

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125486Orig1s000

**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
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: September 19, 2013

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Subject: Evaluation to determine if a REMS is necessary

Drug Name(s): obinutuzumab (Gazyva)

Therapeutic Class: Antineoplastic agent

Dosage and Route: 1,000 mg intravenous infusion that follows a 28-day treatment cycle for six cycles

Application Type/Number: BLA 125486

Applicant/sponsor: Genentech, Inc.

OSE RCM #: 2013-1007

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity obinutuzumab. On April 22, 2013, Genentech submitted an original Biologics License Application (BLA) for obinutuzumab in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia. The sponsor did not submit a proposed REMS or risk management plan.

1.1 BACKGROUND¹⁻⁴

Chronic lymphocytic leukemia (CLL) is a chronic lymphoproliferative disorder characterized by progressive accumulation of a functionally incompetent monoclonal lymphocyte. CLL is considered to be a disease of the elderly with a median age at diagnosis of 70 years. It is the most common leukemia in Western countries. In the U.S., over 15,000 new cases and 4,500 deaths are estimated in 2013. Although approximately 25% of patients are asymptomatic at diagnosis, most patients present with lymphadenopathy, and splenomegaly and hepatomegaly are also common findings on exam. Most patients have a prominent lymphocytosis in the peripheral blood and bone marrow; neutropenia, anemia, and thrombocytopenia may also be observed.

The clinical behavior of CLL is variable with survival times from initial diagnosis that range from approximately 2 to 20 years, and a median survival of about 10 years. The prognosis is associated with the stage of the disease and other genetic and immunologic factors. Patients with advanced stages of disease have a relatively rapid clinical course, and mortality generally occurs within a few years. Most patients die from severe systemic infection, such as pneumonia or sepsis. Bleeding and cachexia are other frequent causes of death.

Not all patients require therapy at the time of diagnosis. Treatment is indicated for patients who develop disease-related symptoms or have evidence of progressive disease. A number of therapeutic options are available, including purine analogs such as fludarabine; the alkylating agents chlorambucil, cyclophosphamide, and bendamustine; monoclonal antibodies that target CD-20 or CD-52 antigens, which include rituximab, ofatumumab, and alemtuzumab; combination regimens of these treatments, and other agents. Treatment regimen decisions are primarily based on the patient's age and frailty, comorbidities, chromosome abnormalities (del(17p) or del(11q) are associated with low response rates), and prior therapy status.

Obinutuzumab is a recombinant humanized monoclonal antibody directed against the CD20 antigen of B-cell lymphocytes. Obinutuzumab was designed to mediate increased direct-cell death and enhanced immune effector cell-mediated killing compared to rituximab.

¹ Siegel R, et al. Cancer Statistics, 2013. *CA Cancer J Clin* 2013;63:11-30.

² Rai KR and Keating MJ. Epidemiology and clinical manifestations of chronic lymphocytic leukemia. In: *UpToDate*, Larson RA (Ed), UpToDate, Waltham MA, 2013.

³ Rai KR and Keating MJ. Overview of the treatment of chronic lymphocytic leukemia. In: *UpToDate*, Larson RA (Ed), UpToDate, Waltham MA, 2013.

⁴ National Comprehensive Cancer Network. *Non-Hodgkin's Lymphomas*, Version 1.2013. NCCN Clinical Practice Guidelines in Oncology, 2012.

1.2 REGULATORY HISTORY

On April 22, 2013, Genentech submitted an original Biologics License Application (BLA) for the use of obinutuzumab in combination with chlorambucil as first-line treatment for patients with CLL. The sponsor previously received orphan drug designation for the CLL indication on February 17, 2012. Obinutuzumab received Breakthrough Therapy Designation on May 9, 2013. The review classification for the application is Priority. The sponsor did not submit a proposed REMS or risk management plan.

