

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**125326**

**OTHER REVIEW(S)**



Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research

Office of Biotechnology Products  
Federal Research Center  
Silver Spring, MD  
Tel. 301-796-4242

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## Memorandum

### PROJECT MANAGER'S REVIEW

**Application Number:** STN 125326/0  
**Name of Drug:** Arzerra™  
**Sponsor:** GlaxoSmithKline  
**Material Reviewed:** Arzerra™ (ofatumumab) Carton and Container Labels  
**OBP Receipt Date:** April 8, 2009  
**Amendment Reviewed:** September 23, 2009

#### Background:

STN 125326/0 for ofatumumab is an original Biologic License Application (BLA) indicated for the treatment of patients with chronic lymphocytic leukemia who have received prior therapy. The product is a sterile, colorless, preservative-free liquid concentrate for intravenous administration. The concentrate is supplied as 100 mg/5 mL in a single use vial.

#### Labels Reviewed:

Arzerra™ (ofatumumab) Container Label  
Vial label  
Arzerra™ (ofatumumab) Carton Label  
Three vial carton label  
Ten vial Carton label  
Arzerra™ Prescribing information

#### Review

The carton and container labels for Arzerra™ (ofatumumab) were reviewed and found to be acceptable under the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57 and 21

3 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

*Z Other Reviews*

b(4)

### **Conclusions**

- Please add the statement “No U.S. standard of potency” to the carton labels to comply with 21 CFR 610.61(r). Change made and acceptable.
- Please indicate how the label is affixed to the vial and where the visual area of inspection is located as per 21 CFR 610.60 (e). Please provide an explanation. Information provided and acceptable.
- Please revise the container label to display the manufacturer per 21 CFR 610.60(2).. Change made and acceptable.
- Please revise the manufacturer and distributor information using one of the qualified statements listed in 21 CFR 610.64 on the carton labeling. Change made and acceptable.
- Please revise the strength presentation of, “100 mg (20mg/mL)” to (“100 mg) followed by 20mg/mL in close proximity) to accurately describe the strength per total volume per the United States Pharmacopeia, 5/1/09-8/1/09, USP 32/NF27, General Chapter, Injection <1> and 21 CFR 201.51. Please refer to the DMEPA review for final presentation recommendation. Change made and acceptable.

- Please revise the inactive ingredients (buffering agents) to alphabetical order per the United States Pharmacopeia, 5/1/09-8/1/09, USP 32/NF27, General Chapter, Labeling of Inactive Ingredients <1091>. Acceptable.
- Please remove the statement,  $\emptyset$  from the carton labels per 21 CFR 201.10. Change made and acceptable. **b(4)**
- Please bold and capitalize the statement "Do Not Freeze" per 21 CFR 201.15 on all labeling. Comment not provided to applicant.
- Revise the presentation of the vial to comply with 21 CFR 201.51(d). Remove  
The resulting presentation should read "3 single use vials". Change made and acceptable. **b(4)**
- If a medication guide is required, please add the Statement "Dispense the enclosed Medication Guide to each patient." to comply with 21 CFR 208.24 and 21 CFR 610.60. A medication guide is not required.
- Please provide font size configurations for the proprietary and established name on carton and container labels for prominence determinations. Prominence revised with colors. Change made and acceptable.
- To comply with 21 CFR 201.57(a)(2) , please revise the Prescribing Information title line to following presentation:

Revised to: ARZERRA™ (ofatumumab)  
Injection, for Intravenous Infusion **b(4)**

Change is acceptable.

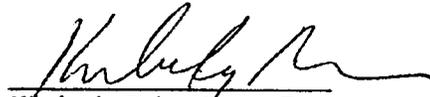
- Please consider revising the "HOW SUPPLIED/STORAGE AND HANDLING" in the prescribing information to a chart format for clarity.

| Vials per carton    | NDC              |
|---------------------|------------------|
| 3 single use vials  | NDC 0173-0808-02 |
| 10 single use vials | NDC 0173-0808-05 |

Revised and acceptable.

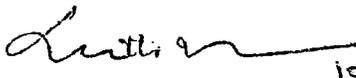
STN 125326/0 Amendment

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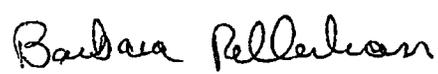
Kimberly Rains, Pharm.D  
Regulatory Project Manager  
CDER/OPS/OBP

Comment/Concurrence:

  
10/27/09

Subramanian Muthukkumar, Ph.D.  
Product Reviewer  
Division of Monoclonal Antibodies  
CDER/OPS/OBP

for

  
10/27/09

Patrick Swann, Ph.D.  
Deputy Director  
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Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research

Division of Biologic Oncology Products  
Tel. 301.796.2320

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## Memorandum

### PROJECT MANAGER'S REVIEW

**Application Number:** STN 125326/0

**Name of Drug:** Arzerra™

**Sponsor:** Glaxo Group Limited d/b/a GlaxoSmithKline

**Material Reviewed:** Arzerra™ (ofatumumab) Carton and Container Labels  
Arzerra™ (ofatumumab) package insert

**Submit Date:** January 30, 2009

**Receipt Date:** January 30, 2009

#### Background:

On January 30, 2009, Glaxo Group Limited d/b/a GlaxoSmithKline submitted an original Biologic License Application for ofatumumab (BL STN 125326/0) indicated for the treatment of patients with alemtuzumab and fludarabine refractory chronic lymphocytic leukemia. This submission contained carton and container labels and a package insert for Arzerra. The product is a sterile, colorless, preservative-free liquid concentrate for intravenous infusion. The concentrate is supplied as 100 mg/5mL (20 mg/mL) in a single use vial. Arzerra will be packaged as 3 single-use vials with 2 filters or as 10 single-use vials with 2 filters. The usual dosage for Arzerra is 2000mg. To achieve this dose, it will require the reconstitution of 20 vials for one dose.

#### Labels Reviewed:

Arzerra™ (ofatumumab) package insert  
Arzerra™ (ofatumumab) Container Label  
Vial label  
Arzerra™ (ofatumumab) Carton Label  
Three vial carton label

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

  X   § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

b(4)

### Review

The Division of Biologic Oncology Products (DBOP) consulted the Office of Biotechnology Products (OBP) and the Office of Surveillance and Epidemiology to obtain CMC and safety expertise on GSK's proposed Arzerra carton and container labels and package insert label submitted on January 30, 2009 with the original BLA submission. Copies of the consult reviews are part of the file.

The consult review from OBP for the Arzerra carton and container label and package insert was received by DBOP on June 19, 2009. The consult review from DMEPA for the Arzerra carton and container label was received by DBOP on July 31, 2009. The consult reviews contained recommendations for labeling revisions. DMEPA's review also noted a concern with the 20 vials/dose configuration that will be marketed for Arzerra prior to approval of the planned  $\frac{1}{2}$  mg single vial configuration which DMEPA had previously identified during the July 22, 2009 review team 'Wrap-Up' meeting. A teleconference was conducted with GSK on September 21, 2009. During this teleconference, GSK agreed to provide a protocol to address any concerns associated with the 20 vial configuration. GSK subsequently communicated by email (dated September 22, 2009) that in lieu of a formal protocol, a detailed survey for pharmacists to complete will be submitted. GSK emailed this survey on September 28, 2009. DBOP, with concurrence from DMEPA, concluded no further action from GSK was necessary because the 20 vial configuration was a dosing convenience issue, not a safety issue.

b(4)

DBOP, OBP and OSE met to discuss label review recommendations. The reviewers agreed on recommendations to be sent to GSK. FDA recommendations were sent to GSK on September 8, 2009.

**Comments communicated the Licensee on 9.08.09:**

*Comments concerning both the carton and container labels*

1. The total drug content is listed as 100 mg without the corresponding volume. Per USP recommendations (USP 32-NF 27), the strength per total volume should be the prominent and primary expression of strength on the principal display panel, followed in close proximity by strength per milliliter in parenthesis. Additionally, the statement of drug concentration appears adjacent to the statement of total drug content. Revise the strength statement in accordance with USP and position the expression of drug concentration directly below the statement of total drug content. For example:

**100mg/5mL**  
(20 mg/mL)

2. Please revise established name and proprietary name as per 21 CFR 201.10(g)(2). Please note that the established name should be printed at least half as large as letters comprising the proprietary name, and that the established name should have a prominence commensurate with the prominence of the proprietary name, e.g., established name and proprietary name presented with same font color.
3. To comply with 21 CFR 600.3, 21 CFR 610.62 and 21 CFR 201.57(a)(2), please revise the Prescribing Information title to following presentation.

