |
| 2) | Strength(s)   | 5 mg of gemtuzumab zogamicin in a 20 mL amber vial. Upon reconstitution with 5 mL of sterile water for injection USP, the final concentration is 1 mg/ml.  |
| 3) | Trade Name  | TBD  |
| 4) | Dosage Form<br>(Route of Administration)  | Intravenous  |
| 5) | Applicant Firm Name   | Wyeth-Ayerst Laboratories  |
| 6) | NDA Number  | 21-174   |
| 7) | Approval Date   | TBD  |
| 8) | Exclusivity - Date first ANDA could be submitted or approved and length of exclusivity period | Pursuant to Section 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii) of the Federal Food, Drug and Cosmetic Act, no ANDA may be submitted prior to 5 years after the date of approval of this NDA.  |
| 9) | Applicable patent numbers and expiration date of each   | U.S. Patent 4,970,198, Normal Expiration Date: November 13, 2007<br>U.S. Patent 5,079,233, Normal Expiration Date: January 7, 2009<br>U.S. Patent 5,585,089, Normal Expiration Date: December 17, 2013<br>U.S. Patent 5,606,040, Normal Expiration Date: February 25, 2014<br>U.S. Patent 5,693,762, Normal Expiration Date: December 2, 2014<br>U.S. Patent 5,739,116, Normal Expiration Date: April 14, 2015<br>U.S. Patent 5,767,285, Normal Expiration Date: June 16, 2015<br>U.S. Patent 5,773,001, Normal Expiration Date: June 30, 2015 |

EXCLUSIVITY SUMMARY for NDA # 21-174 SUPPL # \_\_\_\_\_

Trade Name mylotarg Generic Name gemtuzumab  
ozogamicin

Applicant Name Wyeth-Ayerst Research HFD- 150

Approval Date, if known \_\_\_\_\_ Orphan Design

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES /  / NO /  /

b) Is it an effectiveness supplement? YES /  / NO /  /

If yes, what type? (SE1, SE2, etc.) \_\_\_\_\_

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

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

\_\_\_\_\_  
\_\_\_\_\_

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

\_\_\_\_\_  
\_\_\_\_\_

d) Did the applicant request exclusivity?

YES /  / NO /  /

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

7 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /  / NO /  / OTC Switch /  /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /  / NO /  /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /  / NO /  /

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

NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_

2. Combination product.

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

YES /  / NO /  /

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

NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. 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:

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YES /\_\_\_/ NO /\_\_\_/

- (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



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 _____
_____	!	_____
_____	!	_____



NDA-21-174

Mylotarg (gemtuzumab ozogamicin)

## **Exclusivity Checklist**

**Exclusivity is not applicable due to this drug  
receiving Orphan-drug Status**

## PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

<b>NDA/BLA Number:</b>	<u>21174</u>	<b>Trade Name:</b>	<u>CMA-676(GEMTUZUMAB ZOGAMICIN) 5MG/VIAL IV</u>
<b>Supplement Number:</b>		<b>Generic Name:</b>	<u>GENTUZUMAB ZOGAMICIN</u>
<b>Supplement Type:</b>		<b>Dosage Form:</b>	<u>Injectable; Intravenous</u>
<b>Regulatory Action:</b>	<u>AP</u>	<b>Proposed Indication:</b>	<u>relapsed acute myeloid leukemia</u>

**ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?**

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

**What are the INTENDED Pediatric Age Groups for this submission?**

NeoNates (0-30 Days)     Children (25 months-12 Years)  
 Infants (1-24 Months)     Adolescents (13-16 Years)

Label Adequacy	<u>Inadequate for ALL pediatric age groups</u>
Formulation Status	<u>NO NEW FORMULATION is needed</u>
Studies Needed	<u>STUDIES needed. Applicant has COMMITTED to doing them</u>
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:  
 orphan drug exempt from 1998 Rule

This Page was completed based on information from a REVIEWER, STEVEN HIRSCHFELD

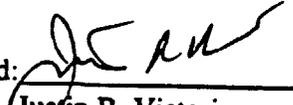
Steven Hirschfeld  
 Signature

29 MAR 00  
 Date

**gemtuzumab zogamicin**  
**NDA No. 21-174**

**Item 16      Debarment Certification**

Wyeth-Ayerst hereby certifies that it did not and will not knowingly use in any capacity the services of any person debarred under subsections (a) or (b) of section 306 of the Federal Food, Drug, and Cosmetics Act in connection with application No. 21-174 for gemtuzumab zogamicin.