2 MATERIALS REVIEWED

- April 22, 2013, Original BLA 125486 submission. Sections reviewed include:
 - Section 1.14, Draft labeling
 - Section 2.5, Clinical Overview
 - Section 2.7.4, Summary of Clinical Safety
- June 10, 2013, slides from Genentech obinutuzumab BLA orientation meeting
- July 23, 2013, slides from BLA 125486 Mid-Cycle Meeting

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

The sponsor completed a single Phase 3 clinical trial in support of the proposed indication. Study BO21004/CLL11 is an ongoing open-label, multi-center, three-arm randomized study in 590 previously untreated CLL patients with comorbidities and/or renal impairment. Patients were randomized 2:2:1 to obinutuzumab plus chlorambucil (G-Clb); rituximab plus chlorambucil (R-Clb); or single-agent chlorambucil (Clb), in two stages. Stage 1 compared G-Clb to Clb alone and R-Clb to Clb alone. Stage 2 randomized an additional 190 patients to compare G-Clb with R-Clb. The results from the primary analysis of G-Clb compared to single-agent Clb form the basis of the BLA.

Patients received up to six cycles of the assigned treatment and each cycle was 28 days in duration. Obinutuzumab was administered as a 1,000 mg infusion on Day 1, 8, and 15 (the first infusion in Cycle 1 was split over two days) of Cycle 1, and was subsequently administered on Day 1 of Cycles 2-6. Patients randomized to the R-Clb arm received 375 mg/m² of rituximab as an intravenous infusion on Day 1 of the first cycle and 500 mg/m² on Day 1 of each subsequent cycle. All patients received 0.5 mg/kg body weight Clb given orally on Day 1 and Day 15 of all treatment cycles.

The primary efficacy endpoint for BO21004/CLL11 was progression-free survival (PFS) as assessed by an independent review committee (IRC). Secondary efficacy endpoints included end of treatment response, event-free⁵ survival (EFS), overall survival, and other endpoints. Based on the IRC data, treatment with G-Clb resulted in a median PFS of 23 months compared to 11.1 months in patients treated with single-agent Clb; the hazard ratio (95% CI) was 0.16 (0.11, 0.24). [In the rituximab arm, treatment with R-Clb showed a median PFS of 14.9 months; the corresponding hazard ratio (95% CI) versus Clb alone was

⁵ Events were defined as progressive disease, death, or the start of a new anti-leukemia treatment.

0.32 (0.24, 0.44).] Patients randomized to the G-Clb arm showed improvement in the proportion experiencing a treatment response as well as improvement in the median EFS times compared with patients who received single-agent Clb. The median overall survival could not be estimated due to the low number of deaths in the study arms.

3.2 SAFETY CONCERNS

For the purpose of this review, severe adverse events associated with obinutuzumab are defined as Grade 3-5 in the NCI Common Terminology Criteria for Adverse Events.

3.2.1 Serious Adverse Events

During the treatment period of BO21004/CLL11, 73/240 patients (30%) randomized to the G-Clb arm experienced serious adverse events (SAEs) of any nature compared with 26/116 patients (22%) in the Clb arm. Serious infusion-related reactions occurred in 27 patients who received obinutuzumab versus none of the patients (as expected) who received single-agent Clb, which accounted for the overall difference in SAEs between the two arms. Serious infections were experienced in a lower percentage of patients in the G-Clb arm (6%) compared with the Clb arm (12%). The proportion of patients experiencing serious blood cell cytopenia events was similar (approximately 5%) between the two groups. Three patients developed tumor lysis syndrome in the G-Clb arm versus none in the Clb arm; the protocol required that all patients with a high tumor burden receive adequate hydration and prophylaxis for hyperuricemia at the first infusion.

Six patients (5%) in the Clb group and five patients (2%) in the G-Clb group experienced an SAE leading to death. One of the five deaths in the G-Clb group was considered by the investigators as related to study treatment. This event involved an 81 year-old man who suffered a hemorrhagic stroke.