Arzerra  
Ofatumumab  
Injection, for Intravenous Infusion

*Comments concerning container label*

4. Please remove the text below “100 mg (20 mg/mL)” to comply with 21 CFR 610.61 (c) and to provide space for revision requested in comment #.1.
5. Please revise the container label to display the manufacturer per 21 CFR 610.60(2). Please note: as per 21 CFR 600.3 (t), the “manufacturer is defined as any person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards, including all steps in the manufacture of the products under the license.
6. Please indicate how the label is affixed to the vial and where the visual area of inspection is located as per 21 CFR 610.60 (e). Please provide an explanation.
7. If space permits, include the following statements on the principal display panel.
  - ‘Single Use Vial, Discard Unused Portion’
  - ‘For Intravenous Infusion Only’

8. Please consider decreasing the space utilized for the bar code to provide space for requested revisions.

*Comments concerning carton labeling*

9. Please add the statement "No U.S. standard of potency" to comply with 21 CFR 610.61(r).

10. Please revise the inactive ingredients (buffering agents) to alphabetical order per the United States Pharmacopeia, 5/1/09-8/1/09, USP 32/NF27, General Chapter, Labeling of Inactive Ingredients <1091>.

11. Please remove the statement, ' / ' from the carton labels per 21 CFR 201.10. This statement is duplicative and the removal of this statement will provide room for other important information as noted above.

b(4)

12. Despite being presented in a yellow bar, the route of administration statement 'For Intravenous Infusion Only' is difficult to read due to the use of all capital letters. Consider presenting the route of administration in mixed case letter presentation to improve readability.

13. The current presentation of the statement / statement on the same line rather than as distinct pieces of information. Revise the presentation to include three separate statements as follows.

b(4)

- a. Per 21 CFR 201.51(d) revise the net quantity statement to read 'Contains XX vials' and 'Contains 2 filters.'
- b. Relocate the 'Single Use vial' statement directly below the net quantity statement and revise it to read as 'Single Use Vials-Discard Unused Portion'. For example:

Contains XX vials  
Contains 2 filters  
Single Use Vials- Discard Unused Portion

- c. Remove the phrase ' / ' from the statement as it is a duplicative of the drug concentration statement.

b(4)

*Comments concerning package insert label*

14. To comply with 21 CFR 600.3, and 21 CFR 201.57(a)(2), please revise the Prescribing Information title to following presentation. The agency is working to standardize the presentation of the Product title and prefers the following presentation:

Arzerra (ofatumumab)  
injection, for intravenous infusion

15. We request that you revise the “HOW SUPPLIED/STORAGE AND HANDLING” in the prescribing information to a chart format for clarity.

| Vials per carton                   | NDC              |
|------------------------------------|------------------|
| 3 single use vials with 2 filters  | NDC 0173-0808-02 |
| 10 single use vials with 2 filters | NDC 0173-0808-05 |

GSK emailed DBOP on September 9, 2009 with requests for clarification. DBOP, OBP, and OSE concurred on responses to GSK’s questions. FDA provided a response to GSK’s questions on September 11, 2009 (see attachment).

On September 15, 2009, GSK submitted revised carton and container labels. Upon review, the review team concluded that GSK satisfactorily addressed FDA’s requests. The container and carton labels are acceptable. Negotiations on content of the package insert label remain ongoing.

STN 125326/0

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RC 10/5/09

Raymond Chiang M.S.  
Regulatory Project Manager  
CDER/OODP/DBOP

Comment/Concurrence:

KJ 10/5/09  
Karen Jones  
CPMS  
CDER/OODP/DBOP

PK 10/5/09  
Patricia Keegan M.D.  
Division Director  
CDER/OODP/DBOP



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

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Memorandum

*Date:* August 25, 2009

*Subject:* Addendum to SEALD Labeling Review

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Addendum to SEALD Labeling Review: Tradenames in mixed case lettering in the package insert is CDER preference, not CDER policy.

**From:** Masucci, Iris  
**To:** Chiang, Raymond;  
**cc:** Gootenberg, Joseph; Lemery, Steven; Jones, Karen;  
**Subject:** RE: Re: Please make any necessary changes/  
comments to most current version of Arzerra label  
**Date:** Tuesday, August 25, 2009 1:13:32 PM  
**Attachments:** Iris 25AUG09 edits to 8 24 09 Arzerra label (JG SL and RC edits) -not clean.  
doc

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Ray et al. -

Attached is my mark-up of the 8/24 Arzerra label. It's looking great. But there were a few comments and questions, and some format changes.

Ray - I already fixed the cross-ref in the Highlights I&U section that you mentioned in your message.

Thanks,  
Iris

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**From:** Chiang, Raymond  
**Sent:** Monday, August 24, 2009 1:45 PM  
**To:** Masucci, Iris  
**Cc:** Gootenberg, Joseph; Lemery, Steven; Jones, Karen  
**Subject:** Re: Please make any necessary changes/comments to most current version of Arzerra label  
**Importance:** High

Iris,

We are going through negotiations with GSK concerning their Arzerra (ofatumumab) package insert label. Please review label and make any necessary changes/comments to the attached Arzerra (ofatumumab) package insert label. Also, please address specific comments addressed to you. This label will be sent to initiate the second round of negotiations. Hopefully, GSK will agree to most of our proposed changes.

thanks,  
ray

Raymond S. Chiang, M.S.  
Consumer Safety Officer/ Regulatory Project Manager  
Division of Biologic Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Email: [Raymond.Chiang@fda.hhs.gov](mailto:Raymond.Chiang@fda.hhs.gov)

phone: 301-796-1940

<< File: 8 24 09 Arzerra label (JG, SL and RC edits) -not clean.doc >>

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       § 552(b)(5) Deliberative Process

FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

## Memorandum

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### **\*\*Pre-Decisional Agency Information\*\***

**Date:** August 19, 2009

**To:** Raymond Chiang, Consumer Safety Officer  
Division of Biologic Oncology Products

**From:** Jeffrey Trunzo, RPh, MBA, Regulatory Review Officer  
Carole Broadnax, Pharm.D., Senior Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications

**Subject:** Arzerra (Ofatumumab)  
BLA: 125326

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DDMAC has reviewed the proposed package insert (PI) for Arzerra™ (ofatumumab), received by electronic mail from DBOP dated July 27, 2009, and offers the following comments. Please feel free to contact me at (301) 796-2029 with any questions or clarifications.

#### **HIGHLIGHTS OF PRESCRIBING INFORMATION**

- *"Injection for Intravenous Use"*

Should the dosage form and administration statement be revised to state, "Solution for Intravenous Injection" or "Solution for Intravenous Infusion"?

#### **INDICATIONS AND USAGE**

- *"The effectiveness of Arzerra is based on the demonstration of durable objective responses; no data demonstrate an improvement in disease-related symptoms or increased survival with Arzerra. (1) [Emphasis added.]*

DDMAC suggests revising this statement in the Highlights and the Full Prescribing Information to state, "No data available demonstrating improvement in disease-related symptoms or increased survival with Arzerra." Reference is made to similar wording in the Avastin PI Highlights-Indications and Usage section for the metastatic breast cancer and glioblastoma indications.

The word "durable" is promotional in tone and will be used promotionally. Is there substantial evidence to support the use of the word "durable" for this Accelerated Approval product? If not, DDMAC suggests deleting the word "durable." Also, reference is made to the use of the word "durable" in the Full Prescribing Information (INDICATIONS AND USAGE and CLINICAL STUDIES) sections.

## DOSAGE AND ADMINISTRATION

- *"Initial dose is 300 mg, followed 1 week later by ARZERRA 2,000 mg once weekly for 7 infusions, followed ~~4~~ weeks later by ARZERRA 2,000 mg once every 4 weeks for 4 infusions."* [Emphasis added.]

b(4)

DDMAC recommends adjusting the dosing schedule to correspond to Section 2.1 Recommended Dosage Regimen, in the Full Prescribing Information.

- *"Premedicate with an intravenous infusion of a corticosteroid (as appropriate), an oral analgesic, and an oral or intravenous antihistamine. (2.2)"* [Emphasis added.]

DDMAC suggests reordering the premedication list for consistency with Section 2.4 of the Full Prescribing Information (analgesic, antihistamine, corticosteroid).

DDMAC recommends deleting ~~the following~~ following corticosteroid, as this implies |

b(4)

DDMAC recommends revising the subsection reference for Premedication from 2.2 to 2.4 to correspond to the subsection in the Full Prescribing Information.