Signed: 

Justin R. Victoria  
Vice President

Worldwide Regulatory Affairs

NDA 21-174

Mylotarg (gemtuzumab ozogamicin) for injection

## **Financial Disclosure**

Please refer to the Medical Officer's review regarding financial disclosure.

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration

Form Approved: OMB No. XXXX-XXXX  
Expiration Date: XX/XX/XX

## CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

### TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

**Please mark the applicable checkboxes.**

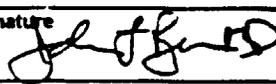
(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator has a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

**Clinical Investigators**

Gemtuzumab Zogamicin (See attached lists)	Studies 101-US, 201-US/CA, 202-EU, 203-US/EU

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

<b>Names</b> John Ryan, Ph.D., M.D. Mr. Richard R. DeLuca	<b>Titles</b> Senior Vice President - Clinical R&D Vice President - R&D Finance
<b>Firm/Organization</b> Wyeth-Ayerst Research	
<b>Signature</b>  	<b>Date</b> 4 Oct 99

**Paperwork Reduction Act Statement**

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing reviewing the collection of information. See comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

Please DO NOT RETURN this form to this address.

MEMORANDUM

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

DATE: APR 28 2000

FROM: Robert Temple, M.D.  
Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Gemtuzumab Ozogamicin (NDA 21-174)

TO: Richard Pazdur, M.D.  
Director, Division of Oncologic Drug Products, HFD-150

The evaluation of gemtuzumab ozogamicin, as well-described by Dr. Bross is, unfortunately, not unusual for new, relatively exciting modalities, but, at least in retrospect, was less than optimal. In the future, we should be even more wary of suggesting reliance on single arm studies for diseases with reasonable incidence rates. The 142 patients treated would have been far better "spent" in randomized comparisons with a standardized regimen or even local choice" usual care." From these single arm studies, in relapsed patients with variable post-gemtuzumab further treatments it is not possible to say how gemtuzumab compares in effectiveness with alternative treatments. This is of particular concern because response rates are plainly lower than alternatives unless one allows CRp (morphologic responses) to "count" as CRs. There is some evidence that survival and time to relapse are similar in cR and CRp but this is not solid and CRp patients at least trend toward a somewhat worse outcome.

Nonetheless, in relapsed patients considered poor candidates for cytotoxic therapies, which apparently translates substantially to patients over 60, there is no doubt that gemtuzumab ozogamicin can produce responses, some of them of decent duration, and the ODAC recommendation for approval for such patients is reasonable. How to define these patients is not so clear (it is hard to believe that "over 60" is a satisfactory description of the population) and I've tried to modify this with more explanation in labeling. I note that, as I understand it, although we have no drugs or combinations specifically indicated for relapsed AML, we do have treatments for AML not further specified, which would, at least technically, include relapsed patients, even though we have not reviewed specific data in those patients. Approval of gemtuzumab ozogamicin under the accelerated approval rule is thus, in my view, based on its different, and to some extent lesser, toxicity, important in more vulnerable patients. This lesser toxicity obviously cannot be based on any direct comparisons with alternatives but seems apparent to experts from the results of the studies conducted and knowledge of the toxicity of alternatives.

Apart from labeling suggestions, I believe we should get updated survival and time to relapse data; the current labeling references to "cut off dates," when we know survival data on all 142 patients and relapse status on the remaining 20 unrelapsed patients are readily available, should make everyone concerned (sponsor and investigators, I mean) uncomfortable.

I note labeling gives no data on survival in patients vs. non-responders. I know such analyses are considered highly suspect; I presume that is why they're not included in labeling. The differences are, however, pretty striking.

I've added a summary paragraph to the clinical trials section and a sentence to indications referring to (1) the state of data and (2) who this drug is for and why. See what you think.

*RS*  
Robert Temple, M.D.