3.2.2 Infusion-related reactions

Infusion-related reactions occurred in 165/240 patients (69%) during the first infusion of obinutuzumab and in 6/210 patients (3%) during the second infusion of Cycle 1. Although no infusion reactions were reported in Cycle 2, between one and three patients experienced an infusion reaction in each of Cycles 3-6. The most common symptoms of infusion reactions were nausea, chills, hypotension (53/240 patients [22%]), and pyrexia. Severe infusion reactions were experienced in 50/240 patients (21%); hypotension was the most common symptom in these severe reactions and occurred in 23/240 patients (10%). None of the adverse reactions were fatal. Several protocol amendments were introduced during the study to minimize the risk of infusion reactions, and the final protocol version required the administration of an antipyretic, antihistamine, and corticosteroid prior to obinutuzumab infusion. In addition, it was made mandatory to administer the first infusion over two days (100 mg on Day 1 and 900 mg on Day 2) and that antihypertensive medication was not to be given on the morning of, or during the infusion.

One patient experienced a Grade 3 anaphylactic reaction during the first infusion. The event was assessed as unrelated to obinutuzumab and resolved without sequelae, but obinutuzumab was discontinued. An additional patient crossed over from Clb treatment to the G-Clb arm and experienced Grade 4 anaphylactic shock during the first infusion.

3.2.3 Hematologic toxicity

Severe neutropenia adverse events were experienced by 82/240 patients (34%) in the G-Clb arm and 17/116 patients (15%) in the Clb arm. Severe neutropenia was managed by delaying the dosing of chlorambucil and administering growth factor support. Severe thrombocytopenia also occurred at a greater frequency in patients who received G-Clb (11%) compared with those who received single-agent Clb (3%).

3.2.4 Infections

The overall incidence of infection was approximately the same (33% G-Clb versus 37% Clb) in each arm of the study, though severe infections occurred in a lower proportion of patients treated in the G-Clb arm compared with the Clb arm (6% versus 11%). However, the prophylactic use of antibiotics and growth factors was higher in patients who received G-Clb than single-agent Clb. One patient in the G-Clb arm experienced febrile neutropenia compared with five patients in the Clb arm.

There were no cases of hepatitis B reactivation observed in patients treated with obinutuzumab, though patients with positive serology for hepatitis B were excluded from the study. Patients positive for hepatitis B core antibody were also excluded from the study unless hepatitis viral DNA was not detectable.

One case of progressive multifocal leukoencephalopathy (PML) was reported in a patient enrolled in a separate clinical study of obinutuzumab for the treatment of relapsed/refractory non-Hodgkin's lymphoma. This patient had previously been treated with rituximab and fludarabine, which are known risks associated with PML.

3.2.5 Proposed Postmarketing Studies

No clinical postmarketing requirements have been determined at the time of this review.

4 DISCUSSION

Obinutuzumab is a recombinant monoclonal antibody directed against the CD20 antigen of B-cell lymphocytes and is proposed for use in combination with chlorambucil for the treatment of patients with CLL, a serious and life-threatening disease. In the pivotal Phase 3 clinical study, the risk of disease progression or death was reduced by 84% (HR=0.16) when obinutuzumab was given with chlorambucil, demonstrating superiority to single-agent chlorambucil. Secondary efficacy endpoint findings supported the improvement in progression free survival. Obinutuzumab has been designated as a breakthrough therapy for the proposed indication.

The safety profile of obinutuzumab appears similar to other members of the class of monoclonal antibodies approved for the treatment of CLL, which include rituximab, ofatumumab, and alemtuzumab. The primary safety concerns for obinutuzumab appear to be infusion-related reactions, blood cell cytopenias, infections, and tumor lysis syndrome. These concerns are listed as boxed warnings and/or described in the warnings and precautions sections of the labeling of the approved products. A high-level comparison of the safety profiles of rituximab, ofatumumab, and alemtuzumab is found in the Appendix.