Should "analgesic" be specific for acetaminophen as stated in Section 5.1 (line 96)? The current wording implies that any analgesic may be used, not just acetaminophen. Reference is also made to the Highlights-Warnings and Precautions-Infusion Reactions section. However, Section 2.4 Premedication states, "Premedicate 30 minutes to 2 hours prior to each dose with oral acetaminophen 1,000 mg (or equivalent). . . ." DDMAC suggests that the references to premedication "analgesic" be consistent throughout the label (e.g., "acetaminophen" or "acetaminophen 1,000 mg (or equivalent)").

DDMAC suggests considering whether any additional information such as Dose Modifications for infusional toxicity should be included in this section.

## WARNINGS AND PRECAUTIONS

- Sponsors can use safety information directly from the HIGHLIGHTS OF PRESCRIBING INFORMATION to satisfy the fair balance of risk information for promotional materials.
- Warnings and Precautions should be listed in decreasing order of importance. Therefore, should Progressive Multifocal Leukoencephalopathy and Hepatitis B be listed prior to Infusion Reactions and Laboratory Monitoring because fatalities occurred with these adverse reactions? If so, DDMAC recommends revising the order of the events in the HIGHLIGHTS, FULL PRESCRIBING INFORMATION-WARNINGS AND PRECAUTIONS (Section 5), ADVERSE REACTIONS (Section 6), and PATIENT COUNSELING INFORMATION (Section 17).
- DDMAC recommends revising the subsection headings "Infusion Reactions" and "Progressive Multifocal Leukoencephalopathy," to correspond to the subsection headings in the Full Prescribing Information. [Emphasis added.]
- DDMAC recommends adding "PML" in parenthesis after Progressive Multifocal Leukoencephalopathy.
- DDMAC suggests adding "Intestinal Obstruction" to this section because it includes a measure to be taken to prevent or mitigate harm, "*Perform a diagnostic evaluation. . . .*"
- "*Infusion reactions: Premedicate with a corticosteroid (as appropriate), an analgesic, and an antihistamine. Monitor patients closely during infusions. Interrupt infusion and institute medical management if infusion reactions occur. (2.1, 5.1)*" [Emphasis added.]

DDMAC suggests reordering the premedication list for consistency with Section 2.4 of the Full Prescribing Information (analgesic, antihistamine, corticosteroid).

DDMAC recommends deleting ~~the following corticosteroid, as this implies~~ following corticosteroid, as this implies

DDMAC suggests adding "and institute medical management" (or similar language) to this statement as suggested above.

b(4)

## ADVERSE REACTIONS

- ***"To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888.825-5249 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)."***

Please move this statement from the "USE IN SPECIFIC POPULATIONS" section to the "ADVERSE REACTIONS" section.

## PATIENT COUNSELING INFORMATION

- Please revise the statement, "See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling" to state, "See 17 for PATIENT COUNSELING INFORMATION" if the product does not have FDA-approved patient labeling.

## FULL PRESCRIBING INFORMATION: CONTENTS

- DDMAC recommends revising the section and subsection headings for consistency with the Full Prescribing Information (Sections 2, 5, and 17). For example, subsection "2.2 Premedication" should be "2.2 Administration."
- DDMAC recommends deleting warnings and precautions which are not part of the Full Prescribing Information (e.g., b(4)
- DDMAC recommends deleting "15 REFERENCES" because this section is not part of the Full Prescribing Information.
- DDMAC recommends revising subsection \_\_\_\_\_ to state "5.6 Intestinal Obstruction" for consistency with the Full Prescribing Information. b(4)

## FULL PRESCRIBING INFORMATION

### 2. DOSAGE AND ADMINISTRATION

#### 2.3 Dose Modification

- DDMAC suggests adding a cross reference to the Infusion Reactions section [*See Warnings and Precautions (5.1).*]

5. WARNINGS AND PRECAUTIONS

- The Full Prescribing Information WARNINGS AND PRECAUTIONS should contain more detailed information than that of the summarized content of the Highlights WARNINGS AND PRECAUTIONS. Please refer to the additional comments for Sections 5.1, 5.3, and 5.4 which follow below and on page 6.
- DDMAC recommends including the incidence (%) of neutropenia, thrombocytopenia, PML, Hepatitis B, and Intestinal Obstruction.
- DDMAC recommends using either "corticosteroid" or "glucocorticoid" as appropriate throughout label for consistency when referring to premedication.

5.1 Infusion Reactions

- *"Premedicate with acetaminophen, an antihistamine, and a glucocorticoid [see Dosage and Administration (2.2, 2.4)]."*

DDMAC recommends adding the statement (or similar language), "Monitor patients closely during infusions" to be consistent with the summarized section of the Highlights section.

- *"Infusion reactions occur **more frequently** with the first two infusions."* [Emphasis added.]

The statement "more frequently" is vague and does not provide meaningful information about the frequency of occurrence of this adverse reaction. DDMAC recommends providing a specific frequency range (X% to X%) to provide more precise information about incidence.

- *"In a study of patients with moderate to severe chronic obstructive pulmonary disease, an indication for which Arzerra is not approved, two of five patients developed Grade 3 bronchospasm."*

If clinically significant adverse reactions appear linked primarily to an unapproved use of the drug, these adverse reactions should generally be described in the context of "other uses" without naming the specific off-label use. Is knowledge of the specific off-label use essential to provide the appropriate clinical context for the bronchospasm adverse event? If not essential, DDMAC recommends deleting this statement. The statement may be used to promote off-label use.

### 5.3 Progressive Multifocal Leukoencephalopathy

- **"Monitor neurologic function and discontinue Arzerra if PML is suspected."**

DDMAC recommends adding the statement (or similar language), "Monitor neurologic function" to be consistent with the summarized section of the Highlights section.

### 5.4 Hepatitis B

- ***"Hepatitis B reactivation including fulminant hepatitis and death occurs with other monoclonal antibodies directed against CD20."***

This statement minimizes the risk of Hepatitis B reactivation with Arzerra. The statement implies that this adverse reaction occurs with other monoclonal antibodies directed against CD20 but not with Arzerra. Is this true? Did this adverse reaction also occur with Arzerra? DDMAC recommends revising this statement so as not to minimize the risk of treatment with Arzerra.

- ***"Screen patients at high risk of HBV infection before initiation of Arzerra."***

DDMAC suggests using "HBV" in parenthesis following the first use of "Hepatitis B Virus."

DDMAC recommends revising this statement to include (or similar language), "Consider prophylactic antiviral therapy" to be consistent with the summarized content of the HIGHLIGHTS section.

## 6. ADVERSE REACTIONS

- DDMAC recommends listing the most common adverse reactions in order of decreasing frequency (e.g., pneumonia-23% before pyrexia-20%). Also, DDMAC recommends including the incidence of neutropenia in Table 3.
- DDMAC suggests listing all of the potentially fatal adverse reactions (e.g., Hepatitis B) described in the Warnings and Precautions Section 5 as a bullet point under "The following serious adverse reactions are discussed in greater detail in other section of the labeling:" and cross-reference to Section 5. Also, is Intestinal Obstruction a potentially fatal adverse reaction? If so, DDMAC recommends including it in this list.

## 6.1 Clinical Trials Experience

- In accordance with the January 2006 Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics — Content and Format, please include the following information to this section:
  - Identify adverse reactions, if any, that resulted in a significant rate of discontinuation or other clinical intervention (e.g., dosage adjustment, need for other therapy to treat an adverse reaction) in clinical trials.

## 6.2 Immunogenicity

- *“Serum samples from 154 patients with CLL treated with Arzerra were tested by ELISA assay for anti-ofatumumab antibodies during the 24-week treatment period.”*
- For consistency with other recent labels such as Avastin and Herceptin, DDMAC recommends spelling out the acronym ELISA at first use, (e.g., “Enzyme-linked immunosorbent assay (ELISA)”).

## 8. USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

- DDMAC recommends including a cross-reference to any other labeling section that contains pertinent information (e.g., [see Clinical Pharmacology (13.3)]).
- The first part of the statement, *“Ofatumumab does not bind normal human tissues other than B lymphocytes; it is not known if binding occurs to unique embryonic or fetal tissue targets.”* [Emphasis added.] is promotional in tone and misleading because the second part of the statement implies that there is a lack of information about binding locations for Ofatumumab. The statement implies that Ofatumumab will not have an adverse effect on normal healthy tissue other than B lymphocytes. DDMAC recommends deleting the misleading statement.

## 11. DESCRIPTION

- *“The antibody was generated via transgenic mouse and hybridoma technology and is produced in a recombinant murine cell line (NSO) using standard mammalian cell cultivation and purification technologies.”* [Emphasis added.]

Does the term "standard" add anything to the description? Could the term imply superiority of Arzerra versus other antibody generation methods (e.g., "gold standard" as a superior product)? If so, DDMAC suggests deleting this term.