# MEMORANDUM

Date: April 18, 2000

From: Paul A. Andrews, Ph.D.  
Pharmacology Team Leader, HFD-150

P.A.A. 4/18/2000

To: Files for NDA# 21-174

Re: Approvability for Pharmacology and Toxicology  
Myelotarg (gemtuzamab ozogamicin)

Myelotarg is a conjugate of the antibiotic calicheamicin with a humanized murine antibody to the CD33 cell surface antigen. Wyeth-Ayerst seeks approval of Myelotarg for treatment of patients with CD33<sup>+</sup> acute myeloid leukemia in first relapse. This product will be the first antibody conjugate approved by the FDA. Although Ontak (denileukin diftitox) is also a targeted therapy (approved by CBER in February 1999), it is a fusion protein of diphtheria toxin with interleukin-2 and does not contain an antibody. Dr. Sandip Roy has provided an exemplary review of the pharmacology and toxicology studies submitted to the Myelotarg NDA. Many of the studies were previously reviewed by myself at the time of the original IND and these reviews are included in the package. Dr. Roy considers the pharmacology and toxicology studies adequate to support approval of the intended indication. I concur with his recommendation.

The non-clinical studies in the NDA covered the core expectations for cytotoxic antibody conjugates in HFD-150 (*Cancer Chemother. Pharmacol.*, 41:173-185, 1998). The package included single dose studies of gemtuzamab ozogamicin in rats, monkeys, and chimpanzees; and single dose studies of various unconjugated calicheamicin derivatives in mice, rats, and dogs. Multiple dose studies were also conducted with gemtuzamab ozogamicin administered weekly for six doses in rats and monkeys. These studies support the proposed administration of two doses of Myelotarg fourteen days apart to humans. As expected for antibody conjugates (and antibodies in CBER), a human tissue reactivity screen was provided along with experiments demonstrating the *in vitro* specificity in cells  $\pm$ CD33 expression. A study of the stability of the conjugate in plasma was submitted, as were numerous pharmacology and pharmacokinetic studies.

An ICH Stage C-D developmental toxicity study (and pilot study) was conducted in rats with gemtuzamab ozogamicin. Wyeth-Ayerst originally proposed to conduct a developmental toxicity study in rats with calicheamicin only. Since it appeared that only small amounts of calicheamicin derivatives are released from the conjugate and contain a portion of the linker, the Division concluded that the proposed study would not adequately convey the risk to fetal development from systemic exposure to gemtuzamab ozogamicin. The Division therefore requested studies in both rodents and non-rodents with the conjugate to adequately assess the risk for developmental toxicity in humans receiving this novel therapeutic. However, after reviewing the unequivocal positive findings with gemtuzamab ozogamicin in the rat pilot study (7/10/98), we agreed that a single study in rats would suffice for the planned indication. Dr. Roy used the Draft Pregnancy Risk Integration Guidance to provide an excellent assessment of the concern for human reproductive and developmental toxicity from gemtuzamab ozogamicin (pp. 26-29 of review). His analysis indicates significant concern for humans for the four endpoints of fertility, developmental mortality, dysmorphogenesis, and alterations to growth (positive signals with net adjustments  $\geq +4$ ).

To assess genetic toxicity, only an *in vivo* mouse micronucleus study was conducted. This study was positive as expected for this enediyene class of antibiotics. These compounds cause sequence specific

double stranded cleavage of DNA after binding in the minor groove. Since the expected genetic toxicity for a calicheamicin-containing therapeutic was established by this study, this single study was deemed sufficient for filing the Myelotarg NDA. Carcinogenicity studies are not necessary to support approval for the intended indication and were not submitted.

A detailed labeling review was provided by Dr. Roy and I agree with the requested changes. AUC data were not used in the label to compare animal exposures associated with critical toxicity endpoints to human exposures because human data were only available for total and free calicheamicin equivalents. Acceptable data was not available for the intact conjugate or total antibody. Note that the drug product contains approximately 50% unconjugated antibody and that the molar ratio of calicheamicin to antibody is not 1:1. In any case, the majority of the toxicity endpoints occurred at doses well below the human dose on a mg/m<sup>2</sup> basis (causing significant concern for human risk) and crude estimations indicate ratios based on AUC data would have been even lower.

**Recommendations:** The pharmacology and toxicology data supports approval of this NDA. There are no unresolved issues.

Original NDA

cc: Div File  
HFD-150

/SRoy

/SBradley

/PAndrews

/PBross

## MEETING MINUTES

**MEETING DATE:** May 4, 2000

**TIME:** 2:30 PM, EST

**LOCATION:** Woodmont Office Complex 2; Conference Room B

**NDA #21-174**

**DRUG:** Mylotarg (gemtuzumab ozogamicin)

**SPONSOR/APPLICANT:** Wyeth-Ayerst Research

### FDA PARTICIPANTS

Richard Pazdur, M.D.