The risk of infusion-related reactions associated with obinutuzumab appears similar to the risk associated with the other monoclonal antibodies approved for the treatment of CLL. Although close to 70% of patients treated with obinutuzumab experienced an infusion reaction and 21% of these were severe reactions, none were fatal. In comparison, infusion reactions occurred in 77% of patients receiving rituximab (for the approved indication non-Hodgkin's lymphoma) and the rituximab labeling includes a boxed warning for fatal infusion reactions. The ofatumumab labeling states infusion reactions occurred in 44% of patients on the day of the first infusion. The alemtuzumab label also includes a boxed warning for fatal infusion reactions and notes that severe reactions occurred in up to 35% of patients.

The risk of hematologic toxicity with obinutuzumab seems consistent with that for rituximab, alemtuzumab, and ofatumumab, though differences in clinical study designs make direct comparisons somewhat difficult to interpret. Of the patients randomized to G-C1b, 34% experienced severe neutropenia and 11% severe thrombocytopenia. These proportions are similar to those stated in the labeling of the approved products, which range from 30 to 42% severe neutropenia and 11 to 14% severe thrombocytopenia (depending on the study design and disease treated).

Other serious or severe adverse events associated with obinutuzumab were not unexpected for an elderly population being treated with a monoclonal antibody that results in B-cell depletion. The sponsor's draft labeling submitted to the obinutuzumab BLA includes warnings for other observed and expected risks, such as tumor lysis syndrome, worsening of pre-existing cardiac conditions (as part of an infusion reaction), hepatitis B reactivation, IgE-mediated allergic reactions including anaphylaxis, and PML.

DRISK does not recommend a REMS for the management of risks associated with obinutuzumab. Patients with a diagnosis of CLL have a serious and life-threatening disease. Obinutuzumab therapy in combination with chlorambucil demonstrated superior efficacy to single-agent chlorambucil. The safety profile of obinutuzumab is similar to monoclonal antibody products approved for the treatment of CLL, and no unexpected safety signals were observed compared to other agents in the class. None of the monoclonal antibodies in the class are approved with a REMS.

5 CONCLUSION

DRISK concurs with the Division of Hematology Products that, based on the available data and the potential benefits and risks of treatment, a REMS is not necessary for obinutuzumab and the risks associated with the product can be managed through labeling. If new safety information becomes available, this decision can be re-evaluated.

APPENDIX

Table 1: Comparison of monoclonal antibodies approved for the treatment of chronic lymphocytic leukemia (CLL)

	Rituximab	Ofatumumab	Alemtuzumab
Description	Chimeric monoclonal antibody against CD20	Human monoclonal antibody against CD20	Humanized monoclonal antibody against CD52
Indication(s)	<ul style="list-style-type: none"> ▪ Non-Hodgkin's lymphoma ▪ CLL ▪ Rheumatoid arthritis ▪ Wegener's granulomatosis and Microscopic polyangiitis 	CLL	B-cell CLL
Date of initial approval	1997	2009	2001
Boxed Warnings	<ul style="list-style-type: none"> ▪ Infusion reactions ▪ Tumor lysis syndrome ▪ Severe mucocutaneous reactions ▪ PML 	None	<ul style="list-style-type: none"> ▪ Cytopenias ▪ Infusion reactions ▪ Infections
Warnings and Precautions	<ul style="list-style-type: none"> ▪ Infusion reactions ▪ Tumor lysis syndrome ▪ Severe mucocutaneous reactions ▪ PML ▪ Hepatitis B reactivation ▪ Infections ▪ Cardiac arrhythmias ▪ Renal toxicity ▪ Bowel obstruction and perforation ▪ Immunizations ▪ Laboratory monitoring 	<ul style="list-style-type: none"> ▪ Infusion reactions ▪ Cytopenias ▪ PML ▪ Hepatitis B infection and reactivation ▪ Intestinal obstruction ▪ Immunizations 	<ul style="list-style-type: none"> ▪ Cytopenias ▪ Infusion reactions ▪ Immunosuppression ▪ Infections ▪ Laboratory monitoring ▪ Immunizations
Risk Management	Prescribing Information	Prescribing Information	Prescribing Information

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/s/

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