- DDMAC recommends using the descriptor "Water for Injection, USP" when describing the solvent. [Emphasis added.]

## 12. CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

- *"Ofatumumab binds specifically to the small and large extracellular loops of the CD20 molecule."* [Emphasis added.]

DDMAC suggests deleting "specifically" from this statement. It can be used promotionally to claim an efficacy or safety benefit.

- *"The data suggest that possible mechanisms of cell lysis include complement-dependent cytotoxicity and antibody-dependent, cell-mediated cytotoxicity."*

DDMAC recommends not including theorized mechanisms of action. If the mechanism of action is not known, DDMAC recommends including a statement about the lack of information.

### 12.3 Pharmacokinetics

DDMAC suggests adding information regarding the time to reach steady state or the accumulation ratio, if it is clinically significant.

## 14. CLINICAL STUDIES

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b(4)

- *“There were no complete responses.”*

DDMAC recommends describing all components of response for the DR group (partial response in addition to complete response).

- *“Anti-tumor activity was also observed in the BFR group and in a multi-center, open-label, dose-escalation study, Study 2, conducted in patients with relapsed or refractory CLL.”*

The overall tone of this statement is promotional in nature. Please consider deleting this statement or including a statement that Ofatumumab is not approved for use in patients with BFR. Is Study 2 an adequate and well controlled study that provides supporting evidence of effectiveness? If not, DDMAC recommends deleting Study 2.

In accordance with the January 2006 Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format, Section B, Studies Not To Include in the Clinical Studies Section:

- The following are the types of studies that should usually not be included in the CLINICAL STUDIES section, unless they also meet one of the factors in II.A. If an exception is made, the limitations of the study and the reasons for inclusion should be stated.
  - Clinical studies with results that imply effectiveness for an unapproved indication, use, or dosing regimen.

17. PATIENT COUNSELING INFORMATION

- DDMAC recommends adding a statement about the potential risk to the fetus with Ofatumumab and the need for adequate contraception.
- DDMAC suggests adding a statement about the potential for serious adverse reaction in nursing infants from Ofatumumab, and the need to consider discontinue nursing or to discontinue the drug.



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

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Memorandum

**Date:** June 30, 2009 and July 1, 2009  
**From:** Raymond Chiang, DBOP/OODP/CDER  
**Subject:** Teleconference: STN BL 125326/0 ofatumumab- Information Request

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**FDA Participants:**

Raymond Chiang

**GSK:**

Philip Witman

FDA requested that GSK submit a revised Protocol OMB 110911 and Statistical Analysis Plan for this study be submitted by July 20, 2009.

GSK agreed to submit requested information.

Teleconference concluded.

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

**DATE:** July 1, 2009

**TO:** Raymond Chiang, Regulatory Project Manager  
Joseph Gootenberg, Team Leader  
Steven Lemery, Medical Officer  
Division of Oncology Drug Products

**FROM:** Sharon K. Gershon, Pharm.D.  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

**THROUGH:** Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections.

**BLA #:** 125326

**APPLICANT:** GlaxoSmithKline

**DRUG:** ARZERRA (ofatumumab)

**NME:** Yes

**THERAPEUTIC CLASSIFICATION:** Priority Review

**INDICATION:** treatment of patients with chronic lymphocytic leukemia who have received prior therapy

**CONSULTATION REQUEST DATE:** February 6, 2009

**DIVISION ACTION GOAL DATE:** August 1, 2009

**PDUFA DATE:** August 1, 2009

**I. BACKGROUND:** Data for this Application comes from one pivotal study, Hx-CD20-406: “A Single-Arm, International, Multi-Center Trial of HuMax-CD20, a Fully Human Monoclonal Anti-CD20 Antibody, in Patients With B-Cell Chronic Lymphocytic Leukemia Who Have Failed Fludarabine and Alemtuzumab” The sponsor (GlaxoSmithKline) identifies two populations to be enrolled and analyzed separately. The two refractory CLL populations are: 1) Double-refractory (DR): Subjects whose disease is refractory to both fludarabine and alemtuzumab and 2) Bulky Fludarabine-Refractory (BFR): Subjects whose disease is refractory to fludarabine and have lymphadenopathy > 5cm for whom GSK states alemtuzumab is inappropriate.

Subjects were treated with 8 weekly infusions, followed five weeks later with 1 infusion every 4 weeks for 4 doses. The first infusion was 300 mg. Each subsequent infusion was 2000 mg. At screening, different blood samples, a physical examination, CT scan and bone marrow exam were done, and the patient was evaluated for eligibility. Disease status was assessed every 4 weeks until Week 28, including physical examination, spleen and liver measurement and blood samples. Patients were followed for survival at 3-month intervals until Month 48.

The primary endpoint was overall response rate by week 24 for each population (DR and BFR). Secondary endpoints can be found in Protocol Section 10, and include things like duration of response, progression free survival, overall survival, reduction in tumor size, resolution of lymphadenopathy, and improvement in hemoglobin and ECOG performance status.

**Rationale for Site Selections:**

The foreign sites were selected for inspection because CZ02 (Mayer) had a high responder percentage, and Site CZ05 (Kozak) listed all patients as responders at this site. The rationale for the U.S. site selections is as follows: Site US02 (Kipps) was the highest enrolling site; Site US01 (Wierda) was the second highest enrolling site; Site US12 (Furman) was the US site with a large responder percentage.

**II. RESULTS (by Site):**

| <b>Name of CI or Sponsor<br/>Location</b>   | <b># of Subjects:</b>     | <b>Inspection<br/>Date</b>  | <b>Final Classification</b>    |
|---|---------------------------|-----------------------------|--------------------------------|
| <b>Jiri Mayer</b><br>Faculty Hospital Brno<br>Internal Hematooncology<br>clinic<br>Jihlavska 20 Brno  | Site #CZ02<br>9 subjects  | May 19 – May<br>22, 2009    | Preliminary NAI<br>Pending EIR |
| <b>Tomas Kozak</b><br>Faculty Hospital Kralovske<br>Vinohrady<br>Srobarova 50, Prague 10  | Site #CZ05<br>5 subjects  | May 24 – May<br>28, 2009    | Preliminary NAI<br>Pending EIR |
| <b>Thomas Kipps</b><br>UCSD Moores Cancer<br>Centre<br>3855 Health Sciences Drive<br>La Jolla, CA 92093-0960  | Site #US02<br>13 subjects | March 19 –<br>April 1, 2009 | VAI                            |
| <b>William Wierda</b><br>The University of Texas MD<br>Anderson Cancer Center<br>1515 Holcombe Blvd.,<br>Box 428<br>Houston, TX 77030-4009  | Site #US01<br>8 Subjects  | April 27-29,<br>2009        | NAI                            |
| <b>Richard Furman</b><br>Weill Medical College of<br>Cornell University Division<br>of Hematology/Oncology<br>520 East 70 <sup>th</sup> Street-Starr<br>Pavillion, Room 340<br>New York, NY 10021 | Site #US12<br>7 Subjects  | March 31 –<br>April 2, 2009 | NAI                            |

|  |         |                       |                                |
|--|---------|-----------------------|--------------------------------|
| <b>Genmab A/S</b><br>P.O. Box 9068<br>Bredgade 34<br>DK-1260 Copenhagen K<br>Denmark | Sponsor | June 23 – 28,<br>2009 | Preliminary NAI<br>Pending EIR |
|--|---------|-----------------------|--------------------------------|

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

**1. Jiri Mayer, Faculty Hospital Brno, Internal Hemato-Oncology clinic, Jihlavská 20 Brno**

**What was inspected:** The inspection reported that 14 subjects were screened, with 12 subjects enrolled, and 2 screen failures. The inspection performed a complete review of 7 of 9 subject's medical records, Case Report Forms, primary and secondary efficacy endpoints, inclusionary criteria, adverse event reporting, and concomitant medications. The inspection corroborated the data listings with the data in the subject medical records, and performed a 100% review of patient Informed Consent Documents (ICD), and confirmed that all subjects signed and dated the ICD prior to entering the study. The only limitation during the inspection was that medical records were translated by a certified translator.

**General Observations/Commentary:** The inspection reported that the records for these subjects were the most detailed patient records she'd ever observed, and that they contained clear and concise documentation of all study procedures. The inspection reported that she found no issues, whatsoever, and that no FDA-483 was issued at the conclusion of the inspection.