Peter Bross, M.D.

Sean Bradley, R.Ph.

Division Director

Medical Officer

Regulatory Project Manager

### INDUSTRY PARTICIPANTS

Mr. Justin Victoria

Mr. Barry Sickels

Dr. Debbie Cooper

Ms. Angela DiRado

Dr. Matthew Sherman

Dr. Mark Berger

Ms. Cathy Eten

Dr. Lance Leopold

Mr. Lew Barrett

Ms. Elaine O'Hara

Ms. Charlene Gallagher

Dr. Robert Maguire

Worldwide Regulatory Affairs

Worldwide Regulatory Affairs

Worldwide Regulatory Affairs

Worldwide Regulatory Affairs

Clinical Research

Clinical Research

Clinical Research

Clinical Research

Marketing

Marketing

Legal

Medical Affairs

### **MEETING OBJECTIVES:**

To discuss the FDA proposed indication for Mylotarg (gemtuzumab ozogamicin) for Injection.

### **DISCUSSION:**

During the teleconference, W/A proposed 3 alternative wordings for the Mylotarg Indications section of the label. W/A expressed a concern that third party insurance stipulations may delay or prevent patient treatment by requiring prior approval from insurance companies before using this drug therapy due to the FDA's narrow proposed indications.

Dr. Pazdur stated that FDA does not consider cost or insurance reimbursement issues when labeling medications. The FDA is concerned with public health issues of the proposed labeling. The data submitted for this drug therapy is based on non-randomized trials and historical comparisons, and the labeling must reflect the limitations of the data. The labeling should remind the physician to consider alternative available options for treatment of acute myeloid



## MEETING MINUTES

**MEETING DATE:** May 3, 2000

**TIME:** 2:30 PM, EST

**LOCATION:** Woodmont Office Complex 2; Conference Room B

**NDA #21-174**

**DRUG:** Mylotarg (gemtuzumab ozogamicin)

**SPONSOR/APPLICANT:** Wyeth-Ayerst Research

### FDA PARTICIPANTS

Richard Pazdur, M.D.

Division Director

Peter Bross, M.D.

Medical Officer

Raji Sridhara, Ph.D.

Statistician

Sean Bradley, R.Ph.

Regulatory Project Manager

### INDUSTRY PARTICIPANTS

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Ms. Angela DiRado

Worldwide Regulatory Affairs

Dr. Matthew Sherman

Clinical Research

Dr. Mark Berger

Clinical Research

Ms. Cathy Eten

Clinical Research

Dr. Lance Leopold

Clinical Research

Dr. Robert Maguire

Medical Affairs

Mr. Robert Herbertson

Biostatistics

### **MEETING OBJECTIVES:**

To discuss the FDA proposed Phase 4 Study Design for Mylotarg (gemtuzumab ozogamicin) for Injection.

### **DISCUSSION:**

Wyeth-Ayerst wanted to use Relapse free survival as the primary endpoint for their studies. They suggested that this endpoint would be "cleaner" and results would be available earlier than with overall survival as an endpoint.

Dr. Sridhara disagreed with the relapse free survival endpoint, since only responders would be evaluated, causing the study to have a treatment dependent outcome. Dr. Pazdur questioned the clinical benefit reflected by relapse free survival.

Wyeth-Ayerst subsequently faxed an agreement to initiate the 302 add-on superiority trial, toxicities permitting, with overall survival as an endpoint, although they would still like to consider using overall response and overall survival as co-primary endpoints.

May 3, 2000; Teleconference

NDA 21-174

Page 2

The meeting concluded at 3:01 PM, EST.

Minutes prepared by:           /S/            
Sean Bradley, R.Ph., Project Manager

Concurrence Chair:           /S/                     S.Y.OO            
(name of chair)

Cc:

Original NDA 21-174

HFD-150/Div. File

/PBross

/SBradley

**MEETING MINUTES**

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## MEETING MINUTES

**MEETING DATE:** April 26, 2000      **TIME:** 1030 AM, EST

**LOCATION:** Woodmont Office Complex 2, Conference Room C

**NDA#** 21-174

**DRUG:** Mylotarg (gemtuzumab ozogamicin) for Injection

**SPONSOR/APPLICANT:** Wyeth-Ayerst Research

**TYPE of MEETING:** CMC Guidance Issues for NDA Submission

### FDA PARTICIPANTS

Eric Duffy, Ph.D.

