

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125326**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**



**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: October 6, 2009

To: Patricia Keegan, MD, Director  
Division of Biologic Oncology Products

Through: Denise Toyer, PharmD, Deputy Director *Denise Toyer 10/6/09*  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Kristina C. Arnwine, PharmD, Team Leader *K. Arnwine 10/6/09*  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Healthcare Practitioner Survey Review

Drug Name(s): Arzerra (Ofatumumab) Injection, 100 mg

Application Type/Number: BLA 125326

Applicant: GlaxoSmithKline

OSE RCM #: 2009-1629

## 1 INTRODUCTION

This review is written in response to a submission from the Applicant for review of the Applicant's health practitioner survey for Arzerra (ofatumumab) Injection.

## 2 BACKGROUND

The submission and review of this survey was initiated based on information submitted by the Applicant. In their document "CMC Responses to FDA for Q5 to Q39", provided in sequence 14, dated May 14, 2009, the Applicant stated "GSK has completed a risk assessment with pharmacists to investigate potential issues in order to mitigate the requirement for 20 vials" b(4)

Additionally in the Applicant's "Responses to FDA Questions received July 13 & 14, 2009" provided in sequence 22, dated July 20, 2009, the Applicant stated "In November 2008, GSK conducted a risk assessment to identify potential failure modes for use of the product in the clinic and to develop mitigation plans. This included an assessment of the requirement for use of 20 vials. GSK participants in this process included pharmacists, CMC and logistics representatives and commercial representatives responsible for training and education of clinicians. GSK is currently verifying the risk assessment relating to dosing with 20 vials with external pharmacists." In the July 20, 2009 document, GSK submitted one component of the November 2008 risk assessment. DMEPA requested that GSK submit the complete methodology and results from the November 2008 risk assessment. Additionally, DMEPA was willing to provide comments on GSK's methodology for the risk assessment involving the external pharmacists.

During a teleconference with the Applicant on September 21, 2009, GSK informed the Agency that they did not have a protocol for the external pharmacists risk assessment. In lieu of a protocol, GSK is proposing to conduct a survey of pharmacists, oncology nurses, and physicians using the proposed insert labeling and the questionnaire in Appendix A to assess whether the preparation instructions for Arzerra are clear and re-enforce the use of the appropriate number of vials for the 300 mg and 2000 mg doses. DMEPA offered to review and provide recommendations on the GSK survey.

## 3 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) with consultation from the Division of Risk Management (DRISK) evaluated the healthcare practitioner survey submitted by the Applicant on September 28, 2009 (see Appendix A).

## 4 DISCUSSION

GSK's proposal to market only the 100 mg vial strength will require 20 vials for each 2000 mg dose. The use of such a large number of vials introduces the potential that medication errors may occur during the preparation of the 2000 mg dose. DMEPA is unable to determine the clinical consequences if the dose does not consist of exactly 20 vials and will defer this determination to DBOP.

To minimize the potential for confusion, GSK has agreed to a post marketing commitment to develop a 1 vial by the end of 2010 and they plan to institute several measures to minimize the potential for medication errors during the interim phase. These measures include 1) providing training for pharmacists, physicians around the importance of using the full dose of Arzerra; 2) packaging the vials in quantities that correlate to the 300 mg dose (3 vials) and 2000 mg dose (10 vials per carton where they have to use two cartons); and 3) providing replacements for missing, broken, or otherwise unsuitable vials by the next business day thru the GSK Response Center. b(4)

Furthermore, GSK plans to survey pharmacists, oncology nurses and physicians to help identify areas for improvement pertaining to the Arzerra dosing and administration. They plan to utilize this survey to ensure that the language used is clear and adequately communicates the correct dosing and preparation of Arzerra. Overall the survey was appropriate; we identify areas of improvement and provide recommendations below.

## 5 CONCLUSIONS AND RECOMMENDATIONS

GSK's proposal to market only the 100 mg vial strength will require 20 vials for each 2000 mg dose. The use of such a large number of vials introduces the potential that medication errors may occur during the preparation of this dose. However, GSK is attempting to mitigate the potential for medication errors using measures such as education, vial packaging configuration, a healthcare practitioner survey and a post-marketing commitment to develop a \_\_\_\_\_ vial by the end of 2010. b(4)

Based on the above measures, DMEPA does not consider the necessity for 20 vials for the 2000 mg dose an approvability issue from a medication error perspective. However, DMEPA defers to DBOP for assessment of the clinical consequences if less than 20 vials are used for a prescribed 2000 mg dose.

Additionally, our evaluation of the proposed GSK survey noted areas where questions can be revised and/or relocated to follow the presentation of information in the insert labeling. We provide recommendations in Section 5.1 (*Comments to the Applicant*). We request the recommendations in Section 5.1 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Sandra Griffith, OSE Regulatory Project manager, at 301-796-2445.

### 5.1 COMMENTS TO THE APPLICANT

We have completed our evaluation of your healthcare practitioner survey and have the following recommendations.

- A. Please describe how this survey will be distributed.
- B. Prior to completing the survey, do not provide respondents with any additional information that will not be provided in the package insert (e.g. information about why or how to order additional vials through the GSK Response Center).
- C. We note the doses are referred to as both "doses" and "infusions". Change all references of "infusions" to "doses" to be consistent with the package insert labeling.

5 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process



**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:** May 12, 2009

**To:** Patricia Keegan, M.D., Director  
Division of Biologic Oncology Products (DBOP)

**Through:** Claudia Karwoski, Pharm.D., Director (Acting)  
Division of Risk Management (DRISK) *Claudia Karwoski 5-11-09*

**From:** Doug Pham, Pharm.D., J.D., Drug Risk Management Analyst  
(DRISK)

**Subject:** Review of Proposed Risk Management Plan (RMP)

**Drug Name(s):** Arzerra (ofatumumab)

**Application Type/Number:** BLA 125326

**Applicant :** GlaxoSmithKline (GSK)

**OSE RCM #:** 2009-243

## **1 INTRODUCTION**

The Division of Biologic Oncology Products (DBOP) requested the Division of Risk Management (DRISK) review the proposed Risk Management Plan submitted with Arzerra's (ofatumumab) original BLA application dated January 30, 2009.

Arzerra (ofatumumab) is a new molecular entity human monoclonal antibody (IgG1<sub>K</sub>) that binds specifically to a distinct epitope on the human CD20 molecule expressed on B-cells to induce cell lysis. The proposed indication for Arzerra is for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received prior therapy.

The Sponsor submitted a BLA on January 30, 2009 with requests for a priority review. The proposed risk management activities (using the EU-RMP format) include professional labeling and pharmacovigilance.

A mid-cycle meeting was held on April 6, 2009 where the safety issues were determined to be adequately addressed through the proposed professional labeling and pharmacovigilance.

## **2 MATERIAL REVIEWED**

- BLA 125326, Risk Management Plan dated January 30, 2009 and submitted with the original NDA

## **3 CONCLUSION AND RECOMMENDATIONS**

DRISK has determined that the Sponsor's submission represents the minimal regulatory approach to risk management. At this time, DRISK considers the proposed risk management approach acceptable. Should DBOP uncover risks associated with ofatumumab that warrant a Risk Evaluation Mitigation Strategy (REMS) including a Medication Guide, communication plan, and/or elements to assure safe use, please re-consult OSE-DRISK.