Medical Officer Steve Lemery made the following specific requests during the inspection:

- a) that **Patient 406118 be checked to see if this patient received any transfusions or growth factors during the study, as this patient had severe anemia that improved significantly at the next visit, and the reticulocyte count was such that it would be very unlikely that the anemia improved on its own.**

With respect to Patient 406118, the inspection discussed this concern with Dr Mayer and was assured that the patient's anemia did, in fact, improve with infusion of the study drug. The inspection collected all related medical records and insurance records to show the patient did not receive any transfusions or growth factors (G-CSF, GM-CSF, etc) during the study. Dr

Mayer's study investigators explained that transfusions and growth factors are extremely expensive in Brno, and must be tracked for payment by the insurance company. The medical records did not document that transfusions or growth factors were administered, and a review of insurance records confirmed that the administration of growth factors or transfusions did not occur. Although the EIR from the inspection at this site has not yet been received, the field auditor stated that she collected these various documents during the inspection and will provide them with the EIR. The inspection reported that the anemia in Patient 406118 did improve after study treatment, as was the case with other study patients; and that Dr. Mayer explained the biological plausibility for these phenomena, which sounded plausible to the investigator.

**b) that Patient 406154 be looked at closely, because at visits on 3/27/07, 4/24/07, 5/22/07, 6/19/07, and 7/17/07, the lymph node measurements were exactly the same during these visits (multiple nodes), and from looking at other patients, it would be unusual for patients with this number of nodes to be enlarged to not have any fluctuations in lymph node sizes.**

The inspection verified the information from each patient visit and noted lymph node size for each visit. The inspection confirmed that for Subject **406154** the source data was consistent with the sponsor's data listings. Visit 14 (June 19, 2007) was the last dose. On Visit 15 (July 17, 2007), the nodes were the same size as Visit 14, and the liver was not enlarged. At Visit 21 (September 11, 2007), the nodes in the neck were 10 mm x 4 mm, axillary were 3 mm x 5 mm, inguinal were 1 mm x 1 mm, submandibular were 3 mm x 2 mm and 1 mm x 1 mm. On December 12, 2007, the patient was entered into the extended follow-up, Study 416. As of May 19, 2009, the patient is still alive.

There were 8 adverse events and 1 SAE documented in medical charts, which was consistent with the sponsor's provided data listings.

**Assessment of Data Integrity:** To summarize, the study appears to have been conducted well, and staff followed the protocol requirements without any type of significant problems. With respect to the 2 issues noted by Dr. Lemery, the inspection verified the integrity of the data by reviewing the medical records for Subject **406118**, and confirming that this subject did not receive transfusions or growth factors in support of the subject's anemia. The inspection also confirmed that for Subject **406154**, the lymph node measurements were accurately reported in that source data corroborated with the sponsor's data. The inspection reported that the patient records were some of the best ever seen, in terms of data points corroborating with the sponsor's data listings. The inspection reported that it appears that this Clinical Investigator (Mayer) and his staff are committed to protocol adherence, despite the amount of time and energy it required to obtain such good documentation, and that other clinical investigators should take some lessons. DSI considers the data acceptable in support of the NDA at this site.

**Observations noted for the Mayer (Site CZ02) inspection are based on e-mails and communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

**2. Tomas Kozak, Faculty Hospital Kralovske, Vinohrady, Srobarova 50, Prague 10**

**What was inspected:** At this site, 5 subjects were screened, and 5 subjects were enrolled. At the time of the inspection 2 subjects had died, and 3 subjects had survived. A complete review of the patient medical records, Case Report Forms, primary efficacy endpoints and secondary endpoints was completed for all 5 of the enrolled study participants. The inspection reviewed all medical records to ensure inclusion criteria were met. The records were translated to include the patient's medical history prior to inclusion in the study, documenting exposure to the required drug treatments as part of the inclusion criteria. Dr. Kozak made mandatory that all patients be hospitalized the day before, and the day after treatment. The inspection reviewed concomitant medications, and verified the adverse events (and SAEs) against the data listings provided from the sponsor.

**General Observations/Commentary:** The inspection reported that all patient records were written with great detail, and provided clear documentation regarding the patients' progression of disease, visitation detail (BP, pulse, temperature, sweating, size of palpable nodes, lab test results, con meds, general patient well being), and use of concomitant medications. Records were all handwritten (compared to type-written at the Mayer CZ02 site), and there were no problems with consistent entries between the data listings and subject's medical records for adverse events, and primary and secondary efficacy endpoints. The inspection performed a thorough review of informed consent documents, and found that all subjects were consented adequately before treatment.

**c. Assessment of data integrity:** No deficiencies were found during this inspection, and DSI recommends the data as acceptable in support of this NDA.

**Observations noted for the Kozak (Site CZ06) inspection are based on e-mail communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

**3. William Wierda, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Box 428, Houston, TX 77030-4009.**

**What was inspected:** A total of 15 subjects were screened, and 13 subjects enrolled at this site. The inspection reviewed data from all 13 study subjects records, including eligibility criteria, adverse events, AE reporting timeframes, monitoring activities, efficacy endpoints, and test article records. The inspection corroborated the subject's electronic source documents to the CRFs and data listings provided from the sponsor.

**General Observations/Commentary:** The inspection found that for 3 subjects (of 13), several vital statistics (blood pressure, heart rate, body temperature) were handwritten in nurse's notes, but not transcribed to the CRF, so that this information was marked as Not Done (ND) on the CRF. However, the inspection verified that vital statistics were done for all subjects during all infusions, as per protocol. The results were not always captured in the source documents. This observation was discussed with Dr. Wierda during the inspection, but not included as an observational item in a FDA-483. Dr. Wierda promised corrective action in the form of staff educations.

**Assessment of Data Integrity:** There were no major issues or deficiencies noted during the inspection of Dr. Wierda. The sponsor's data listings corroborated with the subject's source records. In general, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

**4. Richard Furman, Weill Medical College of Cornell University Division of Hematology/Oncology, 520 East 70<sup>th</sup> Street-Starr Pavillion, Room 340, New York, NY 10021**

**What Was Inspected?** The inspection reviewed records for all 10 subjects. However, only the data for the 7 subjects submitted as part of the application could be compared to the line data provided from GSK. The inspection focus was on inclusion criteria, adverse events; comparison of source records with case report forms and data listings; concomitant medications; ECGs and CT scans; monitoring; and laboratory records.

**General Observations:** Record review found that all subjects met inclusionary criteria and were followed throughout their study involvement. Adverse events (with the exception of 2) were reported on time. A review of source data and case report forms for all 10 subjects found that concomitant therapy and intercurrent illnesses were reported accurately. The 7 subjects reported as part of the IND were compared against their CRFs, source data and line data supplied by the sponsor. The inspection found consistency between CRFs and source data with respect to ECGs, bone marrow testing, CT scans, concomitant therapy, intercurrent illnesses, and adverse events. The inspection found that the source documents were organized, complete, legible and in good condition. The inspection noted that monitoring was performed throughout the study. The inspection noted the following:

- Discrepancies in hemoglobin values between source data, case report forms, and data listings: The review found that line data values were low. Dr. Furman contacted GSK who in turn contacted Genmab (located in Copenhagen). It was found there was a factor of 1.61 to 1.0, in that Genmab was expressing the hemoglobin in millimoles per liter (lower value in the line listings) whereas

- GSK listed the values as grams per deciliter (g/dL). Upon recalculation by Genmab, and resubmitted to Dr. Furman, all values were found to be accurate.
- Discrepancies in lymphocyte count between source data, CRFs and data listings. The laboratory [redacted] resubmitted the recalculated values, and the inspection found the values consistent between case report forms, source data and line data submitted by the sponsor. A Note to File was subsequently written by [redacted] explaining the discrepancy as a difference in calculation between the manual and automated differential counts. b(4)
  - The inspection found several adverse events for Subject 406256 which did not appear in the sponsor's data listings. These included 2 cases of abdominal pain with onset dates of 3/25/2008 and 4/22/2008; and 2 cases of upper respiratory infection with onset dates of 1/2/2008 and 1/31/2008. According to the CRFs, the abdominal events resolved on 4/1/2007 and 4/29/2008, respectively; the upper respiratory infections resolved on 1/8/2008 and 3/4/2008, respectively. It was noted that these adverse events were documented as Grade 1 and not considered serious.

**Data Assessment:** The issue concerning discrepancies in hemoglobin values and lymphocyte counts was not a GCP violation; and after these values were recalculated by using consistent units, no discrepancies were found. With respect to the adverse events for Subject 406256, the inspection found that the events were reported on a Case Report Form at the site, but did not appear in the sponsor's data listings. Therefore, it appears that this was not a site issue, and thus, this finding was not included as a FDA-483 observational item. In general, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

**5. Thomas Kipps, UCSD Moores Cancer Centre, 3855 Health Sciences Drive, La Jolla, CA 92093-0960**

**What was Inspected?** At the site, 18 subjects were screened, 14 subjects were randomized, and 8 subjects completed the study. A total of 8 subject records were reviewed in detail. Random checking of source data with data reported to the Case Report Form and data submitted in the data listings was done, including survival efficacy endpoints, physical examinations, lymph node measurements, clinical laboratory results, concomitant medications, and reporting of adverse events.