Chemistry Team Leader

Xiao Hong Chen, Ph.D.

Chemistry Reviewer

Sean Bradley, R.Ph.

Regulatory Project Manager

### INDUSTRY PARTICIPANTS

Dr. David Smolin

Senior Director, Bio-Process Development

Dr. Parimal Desai

Director, AR&D

Dr. John Simpson

Associate Director, AR&D

Dr. Noel Mellish

Associate Director, Medical Research and Development

Dr. Jim Farina

Principle Research Scientist, AR&D

Mr. Barry Sickels

Associate Director, Worldwide Affairs

**MEETING OBJECTIVES:** FDA request for teleconference to discuss CMC specifications regarding Wyeth-Ayerst's NDA application.

**FDA DISCUSSION ISSUES AND SPONSOR RESPONSES:**

**I. Study Specifications**

- A. **FDA:** *Refer to question 12 submitted to you (DATE), regarding drug substance holding times. This issue was not discussed in your responses submitted April 13, 2000 and these changes of holding times should be reported to FDA. We suggest submitting them in your annual report or submit as an amendment to the NDA.*

W/A: We concur.

- B. **FDA:** *Regarding bulk conjugate, we suggest that the specification for purity of bulk liquid conjugate (drug substance) by reduced SDS PAGE be tightened to NLT to % instead of %.*

W/A: We will perform a tentative specification of %. We will revisit this issue in the future after we have gained more manufacturing experience.

- C. **FDA:** *We recommend that the specification of for Aggregates by method be tightened to % for release, stability and shelf-life for product substance.*

W/A: We will use a tentative value of % until we gain more manufacturing experience and we will address this issue again in future.

**FDA:** *The drug product specifications should be revised to reflect the changes (tightening) of the drug substance specifications.*

W/A: We will change the drug product specifications to reflect the changes. Also, we would like to base shelf life on current data a NLT of %. We will base our future shelf life on the suggested 35 NLT.

- D. **FDA:** *We recommend that the specification for Total Calicheamicin by UV method be tightened to µg/mg protein.*

W/A: We believe we can support this specification and this will be revisited upon further manufacturing experience.

- E. **FDA:** *We suggest the IC50 value specification be changed from ng protein/mL to*

W/A: In our updated protocol submission, we have the current IC<sub>50</sub> at \_\_\_\_\_. This is a tentative value, which will be confirmed after a specified period.

F. **FDA:** *We recommend that the specification for antigen binding ELISA be tightened to \_\_\_\_\_%, instead of the proposed \_\_\_\_\_%.*

W/A: The tentative specification for antigen binding ELISA \_\_\_\_\_% will be established, and this specification be reevaluated after gaining additional manufacturing experience.

G. **FDA:** *The stability protocol you provided says to contain testing for multiple items including particulate matter. However, no stability data for particulate matter is provided.*

W/A: We have suitable particulate matter data, DTR in all time points

H. **FDA:** *The drug product specifications should be revised to reflect the changes (tightening) of the drug substance specifications.*

W/A: The drug product and drug substance specifications will be revised to reflect the changes in specifications. Drug product and shelf-life specifications will be the same.

I. **FDA:** *Please provide test methodology for specification for analyzing the strength and purity of \_\_\_\_\_*

W/A: We will provide a detailed description of the test methods used for analyzing the strength and purity of \_\_\_\_\_ and this will be provided after development of the \_\_\_\_\_ method is completed.

**Additional Questions/Comments:**

**FDA:** *We will request a six-month retest date for the linker. We can revisit this when more batch material is available.*

*The conjugated/unconjugated antibody value was stated as being %. We can accept the use of the word "approximately" regarding this value to state, "approximately % unconjugated." Use this approximate value for unconjugated antibody as a tentative specification. We will further comment on this issue in the labeling review.*

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

There were no unresolved issues.