**General Observations:** The inspection found that all adverse events were accurately reported to the CRFs, and were reported in a timely manner to the sponsor and IRB. All subjects were found to meet the protocol's inclusion criteria. Dropouts were properly documented and reported to the sponsor. With respect to drug accountability, for the 8 subject records reviewed, the inspection found a consistent pattern of failing to

following the protocol's precise regimen with respect to infusion rates, and length of infusions.

i) The protocol specified: **for the first two infusion visits (Visit 2 and Visit 3), subjects were to receive the drug treatment at the rate of 12 ml/hr for the first 30 minutes, 25 ml/hr for the next 30 minutes, 50 ml/hr for the next 30 minutes, 100 ml/hr for the next 30 minutes, and 200 ml/hr for the remainder of the time needed to infuse the full 1000 ml.** For example,

a) At Visit 2 on December 13, 2006, Subject 406152 received a rate of infusion of 25 ml/hr for the first 30 minutes and an infusion rate of 100 ml/hr from 1105 – 1145 (40 minutes);

b) At Visit 3 on May 29, 2007, Subject 406202 received an infusion rate of 12 ml/hr between 1050 and 1105 (15 minutes), and a rate of 50 ml/hr between 1135 and 1220 (45 minutes).

ii) The protocol specified **that for infusions 3 through 12 (Visits 4 through 14 with no infusion at Visit 10), subjects were to receive the drug treatment at the rate of 25 ml/hr for the first 30 minutes, 50 ml/hr for the next 30 minutes, 100 ml/hr for the next 30 minutes, 200 ml/hr for the next 30 minutes and 400 ml/hr for the remainder of the time needed to infuse the full 1000 ml.** For example:

a) At Visit 5 on January 4, 2007, Subject 406152 received the initial rate of infusion at 50 ml/hr and a rate of 300 ml/hr between 1100 – 1130. The 300 ml/hr is not a rate that is prescribed by the protocol;

b) At Visit 11 on March 8, 2007, Subject 406152 received the infusion rate of 100 ml/hr from 1110 to 1210 (60 minutes), and a rate of 50 ml/hr for the first 30 minutes;

c) At Visit 4 on May 29, 2007, Subject 406200 received an initial rate of 50 ml for the first 30 minutes, and at Visit 3 on May 29, 2007, Subject 406202 received the infusion rate of 50 ml/hr from 1135-1220 (45 minutes).

The protocol specified that at a 'minimum', vital signs must be performed every 30 minutes during an infusion. The inspection found that vital signs were not always done every 30 minutes. For example, for Subject 406214, the infusion notes for Visit 9 (August 1, 2007) report that vital signs were taken at 1210, and the next vital signs were taken at 1310, one hour later. For Subject 406152, the infusion notes for Visit 11 (March 8, 2007) indicate that vital signs were taken at 1240 whereas the next time vital signs were taken at 1330, 50 minutes later.

The inspection also observed examples of cross-overs and deletions, with no dates or identifying initials; missing signatures to identify the person who administered the infusion; inconsistencies between infusion notes and the CRF. And a study subject (406104) who was erroneously identified as 406108 and 406114 in several source documents.

Dr. Kipps responded by letter dated April 14, 2009, and provided corrective actions to each of the FDA-483 observations, which appear adequate.

**Data Assessment:** The field classified this inspection as OAI, because of the repeated pattern of documentation errors, and failure to follow the protocol with respect to infusion rates and times. DSI Reviewer Sharon Gershon discussed the many issues with the Medical Officer Steven Lemery, to determine their overall significance with respect to data integrity. Dr. Lemery wrote in an email dated April 3, 2009, that he believes the deficiencies may be significant and that the investigator needs to correct deficiencies at his site, his opinion was that they would not invalidate efficacy or safety data from the site. DSI has reclassified this inspection as VAI, and believes the data from this site is reliable in support of the BLA.

#### **6. Genmab A/S, P.O. Box 9068, Bredgade 34, DK-1260 Copenhagen K Denmark**

**What was Inspected?** The inspection reviewed monitoring reports and adequacy of monitoring for 4 sites – Tom Kipps (US02), Jiri Mayer (CZ02), Tomas Kozak (CZ05) and Martin Dyer (UK06). In addition, the inspection reviewed all IRB correspondences and approvals; correspondences between the monitor and sponsor; drug accountability for 3 sites (not Dyer site– UK06). In addition, the inspection reviewed corrective actions and communications from the sponsor to the monitor and the Clinical Investigator for US02 (Tom Kipps) and UK06 (Dyer) sites.

**General Observations/Commentary:** The inspection reported that no sites were terminated for GCP noncompliance. The inspection reported that a few sites were discontinued for lack of enrollment. The inspection reported that there was active communication between Genmab, the CRA monitor and clinical sites, specifically in efforts to bring sites into compliance (i.e., US02 site (Kipps) and UK06 site (Dyer)). The inspection was classified as NAI.

**Assessment of Data Integrity:** The inspection revealed no major deficiencies. DSI considers the data as acceptable in support of this BLA.

**Observations noted for the Genmab inspection are based on email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

#### **IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

Five clinical sites and the sponsor were audited in support of this application. Based upon EIRs and/or preliminary communication with the field investigator, the data are considered reliable in support of the specific indication.

**Note: Inspection results from Mayer, Kozak and Genmab are based on preliminary communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt of the EIR.**

---

Sharon K. Gershon, Pharm.D.  
Good Clinical Practice Branch *III*  
Division of Scientific Investigations

CONCURRENCE:

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Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

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Sharon K. Gershon, Pharm.D.  
Good Clinical Practice Branch I (U)  
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Division of Scientific Investigations



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: July 31, 2009

To: Patricia Keegan, Director  
Division of Biologic Oncology Products

Through: Kristina Arnwine, Pharm.D., Team Leader *K.Arnwine* 7/31/09  
Denise Toyer, Pharm.D., Deputy Director *D.Toyer*  
Carol Holquist, RPh, Director *K. Holquist acting for C. Holquist* 7/31/09  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Tselaine Jones Smith, Pharm.D., Safety Evaluator *T.Jones* 7/31/09  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Arzerra (Ofatumumab) Injection 100 mg per 5 mL

Application Type/Number: BLA # 125326

Applicant/Applicant: GlaxoSmithKline

OSE RCM #: 2009-244

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with external pharmacist'. The logistics, results and conclusions of the risk assessment were not included as part of the submission.

On July 14, 2009, DMEPA requested a copy of the risk assessment and its findings for our review. On July 20, 2009, the Licensee submitted one step of the risk assessment, 'infuse product into bag', along with mitigations that were established to minimize risk at this step. We note that the risk assessment is incomplete and that the Licensee does not include appropriate participants such as oncology pharmacists and pharmacy technicians that are experienced in preparing chemotherapeutic agents as part of their risk assessment panel.

The Division of Medication Error Prevention and Analysis continues to have safety concerns with the use of 20 vials for one dose. We want to minimize confusion with the 20 vials per dose configuration that will / / Although, we do not believe this is an approvability issue, we would like to meet with the Licensee to discuss their risk assessment and to provide additional guidance on how they can identify and mitigate critical failures with the 20 vials per dose configuration. These concerns were conveyed to the Division in the July 22, 2009 'Wrap-Up' meeting. The Division has agreed to arrange a telephone conference between DMEPA and the Licensee.

b(4)

### C. Presentation of Dosage Form on Labels and Labeling

We note the inconsistent presentation of the dosage form on the labels and labeling. Specifically, the container label and carton labeling present the dosage form as 'injection' while the insert labeling presents it as 'injection for intravenous use'. According to USP General Chapter <1> Injections, 'Injection' is the appropriate nomenclature for representation of the dosage form. The labels and labeling should be consistent. We refer you to ONDQA for further guidance on this issue.

### D. Insert Labeling

1. Remove the abbreviation

2. The dosage form, 'injection', is not included in the 'Dosage Forms and Strengths' section of the *Highlights of Prescribing Information and the Full Prescribing Information*. Revise these sections to include the dosage form 'injection'.

b(4)

## 3.2 COMMENTS TO THE LICENSEE

### A. Container Labels

1. The total drug content is listed as 100 mg without the corresponding volume. Per USP recommendations (USP 32-NF 27), the strength per total volume should be the prominent and primary expression of strength on the principal display panel, followed in close proximity by strength per milliliter in parentheses. Additionally, the statement of drug concentration appears adjacent to the statement of total drug content. Revise the strength statement in accordance with USP and position the expression of drug concentration directly below the statement of total drug content. For example:

100 mg/5 mL  
(20 mg/mL)

2. Relocate the total drug content and the drug concentration statements to immediately follow the established name. The usual presentation of information on labels and labeling is: proprietary name, followed immediately by the established name which includes the dosage form and strength.

Arzerra  
(ofatumumab) injection  
100 mg/5 mL  
(20 mg/mL)

3. If space permits, include the following statements on the principal display panel.

- 'Single Use Vial, Discard Unused Portion'
- 'For Intravenous Infusion Only'

**B. Carton Labeling**

1. See container label comments A1 and A2 above. Revise the carton labeling accordingly.
2. Despite being presented in a yellow bar, the route of administration statement 'For Intravenous Infusion Only' is difficult to read due to the use of all capital letters. Consider presenting the route of administration in mixed case letter presentation to improve readability.
3. The current presentation of the statement, 'Contains XX single use vials of Ofatumumab concentrate (20 mg/mL) for dilution and 2 filters' presents the net quantity, the expression of drug concentration and the 'single use vials' statement on the same line rather than as distinct pieces of information. Revise the presentation to include three separate statements as follows.
  - a. Per 21 CFR 201.51(d) revise the net quantity statement to read 'Contains XX vials' and 'Contains 2 filters.'
  - b. Relocate the 'Single Use vial' statement to directly below the net quantity statement and revise it to read as 'Single Use Vials-Discard Unused Portion'. For example:

Contains XX vials  
Contains 2 filters  
Single Use Vials-Discard Unused Portion
  - c. Remove the phrase ~~from the~~ statement as it is a duplicative of the drug concentration statement.
5. Remove the statement ~~as it is duplicative and the removal of~~ this statement will provide room for other important information as noted above.

b(4)

1   Page(s) Withheld

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

  X   § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

## 1 INTRODUCTION

This review was written in response to a request from the Division of Biologic Oncology Products to evaluate the container labels, carton and package insert labeling for the Arzerra (Ofatumumab) Injection (BLA# 125326), for areas that could lead to medication errors.

## 2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used principles of Human Factors and Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels, carton and insert labeling. We evaluated the Licensee's proposed labels and labeling submitted as part of the February 18, 2009 submission (see Appendices A and B).

## 3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels, carton and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations on the packaging of Arzerra and the insert labeling in Section 2.1 *Comments to the Division* for discussion during the review team's label and labeling meetings. Section 2.2 *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 2.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Licensee with regard to this review. If you have further questions or need clarifications, please contact Sandra Griffith, project manager, at 301-796-2445.

### 3.1 COMMENTS TO THE DIVISION

#### A. Packaging of Arzerra

The usual dosage of this product is 2000 mg. To achieve this dose, it will require the reconstitution of 20 vials for one dose. Requiring health care practitioners to reconstitute 20 vials introduces vulnerability for reconstitution and dosing errors. We foresee errors resulting in under/over dosage because people will lose track of how many vials they have added to the bag. We discussed this concern with the Division and they concur with our assessment.

These concerns were communicated to the Licensee during the February 20, 2009 technical walk-through meeting and in the April 14, 2009, 74-day letter. The 74-day letter requested the Licensee provide the Agency with a written commitment (including timelines) for submission of a Prior Approval Supplement to support the introduction of a new strength or vial size that would better support the usual dosage of this product.

In their May 14, 2009 response to the 74-day letter, the Licensee stated that they will wait until approval of the BLA to request a meeting with the Division to discuss detailed. In addition, the Licensee intends to submit a Prior Approval Supplement in the first quarter of 2010. The supplement will provide for the introduction of 100 mg vials of Ofatumumab Injection, 20 mg/mL, which would help to mitigate medication errors by reducing the number of vials needed for one 2000 mg dose. b(4)

Thus, DMEPA concurs with the Division's request for a Phase 4 Commitment from the Licensee and with the Licensee's proposal to submit a prior approval supplement that introduces 100 mg vials of Ofatumumab Injection, 20 mg/mL.

#### B. Risk Assessment of the Use of 20 vials of Arzerra

Although the Licensee intends to introduce 100 mg vials, they believe the 100 mg vials can be safely used by healthcare practitioners, despite the need for 20 vials per dose. b(4)

In the April 2009 response to the '74-Day-Letter', the Licensee notes that in November 2008, a risk assessment was conducted to identify potential failure modes associated with the use of 20 vials from the receipt of the product at the clinic to the dosing of patients. The Licensee's participants included pharmacists, chemistry, manufacturing and control (CMC) and logistics representatives and commercial representatives responsible for the training and education of clinicians. The Licensee is currently verifying the risk assessment relating to dosing with 20 vials.

# MEMORANDUM

**To:** Raymond Chiang, MS  
Division of Biologic Oncology Products

**From:** Iris Masucci, PharmD, BCPS *Im*  
Division of Drug Marketing, Advertising, and Communications  
for the Study Endpoints and Label Development (SEALD) Team, OND

**Date:** July 14, 2009

**Re:** Comments on draft labeling for Arzerra (ofatumumab) injection  
BLA 125326

---

We have reviewed the proposed label for Arzerra (FDA version dated 7/10/09 and received by SEALD 7/13/09) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the Division after a full review of the submitted data.

Please see attached label for recommended changes.

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  X   § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

  7   Other Reviews



Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research

Office of Biotechnology Products  
Federal Research Center  
Silver Spring, MD  
Tel. 301-796-4242

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## Memorandum

### PROJECT MANAGER'S REVIEW

**Application Number:** STN 125326/0

**Name of Drug:** Arzerra™

**Sponsor:** GlaxoSmithKline

**Material Reviewed:** Arzerra™ (ofatumumab) Carton and Container Labels

**OBP Receipt Date:** April 8, 2009

**Amendment Reviewed:**

#### **Background:**

STN 125326/0 for ofatumumab is an original Biologic License Application (BLA) indicated for the treatment of patients with chronic lymphocytic leukemia who have received prior therapy. The product is a sterile, colorless, preservative-free liquid concentrate for intravenous administration. The concentrate is supplied as 100mg/5 mL in a single use vial.

#### **Labels Reviewed:**

Arzerra™ (ofatumumab) Container Label

Vial label

Arzerra™ (ofatumumab) Carton Label

Three vial carton label

Ten vial Carton label

Arzerra™ Prescribing information

#### **Review**

The carton and container labels for Arzerra™ (ofatumumab) were reviewed and found to be adequate under most of the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57

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       § 552(b)(5) Deliberative Process

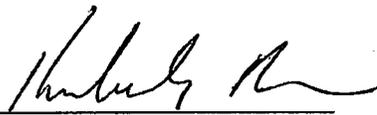
## Conclusions

The following deficiencies were noted in the initial review of the ofatumumab container and carton labels:

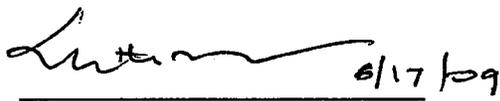
- Please add the statement “No U.S. standard of potency” to the carton labels to comply with 21 CFR 610.61(r).
- Please indicate how the label is affixed to the vial and where the visual area of inspection is located as per 21 CFR 610.60 (e). Please provide an explanation.
- Please revise the container label to display the manufacturer per 21 CFR 610.60(2).
- Please revise the manufacturer and distributor information using one of the qualified statements listed in 21 CFR 610.64 on the carton labeling.
- Please revise the strength presentation of, “100 mg (20mg/mL)” to (“100 mg) followed by 20mg/mL in close proximity) to accurately describe the strength per total volume per the United States Pharmacopeia, 5/1/09-8/1/09, USP 32/NF27, General Chapter, Injection <1> and 21 CFR 201.51. Please refer to the DMEPA review for final presentation recommendation.
- Please revise the inactive ingredients (buffering agents) to alphabetical order per the United States Pharmacopeia, 5/1/09-8/1/09, USP 32/NF27, General Chapter, Labeling of Inactive Ingredients <1091>.
- Please remove the statement, / from the carton labels per 21 CFR 201.10. b(4)
- Please consider revising the route of administration presentation to “For Intravenous Infusion” on the carton label.
- Please bold and capitalize the statement “Do Not Freeze” per 21 CFR 201.15 on all labeling.
- Revise the presentation of the vial to comply with 21 CFR 201.51(d). Remove “Contains” and “of ofatumumab concentrate (20mg/mL) for dilution and 2 filters”. The resulting presentation should read “3 single use vials”.
- If a medication guide is required, please add the Statement “Dispense the enclosed Medication Guide to each patient.” to comply with 21 CFR 208.24 and 21 CFR 610.60.