**ACTION ITEMS:**

<u>Item description</u>	<u>Person Responsible</u>	<u>Due Date</u>
Fax Phase 4 comments to Sponsor	FDA	April 27, 2000
Fax responses to phase 4 comments and follow-up with a submission to The NDA.	Wyeth-Ayerst	April 27, 2000

The meeting concluded at 12:09 PM, EST. There were no unresolved issues or discussion points.

Minutes prepared by:   /S/     27Apr.00    
Sean Bradley, R.Ph., Project Manager

Concurrence Chair:   /S/     4/27/00    
(name of chair)



**Decisions reached:**

- Medical:** Acceptable for filing (AF). This application will be reviewed under a Priority (P) review clock. Dr. Maybee from CBER has been consulted for additional clinical review.
- Chemistry:** AF. The trade name for the drug has not been established and needs to be consulted to OPDRA once submitted. The requirement for an environmental assessment has not been determined. The Establishment Evaluation Request (EER) has been sent, however CBER's product reviewer would like to be included on the site visits.
- CBER:** Dr. Shapiro from CBER is reviewing the antibody section of the drug product. The following pertain to stability data for bulk P67.6:
- 30-month data 1 lot - study is complete should have 36-month data before April 29, 2000
  - 12-month 3 lots - will not have 24-month data until April, May or June 2000; should have 18-month data by April 29, 2000
  - we would give date of 6-months beyond what has been submitted with supporting data and if studies are ongoing
  - could extend expiration date without prior approval if studies ongoing and approved by FDA
- Pharmacology:** Fileability not yet determined. We requested segment 2 studies in rodents and non-rodents, however the non-rodent data has not been submitted. The reviewer will review previous communications between the Agency and the sponsor to determine if the non-rodent data was previously sent or not required.
- Statistics:** AF. The new statistician will review this application once the reviewer reports to the Division.
- Clinical Pharmacology and Biopharmaceutics:** AF. There are a number of deficiencies that need to be resolved in section 6 of the submission but the application is fileable.
- Microbiology:** AF. David Hussong is the assigned reviewer
- DSI:** The inspection request memo was sent on November 24, 1999, however Gus Turner requests that it be resent along with a copy of Vol. 1.1.

ODAC: This application will be discussed at the March 16-17, 2000 meeting.

Other: NDA status meetings are scheduled for January 27 and February 29, 2000. ODAC practices are scheduled for March 7 and 13, 2000. A labeling meeting is scheduled for April 13, 2000.

**Action Items:**

<b>Item:</b>	<b>Responsible Person:</b>	<b>Due Date:</b>
• review previous pharm/tox agreements to determine fileability	Sandip Roy	Complete
• check with Jackie Little/CBER to see if the contract labs used by have been inspected	Marjorie Shapiro	Complete
• check with EER inspectors to see when inspections are scheduled and include CBER product reviewer	Xiao Hong Chen	?
• review EA requirement	Xiao Hong Chen	Complete
• forward PK deficiencies to sponsor	Alvis Dunson	Complete
• resend DSI memo and Vol 1.1	Alvis Dunson	Complete
• schedule team meetings	Alvis Dunson	Complete
• request desk copy of Vols 1.10-1.12 and a copy of the NDA compact discs	Alvis Dunson	Complete

Alvis Dunson 12/17/99  
Project Manager  
Minutes preparer

Concurrence Chair: Peter Bross, M.D.  
Medical Officer

**Post Meeting Note:**

- The pharm/tox reviewer agrees the application is fileable because we agreed in an Agency fax dated July 10, 1998, that a rat only reproductive toxicology study will suffice in supporting an NDA.
- The sponsor plans to submit the safety update on or before January 29, 2000. Please refer to the sponsor submission dated August 30, 1999, serial 188.
- The sponsor submitted a request for categorical exclusion from the requirement of filing an Environmental Assessment.

cc:

NDA Arch: 21-174  
HFD-150/PBross  
/Adunson

cc Electronically only:

HFD-150/RPazdur  
/JBeitz  
/GChen  
/EDuffy  
/XChen  
/ARahman  
/LKieffer  
/PAndrews  
/SRoy  
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HFD-160/PCooney  
/DHussong

HFD-45/GTurner  
HFM-573/PKeeagan  
HFM-570/DMaybee  
HFM-561/MShapiro

drafted: ADunson/12.16.99

final: Adunson/12.17.99/mydocs/wyeth/21174/minutes/filing

MEETING MINUTES