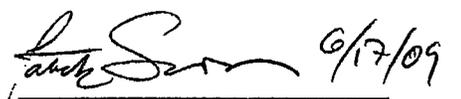
- To comply with 21 CFR 201.57(a)(2) , please revise the Prescribing Information title line to following presentation:  
Azerra™ (ofatumaumab)  
injection, for intravenous use
- Please consider revising the “HOW SUPPLIED/STORAGE AND HANDLING” in the prescribing information to a chart format for clarity.

| Viials per carton   | NDC              |
|---------------------|------------------|
| 3 single use vials  | NDC 0173-0808-02 |
| 10 single use vials | NDC 0173-0808-05 |

  
Kimberly Rains, Pharm.D  
Regulatory Project Manager  
CDER/OPS/OBS

Comment/Concurrence:

  
Subramanian Muthukkumar, Ph.D.  
Product Reviewer  
Division of Monoclonal Antibodies  
CDER/OPS/OBP

  
Patrick Swann, Ph.D.  
Deputy Director  
Division of Monoclonal Antibodies  
CDER/OPS/OBP



## **INTRODUCTION**

GlaxoSmithKline (GSK) submitted an original BLA (125326) on January 30, 2009, for Arzerra™ (ofatumumab) Injection for Intravenous Use, for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received prior therapy. The indication is being negotiated under the provisions of accelerated approval based on studies that have investigated response rate, a surrogate endpoint for clinical benefit. CLL is a cancer of the blood and bone marrow (primarily affecting older adults; rare prior to age 40) in which B-cell lymphocyte proliferation occurs ultimately leading to bone marrow failure and immune system weakening. There are approximately 15,000 cases of CLL diagnosed yearly in the U.S.<sup>1</sup> FDA has granted a priority review status and orphan designation for ofatumumab for the treatment of CLL.

Ofatumumab is a human monoclonal antibody (IgG1κ) that binds specifically to epitopes that encompass the amino acid residues 163 and 166 in the second extracellular loop of the CD20 molecule of B-cell lymphocytes, thereby causing B-cell depletion. Ofatumumab crosses the placenta in cynomolgus monkeys and resulted in B-cell depletion and decreased spleen and placental weights in exposed offspring. No Segment III preclinical developmental toxicity studies have been performed with ofatumumab; therefore, there is no information on perinatal and postnatal effects of B-cell depletion in exposed offspring, nor is there any information on B-cell recovery in exposed offspring.

MHT has been consulted to review the pregnancy and Nursing Mothers section of Arzerra™ labeling.

## **BACKGROUND**

### **Pregnancy and Nursing Mothers Labeling**

The Maternal Health Team has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review provides MHT’s suggested revisions to the sponsors proposed (with DBOP edits dated April 24, 2009) Pregnancy and Nursing Mothers subsections of Arzerra™ (ofatumumab) Injection for Intravenous Use labeling.

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<sup>1</sup> [www.nlm.nih.gov](http://www.nlm.nih.gov)

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*MHT Comments:*

1.



b(4)



2. *MHT recommends that the sponsor conduct clinical lactation studies in lactating women receiving ofatumumab to better inform labeling to allow clinicians and nursing women to make informed decisions regarding breastfeeding during ofatumumab therapy. Preclinical studies in monkeys receiving drug only during lactation would provide information about B-cell depletion effects in nursing infants exposed only through breast milk.*

**MHT SUMMARY**

It is critical that clinicians have adequate and optimal information available to guide them with therapeutic decision making and counseling with regard to drug use in pregnant and nursing women. Adequate preclinical testing should be available before females of childbearing potential are exposed to drug products. We cannot use the lack of preclinical Segment III studies to justify a contraception requirement in females of childbearing potential, as the Segment II studies did not demonstrate teratogenicity or pregnancy loss. Arzerra™ (ofatumumab) Injection for Intravenous Use is likely to be used off-label by females of childbearing potential once approved and pregnancies are likely to occur. Information is needed on the timing of maternal drug exposure and occurrence of offspring B-cell depletion; the recovery (or lack of recovery) of B-cells in exposed offspring born with B-cell depletion; and immunization recommendations for ofatumumab-exposed B-cell depleted neonates and infants. A contraceptive requirement should not be required unless there is documentation of persistent post-natal B-cell depletion in offspring following in-utero exposure.

**Appendix A - MHT Tracked-Changes Labeling Revisions**

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\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

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\_\_\_\_\_ § 552(b)(5) Deliberative Process

# REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

## Division of Biologic Oncology Products

Application Number: BL STN 125326/0

Name of Drug: Arzerra (ofatumumab)

Applicant: Glaxo Limited Group d/b/a GlaxoSmithKline

### Material Reviewed:

Submission Date(s): January 30, 2009

Receipt Date(s): January 30, 2009

Submission Date of Structure Product Labeling (SPL): January 30, 2009

Type of Labeling Reviewed: WORD/SPL

### Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

### Review

The following issues/deficiencies have been identified in your proposed labeling.

1. General Comments:
  - a. Recommend ARZERRA not be in all caps throughout the label.
  - b. Changed  to "intravenous infusion" throughout the label. **b(4)**
  - c. Relocate the horizontal line located between the Table of Contents and FPI to page 1.
  - d. Use command language throughout the label.

2. Highlights Section:

- a. Do not use “TM” after the drug names in Highlights section. Use “TM” only once in the content of the labeling full prescribing information (FPI).
- b. For biologic products, the dosage form and route of administration must be on the next line or underneath the proper name of the drug since the proper name does not include the drug’s dosage form or route of administration (see 21CFR 600.3(k) and Section 351 of PHS Act)
- c. Delete the white space between major headings and the text underneath.
- d. BOXED WARNINGS:
- e. RECENT MAJOR CHANGES:
- f. INDICATIONS AND USAGE:
  - If approved under accelerated approval, add in required statement:  
“Arzerra has been given accelerated approval for the treatment of chronic lymphocytic leukemia (CLL) based on studies that have shown response rate, a surrogate endpoint for clinical benefit. Studies to determine whether Arzerra confers clinical benefit are ongoing.”
- g. DOSAGE AND ADMINISTRATION:
- h. WARNINGS AND PRECAUTIONS:
  - Use bold font to identify each Warnings and Precaution subsection.
- i. ADVERSE REACTIONS:
- j. USE IN SPECIFIC POPULATIONS:

3. Full Prescribing Information: Contents:

4. Full Prescribing Information (FPI):

- a. INDICATIONS AND USAGE:
  - If approved under accelerated approval, add in required statement:  
“Arzerra has been given accelerated approval for the treatment of chronic lymphocytic leukemia (CLL) based on studies that have shown response

rate, a surrogate endpoint for clinical benefit. Studies to determine whether Arzerra confers clinical benefit are ongoing.”

b. WARNINGS AND PRECAUTIONS:

- List the warnings and precautions in decreasing order of importance (i.e., reflecting the relative public health significance) regardless of drug class.

c. ADVERSE REACTIONS:

(1) Clinical Trials Experience:

- Include following statement preceding presentation of adverse reactions from clinical trials: “Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

(2) Immunogenicity:

- Please add standard statement: “The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to DRUG with the incidence of antibodies to other products may be misleading.” Please note: We ask all sponsors with therapeutic proteins to add this standard statement in this section of the label.

d. USE IN SPECIFIC POPULATIONS:

(1) Pregnancy:

- Include regulatory statement required for pregnancy category B.

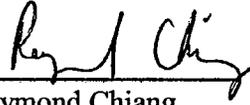
e. CLINICAL STUDIES:

- Please rename Efficacy Study and Dose-Ranging Study as Study 1 and Study 2, respectively.

**Recommendations**

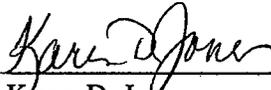
Please address the identified deficiencies/issues and re-submit labeling by April 21, 2009 This updated version of labeling will be used for further labeling discussions.

Regulatory: Product Package Insert Label:



Raymond Chiang  
Regulatory Health Project Manager

Supervisory Comment/Concurrence:



Karen D. Jones  
Chief, Project Management Staff

Drafted: Raymond Chiang/3-31-09

Revised/Initialed:

Finalized:

Filename: CSO Labeling Review Template (updated 1-16-07).doc

**CSO LABELING REVIEW OF PLR FORMAT**